MONOGRAPHS ON THE CHEMISTRY OF NATURAL PRODUCTS

General Editor

SIR ROBERT ROBINSON

The aim of this Series is to record as completely as is possible and desirable the existing state of knowledge in certain fields of the descriptive and structural chemistry of natural products.

The emphasis is placed on the analytic and synthetic investigations which have helped to elucidate some of the classical problems of the chemistry of polycyclic substances which occur in the vegetable kingdom. Such special topics have been selected as are of the greatest intrinsic interest, an interest perhaps most reliably indicated by the number and length of memoirs concerned with their study. The availability of an author who has worked intensively on some aspect of the subject and the association of the present writer with some one of its facets have also been factors in the choice. As far as possible the original literature has been consulted, and it is hoped that these books will be of interest to students and afford both stimulus and help to those engaged in further research.

THE CHEMISTRY
OF THE
MORPHINE ALKALOIDS

BY

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FOREWORD

In 1932 the U.S. Treasury Department (Public Health Service) published an excellent monograph, *Chemistry of the Opium Alkaloids,* by Professor Lyndon F. Small assisted by Associate Professor Robert E. Lutz.

The progress made in the last two decades has been so great, however, that a new work is required. This is all the more timely in that the formal synthesis of morphine by Professor M. Gates and his co-workers has finally established the validity of the constitutional formula proposed by Gulland and the writer in 1925.

The second volume of *The Alkaloids* (Academic Press) by R. H. F. Manske and H. L. Holmes, which contains three long chapters on morphine, thebaine, and sinomenine, appeared in 1952 whilst the present work was in preparation. The apparent duplication is not regretted partly on account of the new matter which it is now possible to include and partly because of the misunderstanding of the stages of development of the structural theory which does not show in true perspective some points where English chemists made a significant contribution.

Holmes (loc. cit., p. 26) remarks that the modern formulae (meaning our own) are but a small modification of those of Knorr and are based on Knorr's results together with a small further piece of evidence.

Again (p. 27) he states that Knorr's formula explained satisfactorily the complex rearrangements of morphine and thebaine. The first statement is misleading and the second will be seen to be incorrect on inspection of the details. For example, Knorr-codeinone to thebenine demands either a migration of carbonyl, or of the ethanamine chain, which cannot be theoretically justified, or based on analogy in any simple manner.

We allow no one to surpass us in respect for Knorr and Pschorr and other pioneers of morphine chemistry. They established the main facts, especially the constitutions of the phenanthrene degradation products, including morphenol and thebaol, and the very important transformation products thebenine, morphothebaine, and apomorphine. But until 1925 there was no consistent explanation of these degradations and transformations in terms of any acceptable structures for the parent bases. What appears to be a very small change in structure involved very great changes in the interpretations, and in fact proved the small key that unlocked a particularly massive door.

This is perhaps a suitable opportunity to recall the circumstances at that juncture, but in doing so it is far from the writer's wish to imply any comparison of the relative value of the key and the door.

In considering this stage of the development it is not difficult to confuse the issue by unduly meticulous attention to the formulae in

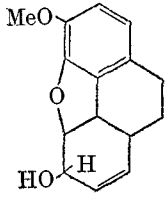
which codeine is represented as unsaturated, ignoring at the same time the equivalence of a bridged-ring structure for certain purposes.

Thus the allylic rearrangement of codeine to pseudocodeine was virtually recognized for the first time by Gulland and the writer in 1923.

The swing of a bridge took the place of that of a bond. In that paper of 1923 the analogy of the process to the geraniol-linalol transformation was specifically indicated.

In 1925 we were sure that codeine is unsaturated, partly because we had made it into a glycerol by the action of very dilute potassium permanganate.

And in that year Wieland and Kotake, and Gulland and Robinson, simultaneously and independently, ascribed the correct positions of *sec*-hydroxyl and double bond to codeine (*iso*codeine) (I) and pseudocodeine (allopseudocodeine) (II). The existence of the oxide ring shown in those formulae had long been established.



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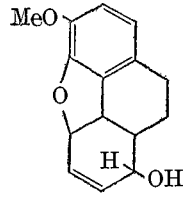

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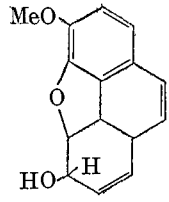

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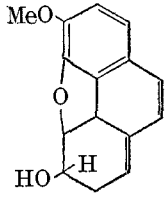

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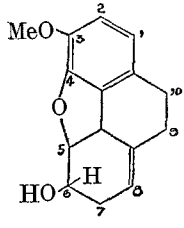


[V]

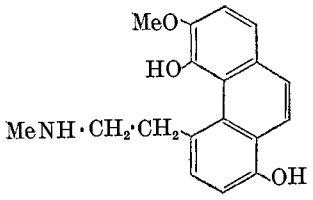
The position attributed to the oxygen was based on the conviction that a carbonyl oxygen (in codeinone and pseudocodeinone) would not migrate. Hence Pschorr's syntheses of 3:4:6-trimethoxyphenanthrene, obtainable from codeinone, and 3:4:8-trimethoxyphenanthrene, obtainable from pseudocodeinone, fixed the positions of the carbonyl group of the ketones, and therefore those of the *sec*-alcoholic groups of codeine and pseudocodeine also.

This led at once to the bis-ethenoid system of α-codeimethine (III) and β-codeimethine (IV).

A year later van Duin, Robinson, and Smith found that neopine (q.v.) is β-codeine (V) and is directly convertible into β-codeimethine. [I to V inclusive are parts of the full structures.]

The appearance of a double bond in the 9:10 position during the formation of α-codeimethine was consistent with the attachment of the basic nitrogen to one of these carbon atoms. Position 9 was generally preferred by the early theorists, probably on conscious or subconscious biogenetic grounds, in that the other opium alkaloids are β-arylethylamine derivatives.

We selected position 9 not only on the basis of the structural relation with *iso*quinoline alkaloids, but also because it was the only position that allowed us to give an explanation of the formation of thebenine (VI) from codeinone (VII).



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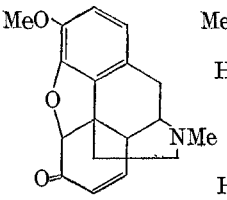

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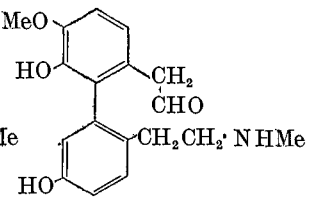


[VIII]

This theory is one to which the writer attaches considerable importance. It was advanced in 1923 on the bridge-ring basis, but is readily translated in terms of the 1925 formula.

We suggested that codeinone (VII) when treated with hot dilute hydrochloric acid undergoes hydrolysis and rearrangement to (VIII). There is then a swing about 180° and a natural type of condensation to give (VI). It will be seen that this scheme will not work plausibly enough if the nitrogen is attached to position 10 of the phenanthrene ring. This point is mentioned because it has been overlooked in subsequent comment.

In regard to the position of attachment of carbon of the ethanamine chain we were guided in 1923 and 1925 by three main considerations as follows:

(*a*) The view that the chain will not be displaced by C—C fission unless its removal is essential for formation of an aromatic nucleus.

(*b*) The mechanism of the codeinone to thebenine transformation.

(*c*) Biogenetic arguments.

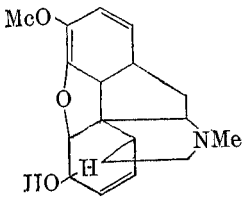
We came to the conclusion that C-13 was the only possible point of attachment.

Thus C-5 (Knorr formula) did not accommodate requirements under (*b*) and (*c*) and in a few cases (*a*) was also not satisfied.

C-14 is excluded by β-codeimethine and C-8 by pseudocodeinone. Only C-13 survived all the tests.

Nevertheless, a tiny loophole existed, namely that the alkaloids might not be phenanthrene derivatives and the phenanthrene ring might

appear only in the course of degradation. Thus codeine might be (IX). This *punctilio* was disposed of by a study of the ultra-violet absorption of α- and β-codeimethines (1947). Naturally the Gates synthesis[1] has now made this matter still less worthy of further consideration. The biogenctic argument was always regarded as a guide to structure, but a conceivably unreliable one. In its simplest form we draw attention to the fact that the skeleton (X) is also that of laudanosine (XI). Fission and rotation of the lower ring, about the axis as indicated, equate the two part-structures.



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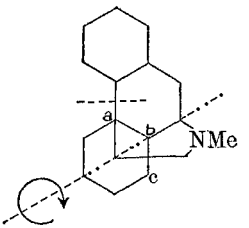

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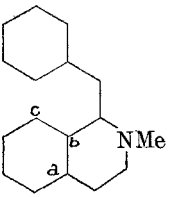
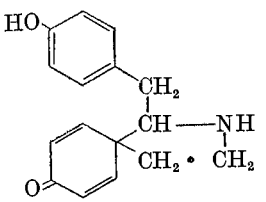


[XI]

The synthesis by Grewe of the morphinane ring system depends on a reversal of this process. As explained elsewhere, this scheme allows of a particularly close relation between sinomenine and a laudanosine derivative. The latter was synthesized and hopefully called protosinomenine, but it has not been available in sufficient amount to enable its properties and possible transformation to sinomenine to be thoroughly examined.

In the case of thebaine and morphine the oxygen atoms are not in the 3:4-position of the best known dihydroxyphenylalanine.



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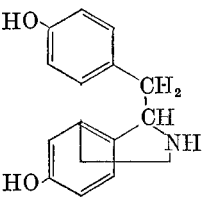


[XIII]

In the Truman Wood Lecture of 1948 to the Royal Society of Arts the writer has suggested a mechanism of oxidative coupling of tyrosine which may be worthy of further study. It involved a migration at one stage and led to the thebaine structure. The usual coupling leading to laudanosine types is assumed to take place at the *p*-position to hydroxyl of tyrosine. This gives (XII) which suffers homiquinone migration to

[1] A private communication (October 1953) discloses that morphine has also been synthesized by David Ginsburg and his colleagues at Rehovoth, Israel.

(XIII). Oxidation, oxidative ring coupling, and methylation can then give thebaine. As always, the order of the processes is undetermined, and as one example of this the starting-point could be 3:4-dihydroxyphenylalanine.

In the last decade the subject of rearrangements in the thebaine group has been twice awakened from sleep. The first occasion was signalled by elucidation of the constitution of phenyldihydrothebaine, discovered by Freund and carefully studied by Small.

It transpired that the final product of Hofmann degradation of this base contained no asymmetric carbon atom and owed its optical activity to restricted rotation of a heavily substituted diphenyl!

Dr. Bentley was associated with the writer in the performance of crucial experiments bearing on the validity of the rather surprising conclusion which we were forced to adopt.

The second occasion, also of great interest, was connected with the re-examination of Schöpf's flavothebaone by Dr. Bentley and Professor J. Dominguez. The complex results are still being scrutinized, but it is already clear that a double migration is involved and that a new and fascinating chapter of thebaine chemistry will be written.

Dr. Bentley has also elaborated the chemistry of the reduction products of thebaine in several directions.

In the volume which follows he has covered critically and exhaustively the whole field of the chemistry of these alkaloids and has thus performed a much needed service to the scientific world. He has carried out his task with remarkable skill backed by the enthusiasm which is felt by all who come into contact with this veritable Proteus among molecules.

R. ROBINSON

ADDENDUM. Kondo, Satomi, and Odera (Annual Reports of the I.T.S.U.U. Institute, 1951, 1952, 1953, Tokyo) have proved that *hasubanonine* from *Stephania japonica* Miers is 3:4:6:7-tetramethoxy-8-oxo-N-methylmorphinane as is suggested on p. 359 formula [CXIX]. Hasubanonine is a ketone and its methiodide affords a methine-base, which on acetolysis yields dimethylethylamine and 0-acetylhasubanol. Hasubanol methyl ether was identified with 3:4:6:8-tetramethoxyphenanthrene. Colour reactions indicate a free *p*-position with respect to the phenolic hydroxyl of hasubanol, which is accordingly sited at position-8. This is clearly a transform of the carbonyl group of the alkaloid. The methoxyl eliminated in the acetolysis of the methine must be at position-7, because hasubanonine was unchanged when an attempt was made to convert it into a hydroxymethylene derivative; sinomenine underwent this transformation with ease under the same conditions.

AUTHOR'S PREFACE

NEARLY a hundred and fifty years have elapsed since the first vegetable alkaloid was discovered, and only recently has the structure proposed for this base in 1925 been vindicated by the total synthesis of the alkaloid. It would seem that the 'morphine' chapter of organic chemistry is now all but closed and that all that remains is the filling in of details; but it would be rash to assert this, as one of the most interesting of molecular rearrangements in this field was only fully elucidated five years ago, while yet another received a credible solution only after the completion of the main text of this monograph. The moment seems opportune, however, for the presentation, in one volume, of a comprehensive survey of the chemistry of all the morphine alkaloids.

In this monograph each chapter is intended to be as far as possible a complete account of one section of the work, even though this has necessitated the duplication of certain parts. It is hoped that all papers relating to the chemistry of the morphine alkaloids published before 1 February 1953 are referred to in the monograph.

The compilation of this monograph has proved to be a more exacting task than was first anticipated and I wish to thank Professor Sir Robert Robinson, O.M., for his unfailing interest and constant encouragement at all stages of the work and for helpful discussion of all points of structural interest that have arisen.

I also wish to express my thanks to the following: Señor Justo Dominguez for his invaluable experimental assistance in the investigations related to flavothebaone; Dr. J. A. Barltrop for helpful discussion in relation to Chapter XXI; Dr. F. B. Strauss and Mr. F. H. L. H. Hastings for the preparation of all but one of the ultra-violet extinction curves embodied in the monograph; Messrs. A. F. Thomas, A. Marchant, and J. M. Swinstead for help with the checking of references and manuscripts; to my wife for her help in the equally laborious tasks of the reading of proofs and the preparation of the index; and finally to the officers of the Clarendon Press, for whom no trouble seems to be too great, for the courteous and efficient manner in which they have carried out their part of the work.

γηράσκω δ'ἀεὶ πολλὰ διδασκόμενος

THE DYSON PERRINS LABORATORY
OXFORD

THE CHEMISTRY DEPARTMENT
THE UNIVERSITY
ABERDEEN

March 1953

CONTENTS

ABBREVIATIONS

Abderhalden's Hanb. biol. Arbeitsmethoden, Abderhalden's Handbuch der biologischen Arbeitsmethoden.

Acta Chem. Scand., Acta Chemica Scandinavica.

Acta Phytochim., Acta Phytochimica (Japan).

Allen's Comm'l Org. Anal., Allen's Commercial Organic Analysis.

Am. J. Pharm., American Journal of Pharmacy.

Anales Asoc. Quím. Argentina, Anales de la Asociación Química Argentina.

Anales Farm. Bioquím. (Buenos Aires), Anales de Farmacia y Bioquímica (Buenos Aires).

Anales real acad. farm., Anales de la real academia de farmacia.

Analyst, The Analyst.

Ann., Annalen der Chemie.

Ann. Chim., Annales de Chimie.

Ann. Chim. Anal., Annales de Chimie Analytique et de Chimie Appliquée et Revue de Chimie Analytique Réunies.

Ann. Chim. Farm., Annali di Chimica Farmaceutica.

Ann. Chim. Phys., Annales de Chimie et Physique.

Ann. Méd. Légale Criminol. Police Sci., Annales de Médecine Légale de Criminologie et de Police Scientifique.

Ann. pharm. Franç., Annales pharmaceutiques françaises.

Ann. Rep. Itsuu Lab., Annual Report of Itsuu Laboratory.

Ann. Sci. Univ. Jassy, Annales Scientifiques de l'Université de Jassy.

Ann. Suppl., Annalen der Chemie Supplement.

Apoth.-Ztg., Apotheker-Zeitung.

Arch. Exptl. Path. Pharmakol., Archiv für experimentelle Pathologie und Pharmakologie.

Arch. ges. Physiol., Archiv für gesamte Physiologie des Menschen und der Tiere.

Arch. Intern. Pharmacodynamie, Archives Internationales de Pharmacodynamie et de Thérapie.

Arch. Pharm., Archiv der Pharmazie und Berichte der deutschen pharmazeutischen Gesellschaft.

Arch. Sci. Biol., Archivio di Scienze Biologiche.

Arq. Biol. (São Paulo), Arquivos de Biologica (São Paulo).

Atti Accad. Gioenia Sci. Nat. Catania, Atti della Accademia Gioenia di Scienze Naturali di Catania.

Atti Accad. Lincei, Atti della Reale Accademia Nazionale dei Lincei.

Atti Soc. Medchir. Padova, Atti della Società Medico-chirurgica di Padova e Bolletino della Facoltà di Medicina e Chirurgica della r. Università di Padova.

Australian J. Pharm., Australian Journal of Pharmacy.

Ber., Berichte der deutschen chemischen Gesellschaft.

Ber. Deut. Pharm. Ges., Berichte der deutschen pharmazeutischen Gesellschaft.

Ber. ges. Physiol. expt. Pharmacol., Berichte über die gesamte Physiologie und experimentelle Pharmakologie.

Ber. Sächs. Akad. Wiss., Berichte über die Verhandlungen der Sächsischen Akademie der Wissenschaften zu Leipzig.

Ber. Ungar. Pharm. Ges., Berichte über die ungarische pharmazeutische Gesellschaft.

Biochem. Z., Biochemische Zeitschrift.

Boll. Chim.-Farm., Bollettino chimico-farmaceutico.

Boll. Soc. Ital. Biol. Sper., Bollettino della Società Italiana di Biologia Sperimentale.

Brit. Pat., British Patent.

Büchner's Rept. Pharmazie, Büchner's Repertorium der Pharmazie.

Bull. Acad. Sci. United Provinces, Agra, Oudh, Allahabad, Bulletin of the Academy of Sciences of the United Provinces of Agra and Oudh, Allahabad.

Bull. Biol. Pharm., Bulletin des Biologistes Pharmaciens.

Bull. Chem. Soc. Japan, Bulletin of the Chemical Society of Japan.

Bull. Health Org. League Nations, Bulletin of the Health Organisation of the League of Nations.

Bull. Hyg. Res. Inst. (*Japan*), Bulletin of the Hygenic Research Institute (Japan).

Bull. Sci. Pharmacol., Bulletin des Sciences Pharmacologiques.

Bull. Soc. Chim., Bulletin de la Société Chimique de France.

Bull. Soc. Chim. Belg., Bulletin de la Société Chimique de Belgique.

Bull. Soc. Chim. România, Bulletin de la Société Chimique de România.

Bull. Soc. Chim. Roy. Yougoslav., Bulletin de la Société Chimique du Royaume de Yougoslavie.

Bull. Soc. Pharm. Bordeaux, Bulletin des Travaux de la Société de Pharmacie de Bordeaux.

Bull. Soc. Roy. Sci. Liége, Bulletin de la Société Royale de Science de Liége.

Byull. Nauch.-Issl. Khim.-Farm. Inst., Byulleten Nauchno-Issledovatel'skogo Khimiko-Farmatsevicheskogo Instituta.

Can. J. Res., Canadian Journal of Research.

Časopis Českoslov. Lékárnictva, Časopis Československého Lékárnictva.

Chem. Abs., Chemical Abstracts.

Chemist and Druggist, Chemist and Druggist.

Chem. News, Chemical News.

Chem. Zent., Chemisches Zentralblatt.

Chem. Ztg., Chemiker-Zeitung.

Chimie et Industrie, Chimie et Industrie.

Chim. Anal., Chimie Analytique.

Chim. ind. agr. biol., La Chimica nell' industria, nell' agricoltura, nella biologia e nelle realizzazioni corporative.

Chûgai Iji Shimpo, Chûgai Iji Shimpo.

Compt. Rend., Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences.

Compt. Rend. Acad. Sci. U.S.S.R., Comptes Rendus de l'Académie des Sciences de l'U.R.S.S.

Compt. Rend. Soc. Biol., Comptes Rendus des Séances de la Société de Biologie et de ses filiales et associées.

Current Sci., Current Science.

Dansk Tids. Farm., Dansk Tidsskrift for Farmaci.

Deut. Med. Wochschr., Deutsche medizinische Wochenschrift.

D. R.-P., Deutsches Reichs-Patent.

Edinburgh New Phil. J., Edinburgh New Philosophical Journal.

Experientia, Experientia.
Farmatisiya, Farmatisiya.
Farm. Nueva, Farmacia Nueva (Madrid).
Farm. Zhur., Farmatsevtichnii Zhurnal.
Frdl., Friedlaender, Fortschritte der Teerfarben-fabrikation.
French Pat., French Patent.
Gazz. Chim. Ital., Gazzetta Chimica Italiana.
Gilbert's Ann. der Physik, Gilbert's Annalen der Physik.
Hanb. Krist.-Phys. Chem., Handbuch der kristall-physikalischen Chemie.
Helv. Chim. Acta, Helvetica Chimica Acta.
Ind. Eng. Chem. (*Anal. Edn.*), Industrial and Engineering Chemistry (Analytical Edition).
Indian J. Med. Res., Indian Journal of Medical Research.
Industria Chimica, Industria Chimica.
J.A.C.S., Journal of the American Chemical Society.
J. Agr. Soc. Japan, Journal of the Agricultural Society of Japan.
Jahresber. Chem., Jahresbericht der Chemie.
Jahresber. Chem. Tech., Jahresbericht der chemisch-technischen Reichsanstalt. Leipzig.
Jahresber. Fortschr. Chem., Jahresbericht über die Fortschritte der Chemie.
Jahresber. Fortschr. Phys. Wiss., Jahresbericht über die Fortschritte der physischen Wissenschaften.
Jahresber. Pharm., Jahresbericht der Pharmazie.
J. Am. Pharm. Assoc., Journal of the American Pharmaceutical Association.
J. Applied Chem. U.S.S.R., Journal of Applied Chemistry of U.S.S.R.
J. Assoc. Official Agr. Chem., Journal of the Association of Official Agricultural Chemists.
J. Biol. Chem., Journal of Biological Chemistry.
J. Chem. Ind. U.S.S.R., Journal of Chemical Industry of U.S.S.R.
J. Chem. Phys., Journal of Chemical Physics.
J. Chem. Soc. Japan, Journal of the Chemical Society of Japan.
J. Chim. Méd., Journal de Chimie Médicale.
J.C.S., Journal of the Chemical Society (London).
J. Gen. Chem. U.S.S.R., Journal of General Chemistry, U.S.S.R.
J. Indian Chem. Soc., Journal of the Indian Chemical Society.
J. Lab. Clin. Med., Journal of Laboratory and Clinical Medicine.
J. Org. Chem., Journal of Organic Chemistry.
J. Pharm., Journal de Pharmacie.
J. Pharm. Belg., Journal de Pharmacie de Belgique.
J. Pharm. Chim., Journal de Pharmacie et de Chimie.
J. Pharm. Elsass Lothr., Journal der Pharmazie von Elsass-Lothringen (Mülhausen).
J. Pharm. Pharmacol., Journal of Pharmacy and Pharmacology.
J. Pharm. Soc. Japan, Journal of the Pharmaceutical Society of Japan.
J. Phys. Chem., Journal of Physical Chemistry.
J. pr. Chem., Journal für praktische Chemie.
J. Soc. Chem. Ind., Journal of the Society of Chemical Industry.
J. Wash. Acad. Sci., Journal of the Washington Academy of Sciences.

Khim. Farm. Prom., Khimiko-Farmatsevticheskya Promyshlennost'.
Khim. Referat. Zhur., Khimicheskiĭ Referativnyi Zhurnal.
Landwirtschaftl. Versuchsstationen, Die landwirtschaftlichen Versuchsstationen.
L'Orosi, L'Orosi, Bollettino di chimica farmacia e scienze affini.
Maanblad voor Naturwettenschappen (*Amsterdam*), Maanblad voor Naturwettenschappen (Amsterdam).
Mem. Proc. Manchester Lit. Phil. Soc., Memoirs and Proceedings of the Manchester Literary and Philosophical Society.
Mikrochemie, Mikrochemie.
Monatsh., Monatshefte für Chemie und verwandte Teile anderer Wissenschaften.
Mon. Prod. Chim., Moniteur des Produits Chimiques.
Münch. Med. Wochschr., Münchener medizinische Wochenschrift.
Nature, Nature.
Naturwiss., Naturwissenschaften.
Natuurw. Tijdschr., Natuurwettenschappelijk Tijdschrift.
Org. Chem. Ind. U.S.S.R., The Organic Chemical Industry (U.S.S.R.).
Pharm. Acta Helv., Pharmaceutica Acta Helvetiae.
Pharm. J. Trans., The Pharmaceutical Journal and Transactions.
Pharm. Monatsh., Pharmazeutische Monatshefte.
Pharm. Post, Pharmazeutische Post.
Pharm. Weekblad, Pharmazeutische Weekblad.
Pharm. Zentralhalle, Pharmazeutische Zentralhalle.
Pharm. Ztg., Pharmazeutische Zeitung.
Phil. Trans. Roy. Soc., Philosophical Transactions of the Royal Society.
Pogg. Ann. der Physik, Poggendorff's Annalen der Physik.
Proc. Chem. Soc., Proceedings of the Chemical Society.
Proc. Imp. Acad. (*Tokyo*), Proceedings of the Imperial Academy (Tokyo).
Proc. Ind. Acad. Sci., Proceedings of the Indian Academy of Science.
Proc. Jap. Pharmacol. Soc., Proceedings of the Japanese Pharmacological Society.
Proc. Soc. Exptl. Biol. Med., Proceedings of the Society for Experimental Biology and Medicine.
Quart. J. Pharm. Pharmacol., Quarterly Journal of Pharmacy and Pharmacology.
Quím. e ind., Química e industria.
Rec. Trav. Chim., Recueil des Travaux Chimiques des Pays-Bas.
Rept. Inst. Sci. Res. Manchoukuo, Report of the Institute of Scientific Research, Manchoukuo.
Rev. Faculté Sci. Univ. Istanbul, Revue de la Faculté des Sciences de l'Université d'Istanbul.
Russ. Pat., Russian Patent.
Schweiz. Apoth.-Ztg., Schweizerische Apotheker-Zeitung.
Schweiz. Wochschr., Schweizerische Wochenschrift.
Science, Science.
Science and Culture, Science and Culture.
Sci. Repts. Natl. Tsinghau Univ., Science Reports of the National Tsinghau University.
Semana Méd. (*Buenos Aires*), La Semana Médica (Buenos Aires).
Sitzber. Akad. Wiss. Wien, Sitzungsberichte der Akademie der Wissenschaften, Wien.
Süddeut. Apoth.-Ztg., Süddeutsche Apotheker-Zeitung.

Svensk Farm. Tids., Svensk Farmaceutisk Tidskrift.
Swed. Pat., Swedish Patent.
Swiss Pat., Swiss Patent.
Trans. Roy. Soc. Edinburgh, Transactions of the Royal Society of Edinburgh.
Trommsdorff's Journal der Pharmazie, Trommsdorff's Journal der Pharmazie.
Ukrain. Gosudarst. Inds. Eksptl. Farm., Ukrainskiĭ Gosudarstvennyi Institut Eksperimental'noĭ Farmatsiĭ (Kharkov).
Univ. Calif. Pub. Pharmacol., University of California Publications in Pharmacology.
U.S. Pat., United States Patent.
U.S. Pub. Health Service Suppl., United States Public Health Service Supplement.
Virginia J. Sci., The Virginia Journal of Science.
Z. anal. Chem., Zeitschrift für analytische Chemie.
Z. angew. Chem., Zeitschrift für angewandte Chemie.
Z. anorg. Chem., Zeitschrift für anorganische Chemie.
Z. Elektrochem., Zeitschrift für Elektrochemie und angewandte physikalische Chemie.
Z. exptl. Path. Therap., Zeitschrift für experimentelle Pathologie und Therapie.
Z. Krist., Zeitschrift für Kristallographie.
Z. Krist. Mineral., Zeitschrift für Kristallographie und Mineralogie.
Z. phys. Chem., Zeitschrift für physikalische Chemie.
Z. physiol. Chem., Zeitschrift für physiologische Chemie.
Zeitschr. Chem., Zeitschrift für Chemie und Pharmazie.

I

INTRODUCTION; HISTORICAL AND GENERAL DISCUSSION OF THE CONSTITUTION OF THE ALKALOIDS

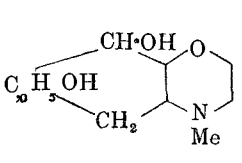
ALMOST a century and a half has elapsed since Sertürner isolated the first organic base clearly recognized as such, a crystalline substance that he obtained from the opium poppy, *Papaver somniferum*, and called morphine [1]. Largely on account of the migration phenomena encountered, the structural puzzle presented by morphine and related alkaloids has absorbed the interest of many chemists during this time, and in the case of scarcely any other natural product have so many constitutional formulae been proposed or such a volume of experimental work recorded. The fundamental researches of Hesse, Vongerichten, Knorr, and Pschorr established the alkaloid as a bridged-phenanthrene type, and the later work of Robinson and Schöpf resulted in the generally accepted structure for this group of bases.

That morphine is a phenol as well as a base was shown by its alkali-solubility [2], and codeine (discovered by Robiquet [3]) was subsequently shown by Grimaux [4–5] to be the methyl ether of morphine. Morphine yields a diacetyl-derivative [6–7] and codeine an acetyl-derivative [6] showing that these bases also contain an alcoholic group, and the hydroxyl of this is replaceable by chlorine when the alkaloids are treated with phosphorus pentachloride [8] or trichloride [9]. Oxidation of codeine with chromic acid affords a ketone, codeinone [10], which can also be obtained by the acid hydrolysis of a third alkaloid of this group, thebaine (discovered by Pelletier [11]), which was thus recognized as the methyl ether of an enolic form of codeinone [12]. The relationship between the three alkaloids was thus clear, and most of the evidence for the structure of the alkaloids of the morphine group is drawn from work on codeine and thebaine. These bases contain a third oxygen atom, which is inactive and was soon recognized as being part of an other system.

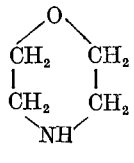
The mode of linkage of the nitrogen atom is clearly shown by the results of exhaustive methylation; with morphine the reaction is blocked by the formation of a phenol betaine [7, 13], but codeine methiodide on boiling with alkali is degraded to a base, α-codeimethine [14], showing that in codeine the nitrogen atom is part of a ring. Further degradation of α-codeimethine involves loss of the whole basic side-chain and formation of a fully aromatic phenanthrene derivative [15].

A similar reaction occurs when morphine methiodide [16] and thebaine methiodide [17] are heated with acetic anhydride, a process usually called acetolysis, and phenanthrene itself is obtained in low yield by the distillation of morphine with zinc dust [18]. These reactions and the empirical formula for codeine led to the conclusion that in the latter one NMe group and two carbon atoms were in some way attached to a partially hydrogenated phenanthrene skeleton.

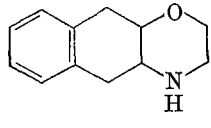
Initially various oxazine formulae for morphine were suggested, based on the theory that β-dimethylaminoethanol, frequently obtained during aromatizing degradations, was produced by the hydrolytic scission of an oxazine system, and Knorr [19] proposed the structure [I] for morphine. Numerous bases were subsequently prepared, all derived from [II], which was called 'morpholine' on account of its supposed relationship to morphine, and of these naphthalanmorpholine [III], a strong, synthetic, alkaloid-like base, was found to undergo exhaustive methylation with production of β-dimethylaminoethanol and naphthalene in the second step [20]. However, the extreme ease with which the last stage of the degradation occurred led Knorr to modify his morphine structure to [IV] [20].



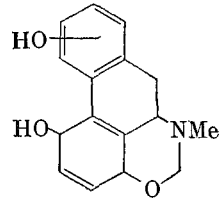
[I]



[II]



[III]



[IV]

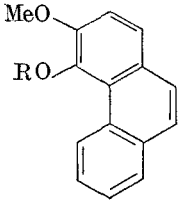
In 1900 Pschorr and Sumuleanu [21] showed by synthesis that dimethylmorphol [V, R = Me] (obtained by hydrolysis and methylation of the product [V, R = Ac] of acetolysis of α-codeimethine [16] and codeine methiodide [16]) is 3:4-dimethoxyphenanthrene, and this was followed in 1902 by the identification of methylthebaol [VI, R = R' = Me] (obtained by hydrolysis and methylation of the product [VI, R = Ac; R' = Me] of acetolysis of thebaine [22] and of the product [VI, R = R' = Ac] of acetolysis of codeinone [23]) as 3:4:6-trimethoxyphenanthrene [24]. In this way the location of oxygen substituents at positions 3:4 and 6 of the phenanthrene system in morphine was demonstrated, and Knorr's oxazine formula was modified to [VII] [23].

However, [VII] failed to explain the following facts.

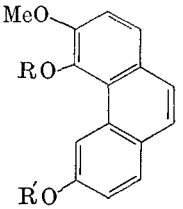
(*a*) The isomerization of α-codeimethine to β-codeimethine on heating in alkaline solution [7].

(*b*) The formation of β-dimethylaminoethyl ethyl ether during some

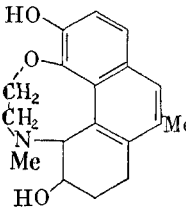
aromatizing degradations. This cannot arise from β-dimethylaminoethanol as the latter does not form ethers under the conditions of these degradations [25–26]. The postulate that the initial product is vinyldimethylamine removed the main support for the oxazine hypothesis [25].



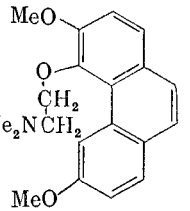
[V]



[VI]



[VII]

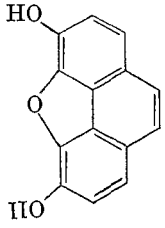


[VIII]

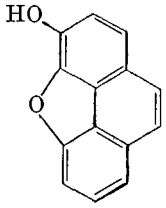
(*c*) The compound [VIII] though readily degraded by acetic anhydride to acetylthebaol [VI, R = Ac, R' = Me] is stable towards sodium ethoxide at 150° C., under which conditions thebaine is decomposed. (See Chap. XXVII.)

The last support of the oxazine hypothesis was removed when it was discovered that metathebainone, in which the function of all three oxygen atoms was known, (one OMe, one phenolic —OH, and one C = O [27]) gave dimethylmorphol [V, R = Me] and β-dimethylaminoethanol on exhaustive methylation and acetolysis, indicating that the latter can arise by scission of a carbon-carbon link [28–29].

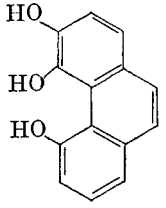
The morphine alkaloids were shown by Vongerichten and Pschorr to be derivatives of 3:6-dihydroxy-4:5-phenanthrylene oxide [IX] by the conversion of morphenol [X] (obtained as methyl ether by the exhaustive methylation of codeine [30]) on fusion with potassium hydroxide at 250° C. to [XI], identified by methylation to 3:4:5-trimethoxyphenanthrene [31] and comparison of the latter with an authentic specimen [32].



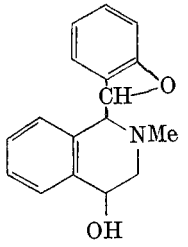
[IX]



[X]



[XI]



[XII]

Meanwhile several other formulae for morphine had been suggested, namely:

(*a*) [XII] by Vis [33] on the groundless assertion that phenanthrene is only formed during the zinc-dust distillation of morphine by a

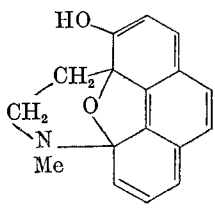
complex rearrangement of the benzyl*iso*quinoline system. This structure was dismissed by Knorr [34];

(*b*) [XIII] by Vongerichten [35], who made no suggestion as to the point of attachment of the alcoholic hydroxyl or the unsaturated portions of the phenanthrene nucleus;

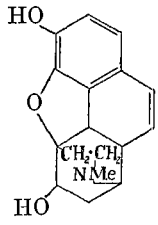
(*c*) [XIV] by Freund [36]. This explains the formation of pyrene during the zinc-dust distillation of thebaine, but cannot explain the morphine-apomorphine conversion (see below);

(*d*) [XV] for morphine and [XVI] for thebaine by Bücherer [37–39].

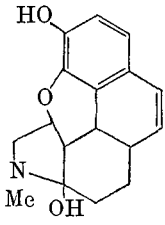
None of these formulae, however, are acceptable and all were quickly abandoned.



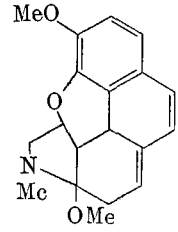
[XIII]



[XIV]

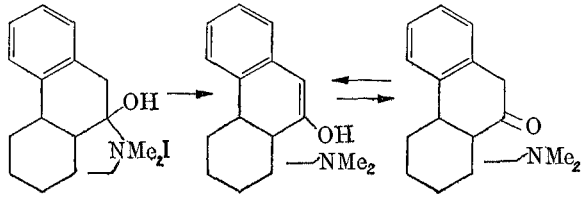


[XV]



[XVI]

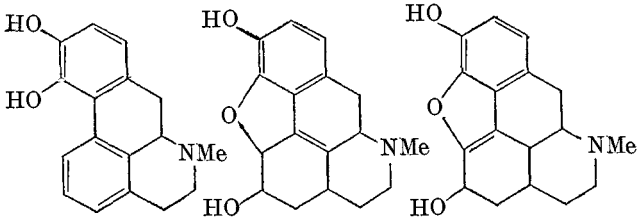
The nitrogen atom in the morphine alkaloids was proved to be attached to position 9 or 10 as follows. Oxidation of codeine with potassium dichromate and sulphuric acid affords hydroxycodeine [10], and this can be degraded to a methoxydiacetoxyphenanthrene [40–41], one acetoxy group of which is located at position 9 or 10 as it is lost during oxidation to a quinone [42]. As codeine can be similarly degraded to 3-methoxy-4-acetoxyphenanthrene, which suffers no loss of groups on oxidation, the new hydroxyl group in hydroxycodeine must be in position 9 or 10. Now hydroxycodeine methiodide can be degraded to a base in which the new oxygen function appears as a carbonyl group [40–42] so that a double bond must be introduced in the 9:10 position as a result of the degradation and therefore the nitrogen must be attached to position 9 or 10 (see [XVII] → [XVIII] → [XIX]).



[XVII] [XVIII] [XIX]

When morphine is heated at 140–150° C. with concentrated hydrochloric acid rearrangement occurs with dehydration and formation of

apomorphine [43–44], and as a result of the researches of Pschorr [45–48] this was allotted the structure [XX]. These results led Pschorr to suggest the *iso*quinoline formula [XXI] for morphine [42, 46, 49], and this was modified by Knorr to [XXII], as the methine base derived from hydroxycodeine would, on the basis of [XXI], be a derivative of β-naphthol and thus be phenolic. Moreover, [XXII] allowed an explanation of the $\alpha \rightarrow \beta$-codeimethine isomerization, by migration of the double bond from its position in [XXII] to that in [XXI].

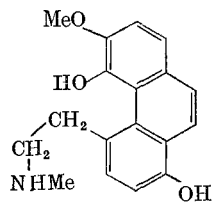


[XX] [XXI] [XXII]

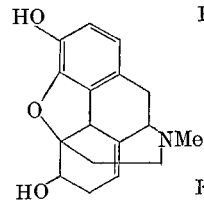
The possibility of the carbon end of the nitrogen-containing chain being attached to position 8 was, however, eliminated by a study of the isomeric codeines. Hydrolysis of the halogenocodides (see Chap. VIII) affords isocodeine [50–52], ψ-codeine [52–53], and allo-ψ-codeine [50–52], and the four codeine isomers can be paired thus: codeine: isocodeine which yield the same codeinone on oxidation [54] and must therefore differ sterically only at the secondary alcoholic group, and ψ-codeine: allo-ψ-codeine which yield the same ψ-codeinone on oxidation [26, 54] and so also only differ from each other sterically at a secondary alcoholic group. Now codeinone on acetolysis yields 3-methoxy-4:6-diacetoxyphenanthrene [23] (identified by conversion to 3:4:6-trimethoxyphenanthrene [23]), but degradation of ψ-codeinone affords 3-methoxy-4:8-diacetoxyphenanthrene [26, 55] (identified by conversion to 3:4:8-trimethoxyphenanthrene, identical with an authentic specimen [55, 48]). Therefore codeine and isocodeine must have a secondary alcoholic group at position 6, whilst ψ-codeine and allo-ψ-codeine must have such a group at C-8, and both these positions must be free from other substituents.

For many years codeinone was thought to have a methylene group at position 7 (see Chap. X), leaving only positions 5, 13, and 14 as points of possible attachment of the side-chain. 13 and 14 were not considered initially, as thebenine (formed by boiling thebaine with dilute hydrochloric acid [56]) was known as a result of the researches of Freund [57 58] and Pschorr [59] to have the structure [XXIII], with the side-chain still attached to the phenanthrene nucleus and attached at position 5, and the formula [XXIV] was proposed by Knorr and Hörlein in 1905 for morphine [55]. The α:β-codeimethine isomerization was

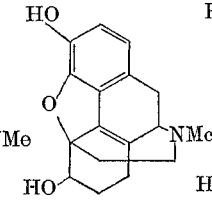
represented as involving a shift of the double bond from the 8:14 to the 13:14 position, though β-codeimethine does not behave on hydrogenation as a fully aromatic naphthalene derivative. Faltis [60] also proposed a 9:5 bridge structure for morphine [XXV] during speculations on the biogenesis of the alkaloids.



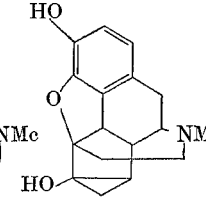
[XXIII]



[XXIV]



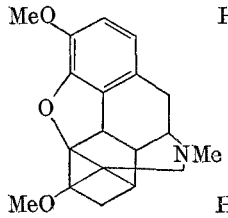
[XXV]



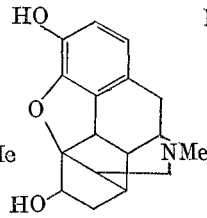
[XXVI]

The Knorr–Hörlein formula was generally accepted for several years, during which time, however, the following formulae were tentatively suggested:

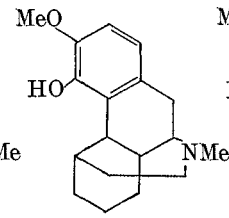
(*a*) [XXVI] for morphine by von Braun [61], on the grounds that morphine does not behave as an allylamine when treated with cyanogen bromide (no fission of the nitrogen ring) and so could not be [XXIV], nor could it have the isomeric $\Delta^{7\cdot8}$ structure as codeinone was believed to have a —CH_2— group at position 7. [XXVI] was abandoned when it was found that partial reduction of α-codeimethine affords the same base as is derived by degradation of dihydrocodeine, as it was expected that the double bond in the methine from [XXVI] would be reduced before the *cyclo*-propane ring. In addition both α- and β-codeimethines are very readily reduced to tetrahydro-derivatives [62].



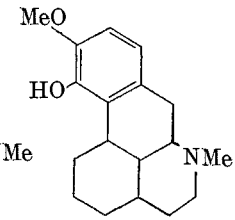
[XXVII]



[XXVIII]



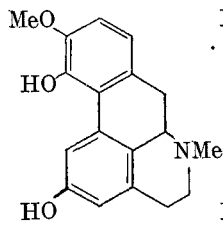
[XXIX]



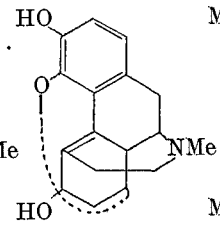
[XXX]

(*b*) [XXVII] for thebaine and [XXVIII] for morphine by Freund and Speyer [64] as a result of work on phenyldihydrothebaine (the product of interaction of phenylmagnesium bromide and thebaine [36]) which strongly resists hydrogenation. Such a 'camphane' structure was particularly suited to explaining the supposed existence of two isomeric tetrahydrodesoxycodeines ([XXIX] and [XXX]) [63], the conversion of morphine to apomorphine [XX], the conversion of thebaine to morphothebaine [XXXI] by hot concentrated hydrochloric acid [65] and to

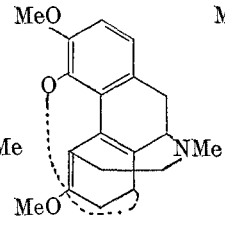
thebenine [XXIII] by hot dilute hydrochloric acid [56]; but against such a formula may be cited the ready hydrogenation of thebaine [66–68] and codeine [69–70], the hydrolysis of dihydrothebaine to dihydrocodeinone [66], and the production of thebaizone, which is the methyl ester of an aldehydic acid, on ozonolysis of thebaine [71–72].



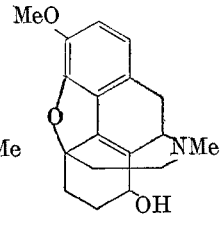
[XXXI]



[XXXII]



[XXXIII]



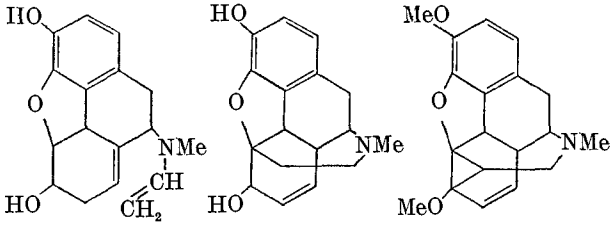
[XXXIV]

(*c*) [XXXII] for morphine and [XXXIII] for thebaine by Faltis [73–74] in an attempt to account for the appearance of a hydroxyl group at position 8 during the hydrolysis of the chlorocodides. The 4:8-oxygen bridge was regarded as being strained in codeine and more so in thebaine. The hydrolysis of α-chlorocodide was assumed to occur with opening of the 4:8-bridge, movement of the double bond and closure of a 4:5 bridge to give [XXXIV] as ψ-codeine. The conversion of ψ-codeine to α-chlorocodide, however, would involve the re-establishment of the highly strained 4:8 oxygen bridge. The Faltis structures were never generally seriously considered.

(*d*) A modified form of [XIV] with the double bond in the 13:14 position suggested without adequate reasons [76] by Gadamer. It can be dismissed on the same grounds as can [XIV].

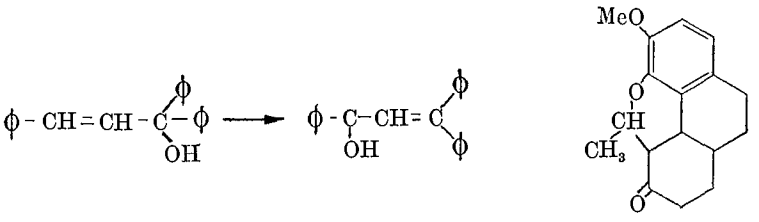
(*e*) [XXXV] suggested for morphine by Wieland and Kappelmeier [77], without direct evidence, in an attempt to account for the ready loss of the side-chain during degradation, the formation of ammonia during gentle oxidation of morphine, and the tenacity with which morphine retains one molecule of water, which they believed was attached to the vinyl group. The formation of methine bases by degradation and of apomorphine and thebenine was assumed to be due to addition of the reactive vinyl group to the phenanthrene nucleus. [XXXV] was abandoned when it was found that neither anhydrous morphine nor its diacetyl-derivative (heroin) could be made to add more than two atoms of hydrogen.

The Knorr–Hörlein formula for morphine has an unsatisfactory placing of the unsaturated linkage and was modified to [XXXVI] by Wieland [70, 78] as the latter gives a better interpretation of the α → β-codeimethine isomerization and also brought the codeine → ψ codeine transformation into line with the conversion of styryldi-



[XXXV] [XXXVI] [XXXVII]

phenylcarbinol [XXXVIII] to [XXXIX] and the rearrangement of dibenzalacetone ketochloride [79–80]. A C-5 linkage of the ethanamine chain was adhered to as thebenone (given the structure [XL]) only condenses with one mole of benzaldehyde or piperonal. Thebaine was given a bridge structure on the curious assertion that it is not an enol ether [81]. However, both thebaine and dihydrothebaine can be hydrolysed as enol ethers, and moreover such a bridge structure, as already stated, cannot give an adequate explanation of the results of ozonolysis.

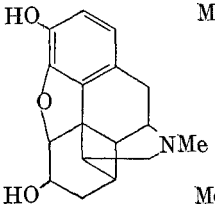


[XXXVIII] [XXXIX] [XL]

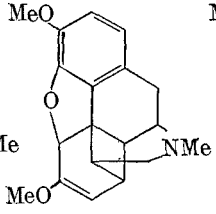
In 1923 Gulland and Robinson [82] made a new survey of the evidence for the constitution of the morphine alkaloids and came to the following conclusions. The most striking and unique property of the morphine alkaloids is their tendency to lose the whole of the ethanamine side-chain during degradation, giving phenanthrene derivatives; it is obvious that this property is due to some peculiarity of the molecule and any adequate formula must be capable of explaining it. 'The driving force behind the change is doubtless the tendency to produce an aromatic nucleus, because extrusion of the side-chain is never observed independently of the formation of an aromatic phenanthrene system. *The formation of the aromatic phenanthrene derivative cannot take place for structural reasons unless the ethanamine side-chain is displaced in favour of a hydrogen atom or a hydroxyl group.*'

On these grounds they proposed attachment of the carbon end of the side-chain at an angular position so that its extrusion is a necessary part of aromatization, and of the two available positions, 13 and 14, the former was selected. These suggestions were embodied in the

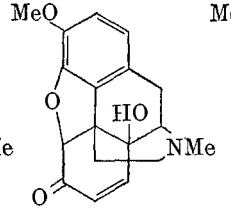
modified camphane formulae [XLI] and [XLII] for morphine and thebaine respectively, as codeine was believed not to contain a double bond.



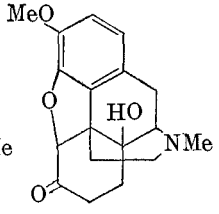
[XLI]



[XLII]

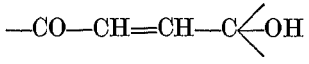


[XLIII]

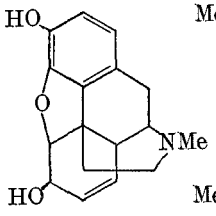


[XLIV]

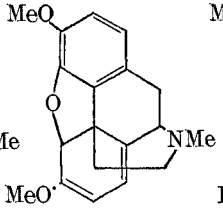
However, subsequent work by the same investigators [83] on hydroxycodeinone [XLIII] indicated that this compound does not contain the system —CO—CH_2— but that dihydrohydroxycodeinone [XLIV] does, facts best explained by postulating the presence of the system



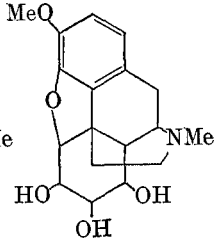
in the former, and if this is so it follows from the proposed mechanism for the production of hydroxycodeinone that thebaine has the system MeO—C=CH—CH=C< (see Chap. XVIII). Accordingly the formulae for morphine and thebaine were modified to [XLV] and [XLVI] respectively, and these structures are now universally accepted. Confirmation of the presence of a double bond in codeine was obtained by the oxidation of the base by 1 per cent. potassium permanganate solution to dihydroxydihydrocodeine [XLVII] [84].



[XLV]

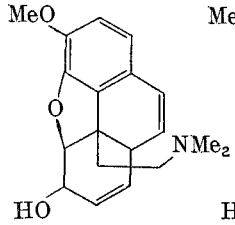


[XLVI]

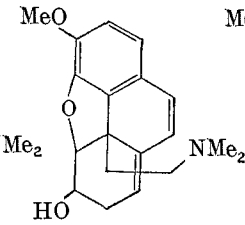


[XLVII]

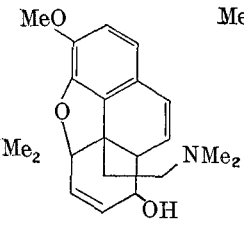
The Gulland and Robinson formulae give satisfactory explanations of all the properties of the morphine alkaloids. The $\alpha \rightarrow \beta$-codeimethine change is represented as a shift of the double bond from the 7:8 to the 8:14 position ([XLVIII] → [XLIX]), whilst in ϵ-codeimethine [L], derived from ψ-codeine [LI] the possibility of an increase in double-bond conjugation does not exist and no isomerization occurs. The transformation of codeine through the halogenocodides to iso-, ψ-, and allo-ψ-codeine is seen to be analogous to the conversion of geraniol [LII] to linalool [LIII] (see Chap. VIII).



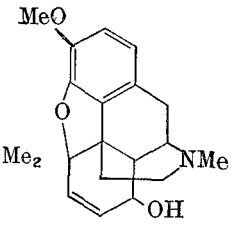
[XLVIII]



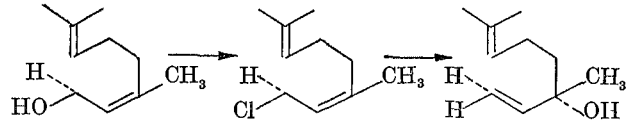
[XLIX]



[L]

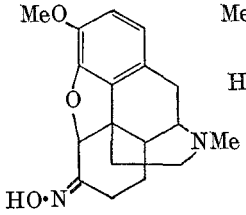


[LI]

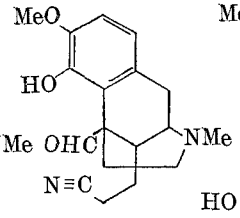


[LII] [LIII]

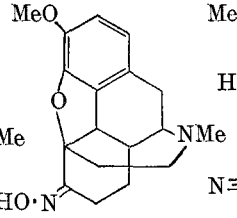
Schöpf sought to obtain direct evidence for the location of the side-chain at C-13 by subjecting dihydrocodeinone oxime to a Beckmann transformation, when, if the side-chain is located at C-13 [LIV], an aldehyde [LV] would be the product, whereas if the point of attachment is C-14 [LVI] a ketone [LVII] would be formed. Neither the oxime nor its methyl ether yielded the desired proof directly, and it was only after a sequence of further degradations that the conclusion was drawn that the product was [LV], indicating C-13 as the point of attachment of the side-chain [85] (see Chap. X).



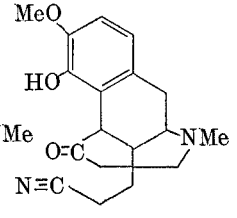
[LIV]



[LV]



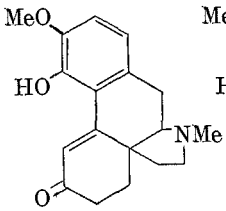
[LVI]



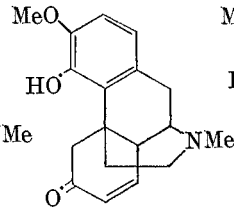
[LVII]

Further work by Schöpf and Borkowsky [86] indicated the need for modification of the structure with attachment of the side-chain at C-14 in metathebainone [LVIII], which is formed by the reduction of thebaine with stannous chloride in concentrated hydrochloric acid [27]. The true thebainone [LIX] was later isolated from the stannous chloride reduction under different conditions. Metathebainone arises as a result of rearrangement of thebaine in concentrated hydrochloric acid, now believed to involve the intermediate [LX], which is also believed to be common to the morphothebaine and thebenine transformations [88–89]. (See Chap. XXV.)

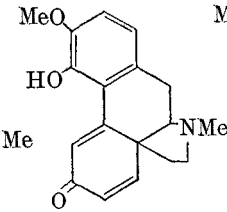
Evidence for the conjugated double-bond system in thebaine is provided by the ready condensation of the alkaloid with maleic anhydride and benzoquinone [90–91].



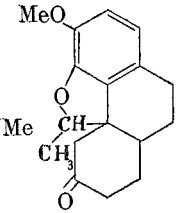
[LVIII]



[LIX]

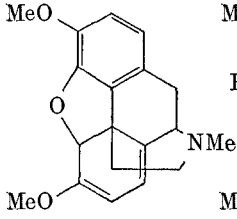


[LX]

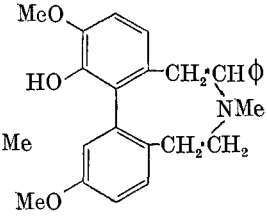


[LXI]

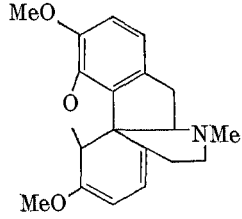
The only evidence against the Gulland and Robinson formulae is negative, namely the failure of thebenone [LXI] to condense twice with aromatic aldehydes and this is of no value as other cases are known where only one of two methylene groups adjacent to carbonyl is capable of condensing with aldehydes [85]. However, the validity of the formulae was recently challenged by Small [92], who claimed that they were incapable of explaining the production from thebaine and Grignard reagents of substances that strongly resist hydrogenation and have other peculiarities. This challenge has been effectively met by Bentley and Robinson [88–89, 93], who have shown that phenyldihydrothebaine arises from thebaine by a complex rearrangement of a new type (see Chap. XX) and has the structure [LXII], which adequately explains all its properties.



[XLVI]



[LXII]

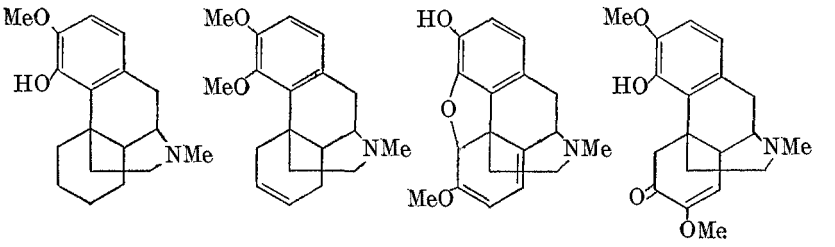


[LXIII]

One alternative formula can be envisaged and this can best be explained by reference to the intermediate [LX] postulated in the complex rearrangements that thebaine undergoes in acid solution. [LX] arises from [XLVI] by migration of the side-chain from 13 to 14 and hydrolysis; it could equally well arise from [LXIII]. The only way of distinguishing between [XLVI] and [LXIII] appears to be by a study of the ultra-violet absorption spectra of α- and β-codeimethines, which strongly support [XLVI], the spectrum of β-codeimethine clearly showing the conjugation of two double bonds with the aromatic nucleus [88–89]. These results

definitely indicate the structure [XLVI] for thebaine, but nevertheless something like [LXIII] might be involved as an intermediate in the biosynthesis of the alkaloid (see Chap. XXVIII).

Final proof of the Gulland and Robinson formulae for the morphine alkaloids has been obtained by the synthesis of racemic tetrahydrodesoxycodeine [LXIV] by Grewe, Mondon, and Nolte [94] and of *dl*-dihydrodesoxycodeine-B methyl ether [LXV] by Gates and Tschudi [95]. The former, whilst fixing the point of attachment of the nitrogen end of the side-chain, did not eliminate the possibility of a spirane structure such as [LXIII], but the latter definitely established the location of the carbon end of the side-chain at C-13. (See Chap. XXVIII.)



[LXIV] [LXV] [LXVI] [LXVII]

Recently the alkaloid oripavine has been shown to have the structure [LXVI] and bears the same relationship to morphine as thebaine does to codeine. On methylation with diazomethane it yields thebaine [96].

Sinomenine, discovered by Ishiwari in *Sinomenium diversifolius* [97], has been shown by the researches of Kondo [98] and particularly of Goto and his co-workers [99–100] to have the structure [LXVII] and to be the optical antipode of 7-methoxythebainone. It is readily converted into antipodes of substances obtainable from thebaine and codeine (see Chap. XXVI). Hasubanonine, an alkaloid isolated from *Stephania japonica*, is believed to be of the morphine type [101] (see Chap. XXVI).

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II

MORPHINE AND ITS ISOMERS

MORPHINE

MORPHINE was the first vegetable base to be isolated and recognized as such, the isolation from opium being first described by Sertürner in 1805 [1] and later years [2–7] (Sertürner's papers relating to morphine have since been reprinted [8]), though as pointed out by Pelletier [9] Séguin described the preparation of the base in 1804 in a report to the Academy of Sciences that was not published until 1814 [10]. The alkaloid was also isolated by Robiquet in 1817 [11–12]. In 1803 Derosne, by extracting opium with water and precipitating the extract with potassium carbonate, obtained an apparently basic crystalline substance that he called 'salt of opium'; this was thought by Sertürner [4] to be morphine acid meconate and by Pelletier [9] and Robiquet [13–14] to be narcotine.

OCCURRENCE

Morphine occurs principally in opium, which is the dried juice of unripe seed capsules of *Papaver somniferum*, the average content of a good grade of opium being about 10 per cent. [15], though it varies between wide limits [16]. A morphine content of 21·8 per cent. in the sap of *Papaver somniferum* two hours after cutting has been reported, but this falls to 12 per cent. in one day as a result of atmospheric oxidation [17]. The poppy seeds themselves have been reported to be alkaloid-free [18–23], but patents have been granted covering the extraction of morphine and codeine from poppy seeds [24–25] and earlier workers also claimed to have isolated morphine from this source [26–28]. Morphine is stated to appear in the plant thirty-six days after sprouting of the seed [18].

In addition to *Papaver somniferum* morphine occurs in the blue poppy [*Fructus papaveris*] [29] and has been stated to occur in *Papaver orientale* [30], but this has never been substantiated [31–33]; in *Argemone mexicana* [*Papaver spinosum*] [34] (unconfirmed [35–37]); in *Papaver rhoeas* [38–39] (other workers have found only rhoeadine in this plant [40–44]), and in *Escholtzia californica* [45] (unsubstantiated [46–48]). Ladenberg [49] said that morphine occurs in American hops and Williamson [50] isolated from these a base 'hopeine' that he said closely resembled but was not identical with morphine, together with 'isomorphine', the identity of which with morphine was not eliminated. Chapman [51] found no trace of morphine in cultivated hops.

Extraction

Methods of extracting morphine are given by references [1–7, 11–12, 24–25, and 52–72 inc.]. For many years the alkaloid was isolated by the 'Gregory process' [59] in which the concentrated opium extract is treated with a concentrated solution of calcium chloride, when calcium meconate, lactate, and sulphate are precipitated and removed by filtration. Concentration of the filtrate yields the 'Gregory salt'—a mixture of codeine and morphine hydrochlorides which is purified, dissolved in water, and the morphine precipitated by ammonia. More modern methods are now available, and these are summarized by Kanewskaja [70] and by Barbier [71]. Morphine can be separated from codeine chromatographically [73–75]. The extraction of morphine and codeine in toxicological analysis is given by Wilson and Rising [76].

Physical Properties

Morphine is obtained as monohydrate as small rhombic prisms [77] often resembling needles [78] on crystallization from aqueous methanol and as anhydrous prisms from anisole [79–80]. Methyl [81–82] and amyl alcohol [83] have been recommended as solvents for recrystallization. The base is sparingly soluble in most organic solvents but readily soluble in benzyl alcohol [84]; solubility measurements are given in references [84–99 inc.] and a table of solubilities by Small and Lutz [100]. The state of aggregation markedly affects the solubility [92]. Morphine, being a phenol, is soluble in alkali hydroxide solutions [101] but only sparingly soluble in alkaline earth hydroxides [102–4]. It can be purified by sublimation [105–12] and as a result of sublimation the alkaloid is present in the smoke from burning opium [113].

The monohydrate [114] loses water at 100° C. [115–16] and the anhydrous base has m.p. 247–248° C. (253–254° C. corrected) [117]. For crystal measurements see [81, 118–22], specific gravity [123], and refractive index [81, 124–7].

The specific rotation of morphine has been given as −130·9° (23° C. in methanol) [82], −131·7° (methanol) [81], and −70·2° for an aqueous solution of the sodium salt at 22·5° C. [128]. Tykociner [129] has determined the rotations of a number of salts all of which give values around −128°.

Titration

Morphine is a strong base, the salts of which are neutral to litmus and methyl orange. The base turns red litmus blue but does not affect phenolphthalein in aqueous solution, though a rose colour is obtained when water is added to an alcoholic solution of phenolphthalein and morphine [130]. The base can be titrated with acids potentiometrically

[131–3] or with methyl red as indicator [134–6]. Other titration methods have been used [137–47 inc.]. The heats of neutralization of morphine with acids and alkalis have been determined by Leroy [130].

Colour Tests

The following colour tests have been recorded for morphine:

Reagent	*Colour*	*References*
conc. H_2SO_4 + 40% H·CHO	violet-red → blue	148–51
conc. H_2SO_4 + $KClO_4$	brown	152–4
conc. H_2SO_4 + $KClO_3$	grass green (rose at edges)	155
conc. H_2SO_4 + conc. HCl 100–120° C.	purple	156
conc. H_2SO_4 + molybdic acid	violet → blue → green → colourless	157
conc. H_2SO_4 + ammonium molybdate	lilac → green on heating	158
conc. H_2SO_4 + ammonium molybdate + KNO_3	red → yellow	158
conc. H_2SO_4 + benzidine	yellow → brown → dark green	159
conc. H_2SO_4 + benzidine, then dilute	violet (extracted by $CHCl_3$)	159
conc. H_2SO_4 + $KReO_4$	grey → violet	160
conc. H_2SO_4 + *p*-dimethylaminobenzaldehyde	blood red	161
conc. H_2SO_4 + $SnCl_2$	red	162
conc. H_2SO_4 + potassium arsenate	blue-violet → brown $\xrightarrow{\text{dilute}}$ green	155, 163
conc. H_2SO_4 + sodium arsenate	blue → violet or green	164
conc. H_2SO_4 + KBr, 100° C.	yellow → brown $\xrightarrow{\text{dilute}}$ emerald	165
conc. H_2SO_4 + ammonium sulphouranate	dirty green	166
conc. H_2SO_4 + 0·1% sodium tungstate	blue-violet (fades rapidly)	167
conc. H_2SO_4 + glyoxylic acid	intense violet	168
conc. H_2SO_4 + mannitol oxidized by Br_2/H_2O	yellow-red → rose → wine → ruby	169
conc. H_2SO_4 + formaldoxime	intense blue-violet	170
conc. H_2SO_4 + Na_3PO_4	violet $\xrightarrow{\text{dilute}}$ red, from which $CHCl_3$ extracts blue	171–2
conc. H_2SO_4 added to base + sugar	blue-green → yellow; sensitivity < by 1 drop Br/H_2O	173–5
conc. H_2SO_4 7 min. at 40° C.; dilute; add conc. ammonia	brown, purple fluorescence develops slowly	176
0·1% ammonium metavanadate + enough conc. H_2SO_4 to destroy yellow	green $\xrightarrow{\text{dilute}}$ blue-green	167
3% H_2O_2 poured carefully over a soln. of base in conc. H_2SO_4	yellow-brown to emerald ring	177
furfurol + base + EtOH layered on to conc. H_2SO_4	violet-yellow ring	178
NaOCl or HNO_3 + warm soln. base in H_2SO_4	carmine red	179–81
conc. HNO_3	orange-red (destroyed by $Na_2S_2O_3$)	182
evap. EtOH + vanillin or piperonal + 0·5 N·H_2SO_4	red-violet	183
conc. HCl + vanillin, 40–50° C.	violet-red	184
conc. HCl + *p*-dimethylaminobenzaldehyde	emerald green	168
$HClO_4$, heat	violet → brown	185

Reagent	*Colour*	*References*
base + basic magnesium hypochlorite in HOAc layered on to conc. H_2SO_4	yellow-brown ring; 3 hrs. purple; 24 hrs. yellow over red	186
$NaNO_3$ + acid then alkali	1st yellow, then orange 1st red, then brown	187 188
warm + dil. H_2SO_4 + $FeSO_4$; add to conc. NH_4OH	blue	189
shake + PbO_2 in dil. H_2SO_4	pink; add NH_3 → brown	190
ferric chloride	blue; $\xrightarrow{\text{warm or add acid}}$ colourless	54
ferric chloride + $K_3Fe(CN)_6$	Berlin blue (sensitive 1 : 10^5)	191–3
diazobenzenesulphonic acid + alkali	intense red	194
dilute uranyl nitrate	red	195–6
boil + Br/H_2O; neutralize + $CaCO_3$; boil	bright red	197
chlorine water	green-yellow $\xrightarrow{NH_3}$ brownish	198–9
excess H·CHO, 1 drop $SnCl_2$, evaporate	blue-violet	200
H_2O_2 + NH_4OH, stir + copper wire	wine colour; gas evolved	201–2
boil + $CuSO_4$ soln.	green	182, 203–5
$CuSO_4$ + trace KCN	yellow-green	206
HIO_3	iodine liberated	207–11
HIO_3 + $(NH_4)_2CO_3$	yellow-gold	210–11
HIO_3 + $(NH_4)_2CO_3$ + 1/1000 $FeCl_3$	intense red-violet	210–11
HIO_3 + $(NH_4)_2CO_3$ + 1/1000 $FeCl_3$ + oxalacetic acid	blue	210–11
HIO_3 + $(NH_4)_2CO_3$ + 1/1000 $FeCl_3$ + HOAc	emerald green over red-violet	210–11
HIO_3 + $(NH_4)_2CO_3$ + 1/1000 $FeCl_3$ + HOAc + oxalacetic acid	yellowish $\xrightarrow{NH_3}$ black	210–11
silver nitrate soln. (warm)	silver precipitated	212
salts + ammonium iodoxybenzoate	straw to garnet	213
K_2ClO_4 or $K_2Cr_2O_7$	brown ppt., base + chromate	214
iodine chloride	iodine pptd. in cold	215
$CuSO_4$ + sodium vanadate in dil. HOAc	ppt. in solns. > 0·1%	216

Precipitation reactions for the detection of morphine have been recorded [215–38 inc.]. In the Straub biological test as little as 0·01 mg. of the alkaloid injected subcutaneously on the back of a white mouse causes the animal to lay its tail over its back [239]. Other methods for the detection of morphine [240–4] and of its diacetyl ester (heroin) [228–30, 233–4, 242, 245–6] are known.

Estimation

Numerous methods have been used for the estimation of morphine, and of these may be cited:

(*a*) The isolation of the base itself [247–8].

(*b*) Quantitative precipitation as an insoluble derivative [249–51].

(*c*) The reduction of potassium ferricyanide or iodic acid [252].

(*d*) Colorimetric methods [251–68 inc.].

(*e*) Other methods [269–301 inc.].

(*f*) Methods of estimation of the alkaloid in opium [302–31 inc.].

Reviews of the methods of estimation are available [310–11, 313, 320–21, 332–3, 202].

Empirical Formula

A number of salts of morphine were prepared and analysed by Choulant [334–5] and the compositions $C_{34}H_{36}O_6N_2$ [336–7] and $C_{35}H_{40}O_6N_2$ [338–41] were first suggested for the base, and it was not until 1847 that Laurent [342] gave the composition $C_{34}H_{38}O_6N_2$ corresponding to the now-accepted $C_{17}H_{19}O_3N$. From cryoscopic results Raoult [343] advocated a C_{34} formula, but later investigations have confirmed the formula $C_{17}H_{19}O_3N$ [344–6].

Morphine [I, R = H] is a tertiary base, readily forming quaternary salts [347–53], and contains one NMe group [354]. It is also a phenol, being soluble in alkalis [101], readily coupling in alkaline solution with diazocompounds to give azo-dyes [187, 194, 355–7], giving a blue colour with ferric chloride [54] and forming ethers.

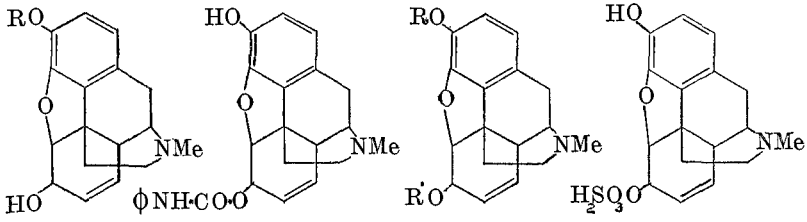
Ethers of Morphine

Morphine methyl ether is codeine (see Chap. IV) and is readily obtained by methylation of morphine under a variety of conditions [358–84 inc.]. Other ethers of morphine are known of the type [I] where R = alkyl [358–60, 364, 367–9, 371, 378, 381, 385–93], hydroxyalkyl [360, 394], chloro- and bromoalkyl [395], methoxymethyl [396–9], benzyl [379, 387, 400–1], aryl [402], quinolyl [403], allyl [360, 395, 404], $CH_2 \cdot COOH$ [405], and —COOR′ (really an ester of carbonic acid) [387, 406–9], and also the bimolecular ethylene-dimorphine formed by the interaction of ethylene dibromide and the sodium salt of morphine [360, 386–7]. The alkylation of morphine in alkalis proceeds best in the presence of reducing agents, such as alkyl oxalates, which minimize losses due to oxidation [410]. The benzyl [411] and methoxymethyl [399] ethers are converted back to morphine by hot acids. Colour tests for benzylmorphine are given by Schneegans [400–1]. Metal derivatives of morphine can be obtained with sodium, potassium, and calcium [412–16].

Esters

Morphine also functions as an alcohol, forming a urethane [II] [417] and other esters. The diacetyl ester [III, R = R′ = Ac] (heroin) is obtained by the action of acetic anhydride [349, 418–19], acetylchloride [387, 420], and ketene [421] on morphine. 3-Acetylmorphine [III, R′ = H; R = Ac] results from the partial hydrolysis of heroin [420, 422–4] and from the esterification of morphine with acetic acid [418]. Like heroin it can be hydrolysed to morphine by acids [418] and enzymes [426]. 6-Acetylmorphine [III, R′ = Ac; R = H] is not produced during the hydrolysis of heroin [422–4] but is obtainable by the restricted action of acetic anhydride on morphine [418]. Other esters including [IV] [427] and mixed esters are known [387, 420, 427–36 inc.].

A triacetylmorphine was reported by Causse to result from the action of zinc-dust and acetic anhydride on morphine [437–40] when a C=O group was supposed to be reduced to CH·OH and the latter esterified. This work has been disproved by Knorr [441]. The tribenzoylmorphine of Polstorff [442] likewise does not exist [420, 429].



HETEROETHERS

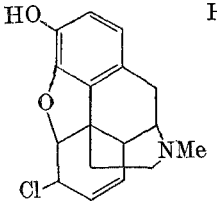
The alcoholic hydroxyl of morphine may also be alkylated. Methylation of the base in cold alkali gives quaternary salts of dimethylmorphine [III, R = R′ = Me] [443–4]. Dimethylmorphine can be obtained by dry-distillation of its methochloride [399], methylation of morphine-N-oxide followed by reduction with sulphurous acid [399], and by methylation of codeine benzyl-chloride and sodium amalgam reduction of the product [445]. Morphine-6-methyl ether (heterocodeine) [III, R = H; R′ = Me] methiodide results from methylating morphine-3-methoxymethyl ether [III, R = $CH_2 \cdot O \cdot CH_3$; R′ = H] and heating the product with acid [399]. The methochloride on dry-distillation does not yield heterocodeine, which can be obtained, however, by methylating and reducing the N-oxide of [III, R = $CH_2 \cdot OCH_3$; R′ = H] [399]. Heterocodeine gives dimethylmorphine with diazomethane [399]. Other heteroethers of morphine may be prepared in the same way [446–8].

3-Glycosides of morphine have been prepared [449–51].

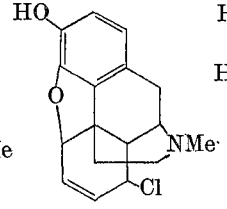
THE HALOGENOMORPHIDES

Replacement of the alcoholic hydroxyl group by chlorine occurs when morphine is treated with phosphorus trichloride [82] or thionyl chloride [187, 452], the product being α-chloromorphide [V], which yields α-chlorocodide on methylation [453–4]. An α:γ-shift of the halogen occurs when α-chloromorphide is heated with concentrated hydrochloric acid [455] and when morphine is treated in the same way [455], β-chloromorphide [VI] being formed. This and a trichloromorphide are by-products in the interaction of morphine and thionyl chloride [456]. The prolonged action of hydrochloric acid on morphine yields dichlorodihydrodesoxymorphine [VII], and this readily loses hydrogen chloride

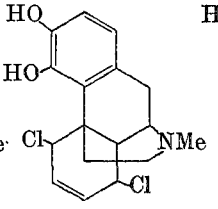
to give β-chloromorphide [456–7]; it and β-chloromorphide are intermediates in the conversion of morphine to apomorphine [456, 458] (see Chaps. VIII and XXII). Catalytic reduction of [VII] affords desoxymorphine-C [VIII] and dihydrodesoxymorphine-D [IX] [459–62] (see Chaps. VIII and IX).



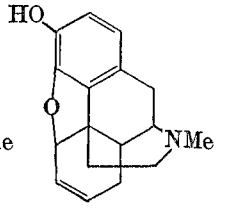
[V]



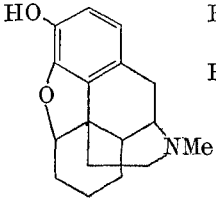
[VI]



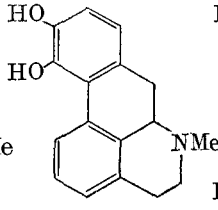
[VII]



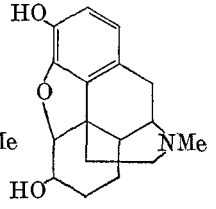
[VIII]



[IX]



[X]



[XI]

Bromomorphide, believed to be analogous to [VI], is formed by the action of phosphorus tribromide on morphine [82]. A mixture of α-, β-, and γ-isomorphines, but no morphine, is obtained by the hydrolysis of the halogenomorphides [454–53, 463–4, 82]. The conversion of morphine through the chloride to isomers of morphine resembles the geraniol-linaloöl conversion [465, 466]. The halogenomorphides are discussed in detail in Chapter VIII.

APOMORPHINE

Extensive rearrangement and dehydration occurs when morphine is heated with concentrated hydrochloric acid at 140–150° C. and apomorphine [X] is produced [467–8]. The same substance is formed when the alkaloid is heated with phosphoric acid [469–71] and zinc chloride [472–4]. This reaction and the properties of apomorphine are fully considered in Chapter XXII. From the interaction of morphine and codeine and hydrochloric acid or zinc chloride Wright reported the production of a desoxymorphine [475–6] and ill-defined amorphous substances claimed to be polymers of morphine, codeine, and apomorphine [475–88 inc.]; these substances are doubtless complex mixtures. The 'sulphomorphide' obtained by the action of sulphuric acid on morphine at 150–160° C. [489–90] (believed by Matthiessen and Wright [487–8] to be apomorphine) like the substance obtained by the action of

concentrated sulphuric acid on morphine at 40° C. [491–2] is probably apomorphine sulphonic acid [493].

Reduction

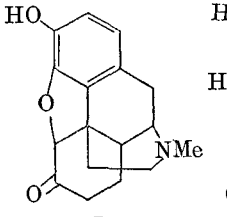
Catalytic hydrogenation [494–9] and electrolytic reduction [500] of morphine affords dihydromorphine [XI], which can also be obtained by the demethylation of dihydrocodeine; the optical antipode can be prepared in the sinomenine series from (+)-dihydrocodeine [502–3] (see Chap. XXVI]. Dihydromorphine can be esterified [504], converted into ethers [371, 504], heteroethers [446–8], and di-ethers [505]. Dihydromorphine dimethyl ether is identical with tetrahydrothebaine [505–7]; it can be demethylated to dihydromorphine [506–7].

Oxidation

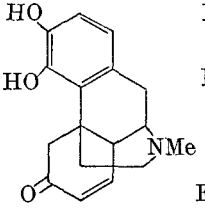
Morphine is very readily oxidized, reducing gold [18] and silver [18, 212] salts to the metal; the platinichloride decomposes in hot water, presumably with oxidation of the alkaloid [508]. Mild oxidation of morphine with a variety of reagents such as alkaline potassium ferricyanide [509–13], nitrous acid [514–17], and atmospheric oxygen in ammonia [518] causes linking of two molecules (in the 1:1′ or 2:2′ positions?) to give pseudomorphine (see Chap. III). More vigorous oxidation, with alkaline permanganate, gives only syrupy products [519]. Oppenauer oxidation of dihydromorphine affords dihydromorphinone [XII] in 71 per cent. yield [520]. An amine oxide is formed by hydrogen peroxide oxidation of the base (see below).

Catalytic Rearrangement

Dihydromorphinone [XII] is also obtainable directly from morphine by rearrangement on heating solutions of the alkaloid in alcohol with [521–5] or without [526] acid, with [521–3] or without [524–6] hydrogen, in the presence of noble metal catalysts.



[XII]



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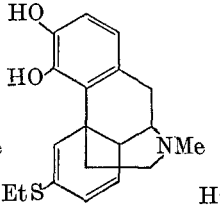

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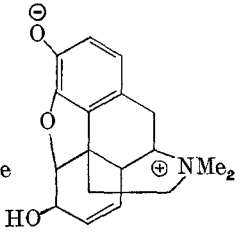


[XV]

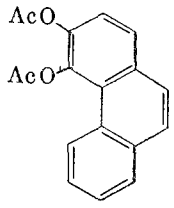
Modification of the conditions of this rearrangement affords up to 60 per cent. of the isomeric O-desmethylthebainone [XIII] [527], previously obtained by the hydrolysis of β-ethylthiomorphide [XIV] [528–9].

HOFMANN DEGRADATION

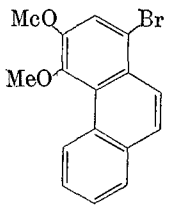
Alkaline degradation of morphine methiodide cannot be achieved owing to formation of a phenol betaine [XV] [349, 530]. However, degradation can be effected by heating the methiodide with acetic anhydride and sodium acetate when the whole of the basic side-chain is lost and diacetylmorphol [XVI] is formed [531] (see Chap. XXVII).

SUBSTITUTION IN THE AROMATIC NUCLEUS

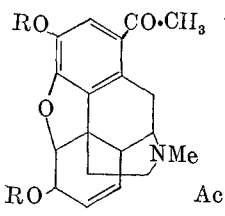
(*a*) The action of chlorine and iodine on morphine was studied inconclusively by Pelletier [532]. Bromination in concentrated hydrobromic acid yields α-tetrabromomorphine, from which only part of the bromine is removed by sodium ethoxide and silver oxide, leaving yellow needles of a substance having the properties of a quinone. α-Tetrabromomorphine is blackened when boiled with alkali and the residue on ether extraction yields phenol. Bromination of morphine in chloroform, ether, or water gives, after subsequent digestion with sodium thiosulphate, β-tetrabromomorphine, from which all the bromine is removed by silver oxide; it is completely destroyed by boiling with alkali. A tribromomorphine is obtainable from the mother liquors of the preparation of the α-tetrabromo compound [533]. Bromination with hydrobromic acid and hydrogen peroxide yields α-tetrabromomorphine or 1-bromomorphine according to the conditions, whilst heroin under these conditions [534] and with bromine water [420, 535] yields 1-bromo-3:6-diacetylmorphine which can be hydrolysed to 1-bromomorphine [535]. The location of the bromine in the latter was demonstrated by methylation to 1-bromocodeine [535] and degradation of this to 1-bromo-3:4-dimethoxyphenanthrene [XVII], found to be identical with an authentic specimen [536]. In this way the earlier belief that morphine generally suffered substitution at position 2 was disproved. 1-Bromomorphine cannot be oxidized to a pseudomorphine derivative, suggesting that the latter may be 1:1′-dimorphine [535].



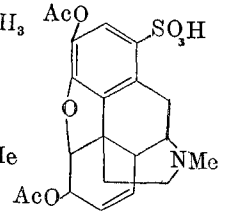
[XVI]



[XVII]



[XVIII]



[XIX]

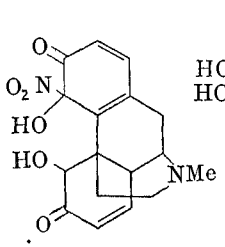
(*b*) An acetyl group is introduced in position 1 of the nucleus when morphine and 3:6-dibenzoylmorphine are heated with acetic anhydride and concentrated sulphuric acid at 85° C., giving 3:6-diacetyl- and

3:6-dibenzoyl-1-acetomorphine [XVIII, R = Ac] and [XVIII, R = ϕ·CO] respectively [441, 537–8]. Hydrolysis of these affords 1-acetomorphine [538].

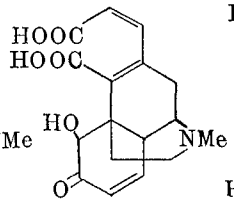
(*c*) Diacetylmorphine sulphonic acid [XIX] results when morphine is stood in acetic anhydride and concentrated sulphuric acid at 25° C. Acyl, alkyl, and alkyl-acyl derivatives of morphine give sulphonic acids under the same conditions [539]. (See also below under morphine-N-oxide.)

(*d*) 1-Nitrodiacetylmorphine is formed by the nitration of heroin [420].

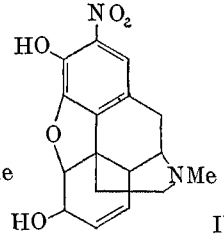
(*e*) A nitromorphine is formed together with an unstable base $C_{17}H_{18}O_6N_2$ for which the structure [XX] is suggested, when nitrous fumes are passed into aqueous solutions of morphine salts. Morphine quinnitrole [XX] is regarded as produced by addition of nitric acid to one ring, hydrolytic scission of the ether link, and oxidation of the alcoholic group. When warmed in aqueous solution it is converted in 30 per cent. yield to morphinic acid [XXI], formed by oxidation of the quinone from which [XX] is derived [187].



[XX]



[XXI]



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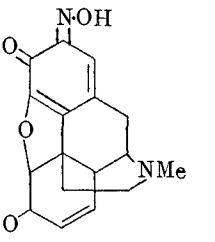


[XXIII]

(*f*) A compound believed by Wieland and Kappelmeier to be 2-nitrosomorphine was obtained by the action of nitrous fumes on morphine hydrochloride at −2° to −3° C. [187]. However, the compound does not reduce Fehling's solution or silver nitrate [187], gives no Liebermann nitroso reaction [540], and the analyses fit better for a nitromorphine than a nitrosomorphine [540]. It is undoubtedly 2-nitromorphine [XXII], as on methylation it affords 2-nitrocodeine, different from 1-nitrocodeine, and 2-nitrocodeine on reduction gives 2-aminocodeine, convertible through the diazonium salt to 2-bromocodeine, and both the latter are different from the 1-substituted codeines [541]. 2-Aminomorphine results from tin-hydrochloric acid reduction of 2-nitromorphine [187] and 2-aminodihydromorphine from catalytic reduction [540]. 2-Aminomorphine can be diazotized, but only morphine is formed on heating solutions of the diazonium salt [187]. 2-Nitromorphine could be formed from morphine via a quinone monoxime with

an ortho-quinone skeleton [XXIII], which could be oxidized to the nitrophenol [XXII] [541].

(*g*) A 2-nitrosomorphine was reported by Mayer [472] to be formed by the reaction of morphine with nitric and arsenic acids.

MORPHINE-N-OXIDE

Morphine, codeine, and ethyl-morphine all yield amine oxides on heating with 30 per cent. hydrogen peroxide; these are stable to acidified potassium iodide, but are reduced to the parent base by sulphurous acid [542]. Morphine-N-oxide is bimolecular [543]. With acetic anhydride and concentrated sulphuric acid it is converted into a sulphonic acid, and this on reduction with sulphurous acid yields a compound $C_{17}H_{21}O_7N \cdot S$ [543–5] which is a hydrate of morphine sulphonic acid [546]. Catalytic reduction of the bimolecular sulphonic acid and of morphine sulphonic acid affords α-dihydromorphine sulphonic acid, also obtainable by sulphonation and reduction of dihydromorphine-N-oxide. β-Dihydromorphine sulphonic acid is formed by the reduction of the sodium salt of oxidodimorphine sulphonic acid (the bimolecular derivative) [546]. Morphine and α-dihydromorphine sulphonic acids can be methylated to the corresponding codeine derivatives [546]. Heroin gives an N-oxide (with hydrolysis of an acetyl group) on oxidation [547], as do ethers of morphine [399, 446–8]. The extraction and identification of morphine-N-oxide (genomorphine) is given by Rosenthaler [548].

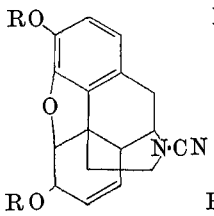
Morphine reacts with sulphur in boiling xylene to give compounds, possibly analogous to amine oxides, containing 1–3 atoms of sulphur per molecule [549].

NORMORPHINE AND ITS DERIVATIVES

Heroin [III, R = R′ = Ac] reacts with cyanogen bromide with replacement of the NMe group by N·CN and production of diacetylcyanonormorphine [XXIV, R = Ac] [550–2]. Hydrolysis of the latter affords first cyanonormorphine [XXIV, R = H] and finally normorphine [XXV] [552]. Cyanonormorphine can be converted into ethers [552–4] and these can be hydrolysed to ethers of normorphine [553–4]. α-chlorocyanonormorphide [XXVI] can be prepared by the action of cyanogen bromide on α-chloromorphide [555] and is converted to 8-diethylaminocyanonormorphide [XXVII] on heating with diethylamine [555] (See Chap. VIII).

N-alkylnormorphines can be prepared [554, 556] and these lose the N-alkyl group when treated with cyanogen bromide if the group is smaller than C_5; with C_5 and larger groups ring-fission occurs [554].

Dihydroheroin can be converted to diacetylcyanodihydronormorphine [550, 552, 555], and this can be hydrolysed to dihydronormorphine which is also furnished by catalytic reduction of normorphine [555].



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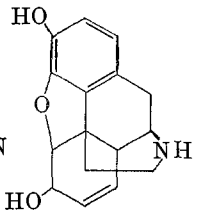

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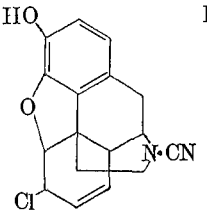
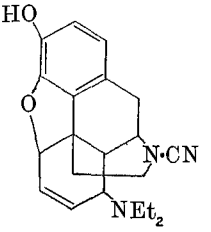


[XXVI]

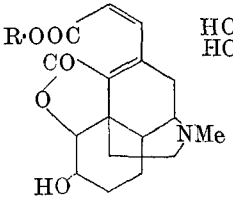


[XXVII]

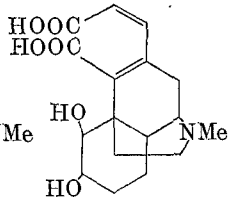
Normorphine cannot be prepared like norcodeine, through the N-nitrosocompound, as nitrous acid oxidizes morphine to pseudomorphine [557]. Conversion of morphine-N-oxide to normorphine by dichromates is unsatisfactory owing to breakdown of the ring structure [556].

Ozonolysis

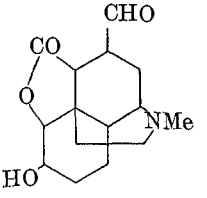
The ozonolysis of dihydrocodeine and dihydroethylmorphine with opening of the aromatic ring to give ozodihydrocodeine [XXVIII, R = Me] and ozodihydroethylmorphine [XXVIII, R = Et] [558] is discussed in Chapter IV. These products on hydrolysis afford the same dihydromorphinic acid [XXIX] [558] and on further ozonolysis the same dihydrocodinal [XXX], which results directly from the ozonolysis of dihydromorphine [559].



[XXVIII]



[XXIX]



[XXX]

Miscellaneous Reactions

(*a*) Phenanthrene is obtained by the zinc-dust distillation of morphine [560–2] together with ammonia, trimethylamine, pyrroline, pyridine, quinoline [561], and 'morphidine', a mixture of two bases, $C_{17}H_{15}N$ and $C_{17}H_{13}N$, probably derived from phenanthrene [562–3].

(*b*) Fusion of the alkaloid with potassium hydroxide affords methylamine [519, 564] and protocatechuic acid [519], while heating with alcoholic potash at high temperatures provides ethylmethylamine [565].

(*c*) With formaldehyde and hydrochloric acid morphine yields an ill-characterized, amorphous substance—dimorphenylmethane [566].

(*d*) The base is reported to react with hydrogen sulphide in the presence of oxygen, but the nature of the product has not been determined [567].

(*e*) Morphine is unaffected by Grignard reagents [568].

(*f*) A monocarbethoxy-derivative and a dicarbethoxy-derivative $C_{17}H_{16}NO_3(COOEt)_2$ are obtained when morphine is shaken with ethyl chloroformate and alkali in ether or chloroform [407, 569].

(*g*) Numerous compounds of therapeutic interest are formed by morphine with barbituric acid derivatives [570–5].

(*h*) Morphine hydrochloride readily forms double salts with narcotine hydrochloride [576–81], and its meconate forms a double compound with urea [582].

(*i*) Morphine acetate solutions slowly deposit morphine [583–7], and the solid salt slowly loses acetic acid [586, 588]. The dithionate loses sulphur dioxide at 170° C. [589–90]. The base readily forms salts with benzaldehyde bisulphite [591] and alloxan bisulphite [592].

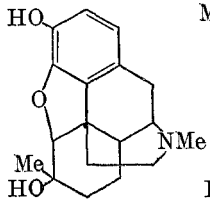
Thermochemical studies of morphine have been made by Leroy [130, 593].

The absorption spectrum of morphine has been determined by Hartley [594], Mayer (in sulphuric-nitric acid) [595], and Kitasato [596], and the ultra-violet absorption spectrum (shown in comparison with that of codeine in Chap. IV) by other workers [597–602].

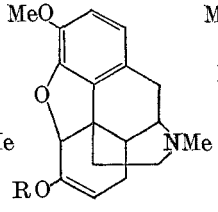
Substituted Morphine Derivatives

(i) Dihydromorphinone [XII] reacts with lithium methyl to give 6-methyldihydromorphine [XXXI] [603].

(ii) Dihydrothebaine [XXXII, R = Me] [604] and dihydrocodeinone enol acetate [XXXII, R = Ac] [605] react with Grignard reagents to give alkyl and aryl derivatives of dihydrothebainone [XXXIII], and these can be converted via derivatives of dihydrocodeinone to alkyl-derivatives of dihydromorphine. The location of the substituent (5 or 7 ?) is not clear. These compounds are discussed in detail in Chapter XIX.



[XXXI]



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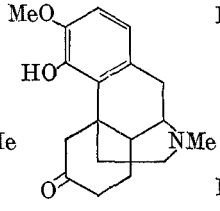

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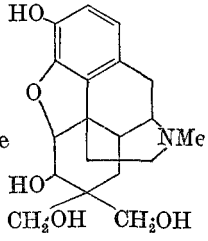
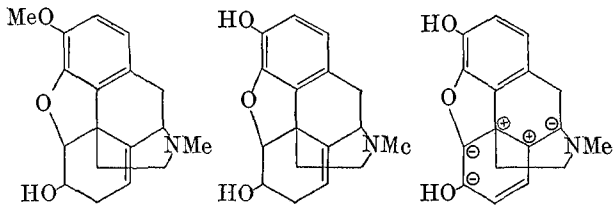


[XXXIV]

(iii) Dihydromorphinone [XII] on heating with methanolic aqueous formaldehyde and calcium oxide yields 7-bis(hydroxymethyl)-dihydromorphine [XXXIV] [606].

(iv) Demethylation of neopine [XXXV] affords neomorphine [XXXVI] [607] (see Chap. VII).



[XXXV] [XXXVI] [XXXVII]

STEREOCHEMISTRY

Following a study of a large number of compounds Emde [608] concluded that the contributions of the various asymmetric centres in morphine to the total rotation are in the senses shown in [XXXVII].

α-ISOMORPHINE

This base is obtained by the hydrolysis of α-chloromorphide [454, 463–4] and of bromomorphide [82, 454, 609]. It differs from morphine only in the spatial arrangement of the alcoholic group as it can be methylated to isocodeine [454, 609–10] which is known to give the same codeinone on oxidation as does codeine [611]. Other ethers and heteroethers can be prepared [446]. With phosphorus trichloride α-isomorphine yields what is probably β-chloromorphide [82, 609] and bromomorphide with phosphorus tribromide [609]. Catalytic reduction of the base affords a quantitative yield of dihydro-α-isomorphine, which can be methylated to dihydroisocodeine [612]. Mild oxidation of α-isomorphine affords α-pseudomorphine [613]. Alkaline degradation of α-isomorphine methiodide gives only a phenol betaine, but acetic anhydride degradation gives diacetylmorphol [XVI] [82].

β-ISOMORPHINE

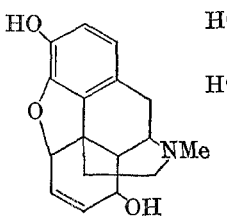
This isomer of morphine also results from the hydrolysis of α-chloromorphide [453–4, 464] and of bromomorphide [454]. It differs from morphine in having the double bond at C-6:7 and the alcoholic group at C-8, as is shown by its methylation to allo-ψ-codeine [453–4, 611] which can be degraded to 3:4:8-trimethoxyphenanthrene [538] (see Chap. IV). β-Isomorphine [XXXVIII] on catalytic reduction undergoes opening of the cyclic ether link to give tetrahydro-β-isomorphine

[XXXIX] (which can be methylated to tetrahydroallo-ψ-codeine) and some loss of the alcoholic hydroxyl group to give tetrahydrodesoxymorphine [XL] [612]. Allo-ψ-codeine behaves similarly on reduction [614]. These reactions can be largely suppressed by hydrogenation of the hydrochloride in N hydrochloric acid using a platinum oxide catalyst when dihydro-β-isomorphine [XLI] is obtained. This can be methylated to dihydroallo-ψ-codeine A [612] which is obtained by reduction of allo-ψ-codeine under similar conditions [614].

Ethers and heteroethers can be prepared from β-isomorphine and dihydro-β-isomorphine [446]. Heteroethyl-β-isomorphine is obtained by heating bromomorphide with alcohol [446]. Mild oxidation of β-isomorphine affords β-pseudomorphine [613].

γ-ISOMORPHINE

This base, which has also been called neoisomorphine, can be prepared like α- and β-isomorphines by the hydrolysis of α-chlorocodide [453–4, 463, 611] and of bromomorphide [454]. It differs from β-isomorphine only in the arrangement of the alcoholic group, as is shown by its methylation to ψ-codeine [453–4, 463, 611], which on oxidation gives the same ψ-codeinone as does allo-ψ-codeine [464, 611, 615].



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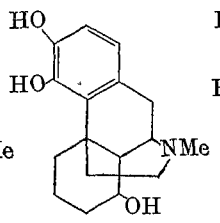
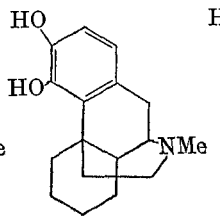
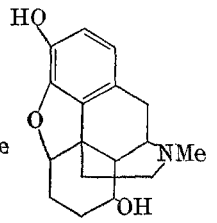


[XXXIX]



[XL]



[XLI]

Catalytic reduction of the base in dilute acetic acid with palladised barium sulphate as catalyst yields tetrahydro-γ-isomorphine [C-8 epimer of XXXIX] (also available by the demethylation of tetrahydro-ψ-codeine), but no tetrahydrodesoxymorphine [XL], whilst hydrogenation of the hydrochloride in glacial acetic acid with a platinum oxide catalyst affords 50 per cent. tetrahydro-γ-isomorphine and 50 per cent. dihydro-γ-isomorphine [C-8 epimer of XLI], which is best prepared by the demethylation of dihydro-ψ-codeine-A [616]. The catalytic reduction of ψ-codeine follows a similar pattern [617] (see Chap. IV).

Ethers and heteroethers of γ-isomorphine and dihydro-γ-isomorphine can be prepared, the γ-isomorphine heteroethers best by the action of alcohols on α-chloromorphide [446].

γ-Pseudomorphine results from the oxidation of γ-isomorphine, whilst the oxidation of an equimolecular mixture of morphine and γ-isomorphine gives morphine-γ-isomorphine [613] (see Chap. III).

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Morphine	247–248	MeOH	prisms	−130·9	23	MeOH	82, 117
— hydrochloride·3H_2O	..	H_2O	needles	−99 5	15	H_2O	128
— hydrochloride (anhyd.)	200	EtOH	..	−111·5	25	..	82, 618, 619
— hydrobromide·2H_2O	..	H_2O	needles	..	..	..	620
— hydrobromide (anhyd.)	..	EtOH	..	−100·4	15	..	82
— hydriodide·xH_2O	..	H_2O	needles	..	..	..	620–3
— hydrofluoride	..	H_2O	prisms	..	..	..	624
— perchlorate·2H_2O	150	H_2O	prisms	..	..	..	625–6
— sulphate·5H_2O	..	H_2O	needles	..	..	..	78, 339 341, 126
— thiosulphate·4H_2O	..	H_2O	needles	..	..	..	627
— nitrate	..	..	needles	..	..	..	4–5
— phosphate	..	..	cubes	..	..	..	628
— acid phosphate	..	..	needles	..	..	..	628
— carbonate	..	..	prisms	..	..	..	335
— thiocyanate·½H_2O	c. 100	..	needles	..	..	..	629
— periodides	..	..	..	..	..	..	223, 621, 630–1
— tetrachloroiodide	78	HOAc	orange needles	..	..	..	632
— platinichloride	..	..	..	..	..	..	508, 633
— platinocyanide	..	..	needles	..	..	..	634
— mercurichloride	..	..	pptd. cryst.	..	..	..	217
— mercuriiodide	..	..	pptd. cryst.	..	..	..	635–8
— stibnichloride·4H_2O	..	..	plates	..	..	..	639
— bismuthiiodide	..	..	..	..	..	..	640, 638
— tetrafluoroborate	..	..	needles	..	..	..	641
— hexafluorophosphate	..	..	needles	..	..	..	642
— difluorophosphate	..	..	..	..	..	..	643
— fluorocolumbate	..	..	..	−82	..	H_2O	644
— dithionate·2H_2O	..	..	needles	..	..	..	547
— vanadate	..	..	..	..	..	..	225
— chromate	..	..	needles	..	..	..	122, 645
— dichromate	..	..	..	..	..	..	122
— ferrocyanide	..	..	cryst.	..	..	..	646
— Reineckate	..	..	red cryst.	..	..	..	222, 226
— acetate·3H_2O	..	..	..	−104 −77	.. ..	EtOH H_2O	586, 647–8
— monochloracetate	..	..	..	..	..	..	87–88
— dichloracetate·½H_2O	..	..	..	..	..	..	87–88
— trichloracetate·1½H_2O	..	..	..	..	..	..	87–88, 649
— monobromacetate	..	..	..	..	..	..	87–88
— benzoate	..	H_2O	..	..	..	..	584
— butyrate	D. < 100	..	rhombs.	..	..	..	122, 650
— citrate	..	..	..	..	..	..	651
— cyanurate	..	..	prisms	..	..	..	624
— *d*-galactouronate	162–163	..	..	−56·6	20	..	652
— caseinate	..	..	..	..	..	..	653
— helianthate	..	..	orange plates	..	..	..	654
— lactate	D. > 100	..	..	..	..	..	122, 655
— trichlorolactate·5H_2O	..	..	..	..	..	..	87–88
— malate	..	..	cryst.	..	..	..	122
— *d*-, *l*-mandelates	..	..	..	..	..	..	656
— meconate	..	..	..	..	..	..	11, 657
— formate	..	..	prisms	..	..	..	658
— mellitate	..	..	needles	..	..	..	659
— phthalate·5H_2O	..	..	..	..	..	..	584
— picrate	163–165	..	..	..	..	..	660
— oxalate·H_2O	D. > 105	..	rhombs.	..	..	..	122
— tartrate·3H_2O	..	..	needles	..	..	..	651, 662
— acid tartrate·½H_2O	D. > 140	..	prisms	..	..	..	662
— antimonyltartrate	..	..	..	..	..	..	122
— urate	..	..	..	..	..	..	624
— hippurate	..	..	amorph.	..	..	..	624
— *iso*valerianate	..	..	rhombs.	..	..	..	651, 663
— *l*-xylonate	158	15%OH	needles	..	..	..	664

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Morphine phenylacetate	92	..	..	..	..	..	650, 87, 88
— diallylbarbiturate	258	H_2O	needles	..	..	..	573, 575
— phenylethylbarbiturate	250	..	needles	..	..	..	574
— violurate	..	..	..	−43·7	30	..	665
— diphenylthiovioluratc	93	..	crystals violet-black	..	..	..	666
— camphorsulphonate·$2H_2O$	197	H_2O	prisms	−59·3	20	H_2O	667–9
— styphnate	182	..	..	..	..	..	670
— *l*-boruylhydrogencitraconate	185–190d.	..	..	−86·9	18	..	671
— 2-(2′:4′-dihydroxybenzoyl)-benzoate	269	..	prisms	..	..	..	672
— *tris*-(*p*-hydroxyphenyl)-arsenate	227	H_2O	..	..	..	..	673
— 5:5′-dichlordiphenyl-3:3′-dicarboxylic acid (acid salt)	218–219	MeOH	..	−30	..	EtOH	674
— benzenethiosulphonate	..	H_2O	needles	..	..	..	675
— *p*-toluenethiosulphonate	..	H_2O	cryst.	..	..	..	675
— o-guaiacolsulphonate	..	..	..	..	..	..	676
— β-naphthalenethiosulphonate	..	..	cryst.	..	..	..	675
— α-naphthalenethiosulphonate	..	..	cryst.	..	..	..	675
— alloxanbisulphite	..	EtOH	cryst.	..	..	..	592
— benzaldehydebisulphite	114d.	..	..	..	..	..	591
— α:3:4:6-tetramethyl-2:5-dinitrocinnamate	178–184	..	..	..	..	..	677
— 2-[2′-carboxy-6′-chlorophenyl]-pyridine-3-carboxylate (neutral salt)	200–204	..	..	−69·1	..	..	678
— 1-phenyl-2:3-dimethyl-4-methylamino-5-pyrazolone-4-methylsulphonate	..	..	..	..	..	..	679–80
— *cis*-*d*-3-carboxy·1:1-dimethyl-*cyclo*propane-2-propionate (neutral salt)	177–178	..	..	..	..	..	681
— *d*-oximino*cyclo*hexane-4-carboxylate	..	EtOH	prisms	+64·6†	..	..	682
— *p*-aminobenzenesulphonylacetamide salt	c. 160	..	..	..	..	..	683
— alkylammoaryl-phosphinites	..	..	..	..	..	..	684
— zinc chloride	..	..	..	..	..	..	685
Morphine meconate-urea	..	..	..	..	..	..	582
Morphine-narcotine — hydrochloride	200	..	yellow prisms	..	..	..	577, 580
— hydrobromide·$2H_2O$	D. c. 170	..	..	..	..	..	577, 580
— sulphate·$4\frac{1}{2}H_2O$	..	..	..	..	..	..	576, 578
— meconate·$4H_2O$; $6H_2O$	c. 168d.	..	..	..	..	..	516, 578, 581
— phenoldisulphonate·$2H_2O$	..	H_2O	..	..	..	..	578
— benzenetrisulphonate·$2H_2O$	..	..	..	..	..	..	576
Morphine-dinarcotine benzenetrisulphonate·$2H_2O$	..	H_2O	..	..	..	..	578
Morphine-dinarcotine salicyldisulphonate·H_2O	..	..	..	..	..	..	576
Dimorphine-narcotine benzenetrisulphonate·$2H_2O$	..	..	..	..	..	..	576, 578
Morphine methochloride·$2H_2O$	285d.	H_2O	prisms	−84·9	29	H_2O	581, 686
— methobromide	265–266	H_2O	needles	..	..	.	350, 352
— methiodide·H_2O	286d.	H_2O	needles	−72·9	25	H_2O	347, 349, 464, 82
methomethylsulphite	..	..	..	..	..	..	353
methohydroxide·$5H_2O$	..	..	..	..	..	..	348
methoplatinichloride·H_2O	..	H_2O	needles	..	..	..	349
ethochloride	255	H_2O+ acetone	needles	..	..	..	352
ethobromide	245	H_2O	needles	..	..	..	350, 352
ethiodide·$\frac{1}{2}H_2O$	..	H_2O	needles	..	..	..	347
Sodium morphinate	..	..	..	..	..	..	413
Potassium morphinate·$3H_2O$	..	..	..	..	..	..	349, 414–15

† Molar rotation

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Calcium morphinate·$4H_2O$	..	..	..	..	..	..	416, 414, 412
Barium morphinate·$2H_2O$	..	..	..	..	..	..	414
Formylmorphine	220–225	..	..	..	..	..	430, 432–3
3-acetylmorphine (α)	187	Et_2O	..	..	..	..	418, 420, 429
— hydrochloride·xH_2O	D. 280	..	..	..	..	..	420, 387
— platinichloride	..	..	..	..	..	..	418
— ethiodide·$\frac{1}{2}H_2O$	..	85% EtOH	..	..	..	..	100
6-acetylmorphine (β)	..	..	amorph.	..	..	..	418, 420
— hydrochloride	..	..	amorph.	..	..	..	418
— platinichloride	..	..	amorph.	..	..	..	418
γ-acetylmorphine†	..	Et_2O	..	..	..	..	487
— ethiodide·$3H_2O$	..	85% EtOH	..	..	..	..	487
Diacetylmorphine (heroin)	173	EtOAc	prisms	−166	15	MeOH	387, 420 349 418–19
— hydrochloride	231–232d.	..	prisms	..	..	..	687
— aurichloride	..	..	amorph.	..	..	..	420
— platinichloride	..	..	amorph.	..	..	..	420
— styphnate	222	..	..	..	..	..	670
— *o*-guaiacolsulphonate	..	..	amorph.	..	..	..	676
— dipropylbarbiturate	..	..	cryst.	..	..	..	570–1
— ethylallylbarbiturate	67	..	cryst.	..	..	..	570–1
— phenylallylbarbiturate	..	..	cryst.	..	..	..	570–1
— diallylbarbiturate	186	EtOAc	cryst.	..	..	..	573–4
— methochloride	..	..	prisms	..	..	..	349
— methiodide	252	..	needles	−107	15	H_2O	463
— methoplatinichloride	..	H_2O	yellow needles	..	..	..	349
— ethochloride	..	..	cryst.	..	..	..	487
— ethiodide·$\frac{1}{2}H_2O$	..	..	cryst.	..	..	..	487
3-chloroacetylmorphino	D. 234	EtOH	needles	..	..	..	431, 187
Di-[chloroacetyl]-morphine	135	Et_2O	..	..	..	..	187
3-acetyl-6-benzoylmorphine	..	..	cryst.	..	..	..	487, 428
— hydrochloride	..	..	amorph.	..	..	..	487
— platinichloride	..	..	..	..	..	..	487
— ethiodide·$\frac{1}{2}H_2O$	..	85% EtOH.	..	..	..	..	487
Dipropionylmorphine	107	..	amorph.	−671‡ −685‡	..	dil. HCl EtOH	608 349, 608
— hydrochloride	210	..	amorph.	−613‡	..	H_2O	349
— platinichloride	..	..	amorph.	..	..	..	349
3-butyrylmorphine	..	Et_2O	cryst.	..	..	..	428
— hydrochloride	..	..	cryst.	..	..	..	428
— platinichloride	..	..	..	..	..	..	428
— ethiodide	..	..	..	..	..	..	487
6-butyrylmorphine	..	..	amorph.	..	..	..	428
Dibutyrylmorphine	..	..	amorph.	..	..	..	428
— hydrochloride	..	..	amorph.	..	..	..	428
— platinichloride	..	..	amorph.	..	..	..	428
— ethiodide	..	..	amorph.	..	..	..	428
3-succinylmorphine·$4H_2O$	..	80% EtOH	cryst.	..	..	..	486
— hydrochloride	..	..	cryst.	..	..	..	486
— platinichloride	..	..	..	..	..	..	486
Di-(α-bromo*iso*valeryl)-morphine	D. 133	..	..	..	..	..	431
Ethoxyacetylmorphine	155	..	..	..	..	..	435
— hydrochloride	186	..	needles	..	..	..	435
Di-(ethoxyacetyl)-morphine	..	..	oil	..	..	..	435
— hydrochloride	D. 142	..	leaflets	..	..	..	435
Phenoxyacetylmorphine	D. C. 125	Et_2O	cryst.	..	..	..	435
Camphorylmorphine	..	..	amorph.	..	..	..	486
— hydrochloride	..	..	amorph.	..	..	..	486
— platinichloride	..	..	amorph.	..	..	..	486
3-benzoylmorphine	145	EtOH	needles	..	..	..	428
— hydrochloride	176–177d.	..	..	..	..	..	327, 428
— platinichloride	..	..	cryst.	..	..	..	428

† Existence very doubtful (420). ‡ Molar rotation.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
6-benzoylmorphine	269–270	..	..	..	..	..	688
6-benzoylmorphine hydrochloride	241–243	..	..	..	..	..	688
— bitartrate	c.136–138	..	..	..	..	..	688
Dibenzoylmorphine	189–190·5	EtOH	prisms	..	..	..	428
— hydrochloride·H_2O	..	..	cryst.	..	..	..	387
— platinichloride	..	..	amorph.	..	..	..	487
— ethiodide·$\frac{1}{2}H_2O$	..	85% EtOH	cryst.	..	..	..	487
p-hydroxybenzoylmorphine	D. 230	50% EtOH	leaflets	..	..	..	436
— hydrochloride	..	..	cryst.	..	..	..	436
— methobromide	..	..	cryst.	..	..	..	436
p-acetoxybenzoylmorphine	D. 232	EtOAc	needles	..	..	..	436
— hydrochloride	..	..	prisms	..	..	..	436
— methobromide	..	..	prisms	..	..	..	436
p-carbomethoxybenzoylmorphine	D.175–176	EtOH	prisms	..	..	..	436
— hydrochloride·EtOH	D. 190	EtOH	..	..	..	..	436
3-benzenesulphonylmorphine	165	Et_2O	..	..	..	..	187
— benzenesulphonate	140	H_2O	needles	..	..	..	187
p-toluenesulphonylmorphine	61–68	..	..	..	..	..	704
— hydrochloride	118	..	plates	..	..	..	704
— picrate	190–194	EtOH	..	..	..	..	704
Morphine-sulphuric acid·$2H_2O$	..	H_2O	needles	..	..	..	427
Carbomethoxymorphine	120	..	cryst.	..	..	..	406
— hydrochloride	..	..	cryst.	..	..	..	407
— sulphate	225	..	..	..	..	..	407
— platinichloride	..	..	cryst.	..	..	..	407
Acetylcarbomethoxymorphine	168	..	prisms or needles	..	..	..	408, 409
Carboethoxymorphine	{123–124 { 113	..	..	−143·7	..	EtOH	569 407
—hydrochloride	..	..	..	..	..	..	407
—sulphate	..	..	..	..	..	..	407
—platinichloride	..	..	..	..	..	..	407
—oxalate $2H_2O$	..	H_2O+ EtOH	..	..	..	..	407
—bitartrate	121–122d.	EtOH	..	−51·4	..	H_2O	569
Acetylcarbocthoxymorphine	155	EtOH	needles	..	..	..	408–9
— hydrochloride	D. 185	..	needles	..	..	..	408
— platinichloride	210	..	needles	..	..	..	408
Carbopropoxymorphine	..	..	..	..	..	..	387
— hydrochloride	..	..	..	..	..	..	387
— platinichloride·$2H_2O$	..	..	..	..	..	..	387
Acetylcarbopropoxymorphine	120	..	needles	..	..	..	408–9
Carbo*iso*propoxymorphine	..	..	..	..	..	..	387
Carboamoxymorphine	..	..	..	..	..	..	387
Morphine phenylurethane	127–130	..	..	..	..	..	417
Morphine-3-methyl ether: *see* codeine							
Morphine-6-methyl ether (heterocodeine)	242	EtOH	..	..	..	..	399
— hydrochloride·$2H_2O$	103	H_2O	..	−153·7	25	H_2O	399, 689
— methochloride	> 270	H_2O+ EtOH	..	..	..	..	399
Morphine-3-ethyl ether (ethylmorphine; codethylin)	93	H_2O	prisms	..	..	..	364, 367–9, 371, 378, 385–6, 389
— hydrochloride·H_2O	123–125d.	..	..	..	..	..	690
—sulphate·$5H_2O$	207	H_2O+ EtOH	..	..	..	..	691
— camphorsulphonate·H_2O	154	..	..	−55·5	..	H_2O	667
— o-guaiacolsulphonate	..	H_2O	cubes	..	..	..	676
—styphnate	115	..	..	..	..	..	670
— ethylallylbarbiturate	67	..	..	..	..	..	570–1
— ethylphenylbarbiturate	87	..	..	..	..	..	587, 574
— diallylbarbiturate	285	..	..	..	..	..	573, 575
— methobromide·H_2O	267–268	..	prisms	..	..	..	351
methiodide	..	..	..	..	..	..	386
ethobromide	225	H_2O+ EtOH	needles	..	..	..	351
— ethiodide	..	EtOH	needles	..	..	..	602

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Morphine-3-ethyl ether N-oxide	220–221	H_2O	needles	..	..	..	542
— N-oxide hydrochloride	..	..	..	..	..	..	542
— N-oxide sulphate	..	..	..	..	..	..	542
— N-oxide nitrate	..	..	..	..	..	..	542
Morphine-6-ethyl ether·H_2O	110–112	EtOAc	..	−178·8	23	EtOH	446
— hydrochloride·$3H_2O$	241–243	H_2O	..	−134·9	24	H_2O	446
— hydrobromide·$2H_2O$	285–287	H_2O	..	−119·2	23	H_2O	446
— hydriodide·$2H_2O$	171–174 and 282	H_2O	..	−115·8	24	H_2O	446
— perchlorate	249–250	H_2O	..	−126	24	EtOH	446
— methiodide	255–265	H_2O	..	−104·6	24	H_2O	446
Morphine-3-β-chloroethyl ether	75–76 and 105	..	..	..	..	..	395
— (anhydrous)	118–120	..	..	..	..	..	395
— hydrochloride·H_2O	150–151	Acetone + H_2O	..	..	..	..	395
— hydrochloride (anhyd.)	166–168	..	..	..	..	..	395
— hydriodide	212–213	H_2O + MeOH + HI	..	..	..	..	395
— sulphate	115–120 and 235–240	EtOH	needles	..	..	..	395
— phosphate	D. 110	..	..	..	..	..	395
— oxalate	85–87	..	..	..	..	..	395
Morphine-3-β-bromoethyl ether	135–136 and 185–187	..	..	..	..	..	395
— impure hydrochloride	210–230	..	..	..	..	..	395
Morphine-3-*n*-propyl ether·$\frac{1}{2}H_2O$	69–70	..	..	..	..	..	389, 393
— hydrochloride·H_2O	111–114	..	..	..	..	..	393
— hydrochloride (anhyd.)	146–153	..	..	..	..	..	393
Morphine-3-(β:β′-dichloro-*iso*propyl)-ether	115	..	..	..	..	..	395
— hydrochloride	147	..	..	..	..	..	395
Morphine-3-*n*-butyl ether	..	..	not cryst.	..	..	..	393
— hydrochloride·H_2O	101–104	..	..	..	..	..	393
— hydrochloride (anhyd.)	119–122	..	..	..	..	..	393
Morphine-3-benzyl ether (benzyl-morphine)	..	..	..	..	..	..	693–4
— hydrochloride·$\frac{1}{2}H_2O$	..	H_2O	..	..	..	..	695–6
— N-oxide	236–238	EtOH	..	−53·2	23	EtOH	446
— ethanesulphonate	..	..	..	..	..	..	697–700
— propanesulphonate	..	..	..	..	..	..	697–700
6-benzoylmorphine-3-benzyl ether	130–135	..	..	..	..	..	688
Morphine-3-allyl ether	67–68	..	..	..	..	..	395, 404, 573
— hydrochloride·H_2O	130–132	..	..	−85·7	19	H_2O	395
— hydrochloride (anhyd.)	152–153	..	..	..	..	..	395
— hydriodide	225–226	H_2O + HI	prisms	..	..	..	395
— acid sulphate	202–203	EtOH	..	..	..	..	395
— sulphate·H_2O	167–168	H_2O	..	..	..	..	395
— sulphate (anhydrous)	172–173	EtOH	..	..	..	..	395
— dihydrogen phosphate	186	Acetone + H_2O	..	..	..	..	395
— phosphate	100	..	..	..	..	..	395
— oxalate	103 and 203	EtOH	..	..	..	..	395
Morphine-3-methoxymethyl ether	94–96	..	needles	..	..	..	399, 398, 396
— sulphate·$10H_2O$	..	..	cryst.	..	..	..	399, 398, 396
— methiodide	225d.	EtOH	needles	..	..	..	399, 398, 396
— N-oxide	..	..	..	..	..	..	448
Morphine-3-β-hydroxyethyl ether	190	..	..	−124·8	..	MeOH	394
Morphine-3-carboxymethyl ether	D. *c.* 192	EtOH	needles	..	..	..	405
— potassium salt	..	..	needles	..	..	..	405
Morphine-(2:4-dinitrophenyl) ether	..	..	..	..	..	..	402
Morphine-3-quinolyl ether	158	MeOH	prisms	..	..	..	403
— hydrochloride	..	..	poorly cryst.	..	..	..	403

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Morphine-3-quinolyl ether sulphate ·3H_2O	257d.	H_2O	..	−66·5	..	dil.HCl	403
— chromate	..	..	..	..	..	..	403
— picrate	250–252d.	..	cryst.	..	..	..	403
— tartrate	98d.	EtOH	prisms	..	..	..	403
Morphine-3-benzyl-6-methyl ether	..	..	..	..	..	..	446
— hydrochloride	233–236	H_2O	..	−88·9	28	H_2O	446
— acid sulphate	247–249	H_2O	..	−90·1	25	H_2O	446
— methiodide	155–157	50% EtOH	..	−75·8	24	50% EtOH	446
Morphine dimethyl ether: *see* codeine methyl ether (Chap. IV).							
Morphine-3-methoxymethyl-6-methyl ether							
— methochloride	D. 200	..	..	..	..	..	399, 398, 396
— methiodide	253d.	80% EtOH	..	..	..	..	399, 398, 396
Dimorphine-3:3′-ethylene ether	188	EtOH + H_2O	needles	..	..	..	386–7
— hydrochloride	..	..	cryst.	..	..	..	386
Dimorphine-3:3′-pentamethylene ether	70–100	..	amorph.	..	..	..	554
Morphine glucoside	c.183–193	50% EtOH	needles	..	..	..	449
Morphine tetraacetylglucoside	154–156	EtOH + H_2O	needles	..	..	..	449
— hydrochloride	c. 220d.	..	..	..	..	..	449
α-Morphine-3-β-6-cellobioside-β-*d*-glycoside	120–121	..	amorph.	..	..	..	450
β-Morphine 3-β-6-cellobioside-β-*d*-glycoside	176–177	..	cryst.	..	..	..	450
Morphine amino acid estors and derivatives	..	..	amorph.	..	..	..	701
Dihydromorphine·H_2O	155–157	EtOH	..	..	..	..	494–501
— hydrochloride	..	..	prisms	..	..	..	494
— hydriodide	275	..	..	..	..	..	..
— picrate	139	..	prisms	..	..	..	498
— diallybarbiturate	125	H_2O	..	..	..	..	572–3
Racemate with antipode from sinomenine series	154	..	..	0	..	..	503
— hydriodide	261	..	..	..	..	..	503
— methiodide	267	..	..	..	..	..	503
(l)dihydromorphine	159	..	..	+151·5	29	EtOH	503
— hydriodide	..	..	..	+87·9	29	H_2O	503
methiodide	..	..	..	+74·9	30	H_2O	503
Diacetyldihydromorphine	165–167	..	needles	..	..	..	504, 552
hydrochloride	..	..	cryst.	..	..	..	552
Dihydromorphine-3-methyl ether: *see* dihydrocodeine (Chap. IV).							
Dihydromorphine-6-methyl ether (Dihydroheterocodeine)	217–219	EtOH	..	−178·0	26	EtOH	689, 446
hydrochloride	299–299·5	..	..	−136·5	26	H_2O	446, 689
hydriodide	269	H_2O	..	−98·9	25	H_2O	446
perchlorate	258–260	H_2O	..	−110·0	28	H_2O	446
acid fumarate	215–216	95% EtOH	..	−110·0	28	H_2O	446
methiodide	260–261	MeOH	..	−91·4	28	MeOH	446
Dihydromorphine-3-ethyl ether	..	..	oil	−135·9	24	EtOH	446
acid nitrate·H_2O	158–159	EtOH	..	..	..	..	504
acid tartrate	167	..	..	−59·4	25	H_2O	446
methiodide	260	EtOH	..	−66·9	25	H_2O	446
Dihydromorphine-6-ethyl ether	189–190	EtOAc	..	−164·8	23	EtOH	446
hydrochloride·3H_2O	95–110 and 274–276	H_2O	..	−121·7	24	H_2O	446
hydrobromide·2H_2O	282–284	H_2O	..	−125·1	25	H_2O	446
hydriodide	291–293	H_2O	..	−110·6	25	H_2O	446
perchlorate	234–235	H_2O	..	−98·0	23	EtOH	446
methiodide	250–251	..	..	−79·4	25	MeOH	446
Dihydromorphine-3-benzyl ether	95–97	EtOAc	..	−88·1	24	EtOH	446
hydrochloride·H_2O	233–235	H_2O	..	−52·1	20	H_2O	446
hydrobromide·H_2O	103–105	H_2O	..	−44·0	24	H_2O	446
hydriodide	215–217	H_2O	..	−45·3	24	H_2O	446

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Dihydromorphine-3-benzyl ether perchlorate	188–192	20% EtOH	..	−59·5	23	EtOH	446
— methiodide	242–244	MeOH	plates	−43·2	24	MeOH	446
— N-oxide	..	..	..	..	..	..	448
Dihydromorphine-3-methoxymethyl ether	99–101	acetone	..	−154·5	24	EtOH	446
— hydrochloride	124–126	..	..	−71·8	24	H_2O	446
— sulphate	49	..	..	−72·8	24	H_2O	446
— methiodide	201–203	EtOH	..	−61·8	24	H_2O	446
— N-oxide	..	..	..	..	..	..	448
Dihydromorphine dimethyl ether: *see* dihydrocodeine methyl ether (Chap. IV).							
Dihydromorphine-3-benzyl-6-methyl ether	..	..	not cryst.	..	..	..	446
— methiodide	155–157	EtOH	..	−54·6	24	H_2O	446
1-bromomorphine·$\frac{1}{2}H_2O$	..	EtOH	prisms	..	..	..	534–5
— hydrochloride·$3H_2O$	..	H_2O	needles	..	..	..	534
— hydrobromide·$3H_2O$	D. 221	H_2O	needles	..	..	..	534
— methiodide·H_2O	252	H_2O	prisms	..	..	..	534
— methohydroxide	..	..	..	..	..	..	535
Diacetylbromomorphine	208	MeOH	..	..	..	..	535
— hydrobromide	..	..	needles	..	..	..	534
— methiodide·$1\frac{1}{2}H_2O$	200	..	..	..	..	..	535
Tetrabromomorphine (two isomers)	..	..	..	..	..	..	533–4
— α-hydrobromide	218	..	..	..	..	..	533
— β-hydrobromide	178	..	..	..	..	..	533
— α-sulphate·H_2O	..	..	..	..	..	..	533
— α-oxalate	..	..	..	..	..	..	533
— barium salt	..	..	..	..	..	..	533
Tribromomorphine	..	..	..	..	..	..	533
1-nitrodiacetylmorphine	..	..	..	..	..	..	420
2-nitromorphine	225d.	EtOH	orange needles	..	..	..	187, 540
— hydrochloride	248d.	dil. HCl	yellow needles	..	..	..	187
— ammonium salt	D.173–174	..	dark red leaflets	..	..	..	187
— sodium salt	D. > 220	..	garnet needles	..	..	..	187
— silver salt	181–182d.	..	black	..	..	..	187
2-aminomorphine	258	EtOH	plates	..	..	..	187
— dihydrochloride	..	EtOH	..	−90	..	H_2O	187
— picrate	D. 172	H_2O	needles	..	..	..	187
2-aminodihydromorphine	..	..	..	..	..	..	540
— hydrochloride	D. 325	..	..	..	..	..	540
Tribenzoyl-2-aminodihydromorphine	185	..	..	..	..	..	540
Nitrosomorphine?	D.	..	..	..	..	..	472
Diazomorphine anhydride	..	..	..	..	..	..	187
— hydrochloride	D. c. 98	..	..	..	..	..	187
2-hydroxymorphine hydrochloride	..	..	amorph.	..	..	..	187
1-nitroethylmorphine	166–167	..	..	..	..	..	702
1-aminoethylmorphine	115–116	..	..	..	..	..	702
Acetyl-1-aminoethylmorphine	..	..	..	..	..	..	702
— hydrochloride	..	..	..	..	..	..	702
Diacetyl-1-aminoethylmorphine	156	..	..	..	..	..	702
2-phenylazomorphine	175d.	..	needles	..	..	..	187, 355
2-(2′-methylphenyl)azomorphine	210d.	..	amorph.	..	..	..	357
2-(4′-chlorophenyl)azomorphine	> 300	..	amorph.	..	..	..	356–7
2-(2′:4′:6′-tribromophenyl)azomorphine	> 300	..	amorph.	..	..	..	357
2-(4′-hydroxyphenyl)azomorphine	> 300	..	amorph.	..	..	..	357
2-(2′-methoxyphenyl)azomorphine	> 300	..	amorph.	..	..	..	357
2-(2′-nitrophenyl)azomorphine	> 300	..	amorph.	..	..	..	357
2-(3′-nitrophenyl)azomorphine	> 300	..	amorph.	..	..	..	357
2-(4′-nitrophonyl)azomorphine	> 300	..	amorph.	..	..	..	357
2-(α-naphthyl)azomorphine	> 300	..	amorph.	..	..	..	357
2-benzildiuotetrazomorphine	> 300	..	amorph.	..	..	..	357
1-acetomorphine	260–262·5	40% EtOH	..	−156	20	EtOH	538
— hydrochloride	235–237	65% EtOH	..	−121	20	H_2O	538
— perchlorate	201–202·5	H_2O	..	−111	20	MeOH	538
Diacetyl-1-acetomorphine	200–208	MeOH	..	−207	20	$CHCl_3$	537–8

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Diacetyl-1-acetomorphine hydrochloride	..	..	..	..	..	..	537
6-acetyl-1-acetodihydromorphine	242	MeOH	..	−97·2	20	$CHCl_3$	538
3:6-diacetyl-1-acetodihydromorphine	..	..	glass	..	..	..	538
Morphine-N-oxide	247–275	50% EtOH	prisms	..	..	..	542–3
— nitrate	206–208	..	..	..	..	..	543
Acetylmorphine-N-oxide·$3H_2O$	205	..	..	−144	..	EtOH	547
Dihydromorphine-N-oxide	D. 261	EtOH	plates	..	..	..	546
Oxidodimorphine sulphonic acid	280	needles	..	..	..	..	545–6
Morphine sulphonic acid·H_2O	> 300	..	prisms	..	..	..	543–6
Dihydromorphine-N-oxide sulphonic acid	D. > 360	..	prisms	..	..	..	546
α-dihydromorphine sulphonic acid	D. > 360	50% EtOH	scales	..	..	..	546
β-dihydromorphine sulphonic acid	D. > 360	..	..	..	..	..	546
Diacetylmorphine sulphonic acid (heroin sulphonic acid)	> 280	..	..	..	..	..	539
Normorphine·$1\frac{1}{2}H_2O$	272–273	..	needles	..	..	..	552, 550
— hydrochloride·H_2O	D. 305	..	..	..	..	..	552
— sulphate·$3H_2O$	..	..	cryst.	..	..	..	552
— platinichloride·$3H_2O$	D.230–231	..	..	..	..	..	552
— picrate	..	..	..	..	..	..	552
Dibenzoylnormorphine	208	..	..	..	..	..	552
Triacetylnormorphine	164	EtOH	..	..	..	..	552
Normorphine-3-methyl ether: *see* norcodeine (Chap. IV).							
Normorphine-3-ethyl ether	156	..	..	..	..	..	554
— hydrochloride·$2H_2O$	295	H_2O	needles	..	..	..	554
— platinichloride	299	..	..	..	..	..	554
Normorphine-3-*iso*amyl ether	100	..	..	..	..	..	552
— hydrochloride	278	Et_2O+ EtOH	..	..	..	..	552
Normorphine-3-allyl ether	164	EtOH	..	..	..	..	554
— hydrochloride·H_2O	240	H_2O	needles	..	..	..	554
— platinichloride·H_2O	D. 250	..	..	..	..	..	554
Normorphine-3-*p*-nitrobenzyl ether	180	EtOH	..	..	..	..	553
— hydrochloride	D. 297	..	..	..	..	..	553
Dinormorphine-3:3′-pentamethylene ether	133–132	..	..	..	..	..	554
— dihydrochloride	235–240	..	..	..	..	..	554
— platinichloride	D.240–250	..	..	..	..	..	554
N-allylnormorphine	92–93	..	..	..	..	..	556
— hydrobromide	126	..	..	..	..	..	556
N-nitrosonormorphine	D. 267	EtOH	needles	..	..	..	557
— 3-ethyl ether	205	..	..	..	..	..	554
— 3-*iso*amyl ether	186	..	..	..	..	..	552
— 3-allyl ether	176	..	..	..	..	..	554
Diacetyl-N-nitrosonormorphine	202–203	EtOH+ H_2O	..	..	..	..	557
Di-(N-nitrosonormorphine)-3:3′-pentamethylene ether	145–150	..	..	..	..	..	554
Di-(N-aminonormorphine)-3:3′-pentamethylene ether	140–145	..	..	..	..	..	554
N-(phenylthiocarbamino)-normorphine	245	..	..	..	..	..	554
N-carbaminonormorphine-3-*p*-aminobenzyl ether	297	..	..	..	..	..	553
Cyanonormorphine	295–296	EtOH	..	..	..	..	550, 552
Diacetylcyanonormorphine	240	EtOH	..	..	..	..	552
Benzoylcyanonormorphine	265	EtOH	..	..	..	..	552
Cyanonormorphine	240	..	..	..	..	..	552
- 3-ethyl ether	225–226	..	..	..	..	..	554
- 3-*iso*amylether	225	..	..	..	..	..	552
- 3-allyl other	221	..	..	..	..	..	554
- 3-*p*-nitrobenzyl ether	229	EtOH	..	..	..	..	553
Di-(cyanonormorphine)-3:3′-pentamethylene ether	226–230	..	..	..	..	..	554
Dihydronormorphine	267	..	needles	..	..	..	550, 555
hydrochloride	303	..	needles	..	..	..	555
platinichloride	..	..	ppt.	..	..	..	555
Cyanonordihydromorphine	201	EtOH	leaflets	..	..	..	550, 555
Diacetylcyanonordihydromorphine	138–139	..	needles	..	..	..	550, 552

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Morphine quinitrol	..	..	..	..	..	..	187
— nitrate·H_2O	..	..	orange prisms	..	..	..	187
Morphinic acid	..	..	..	..	..	..	187
— hydrochloride·$2H_2O$	..	H_2O	needles	..	..	..	187
— nitrate·H_2O	D.	..	..	..	..	..	187
— oxime hydrochloride	..	..	cryst.	..	..	..	187
Dimorphenylmethane	..	..	amorph.	..		..	566
— hydrochloride	..	..	..	..		..	566
6-methyldihydromorphine	209–211	acetone	..	−147·0	20	EtOH	603
—hydrochloride	308–309	Et_2O+EtOH	..	−121·0	20	EtOH	603
— methiodide	277–278	MeOH	..	−86·8	20	EtOH	603
7:7-bis-[hydroxymethyl]-dihydromorphine: *see* Chapter X.							
Other substituted dihydromorphines: *see* Chapter XIX.							
α-isomorphine	251–252	EtOAc+MeOH	needles	−167·0	15	MeOH	82, 463
— hydrochloride	..	EtOH	..	−150·0	20	H_2O	82
— hydrobromide·H_2O	..	H_2O	..	−127·2	15	H_2O	82
— methiodide	276	H_2O	..	−91·5	23	H_2O	82
— methohydroxide	..	..	..	..	..	..	82
Diacetyl-α-isomorphine	..	..	not cryst.	..	..	..	609
— methiodide	241–242	MeOH	needles	..	..	..	609
α-isomorphine-3-methyl ether: *see* isocodeine (Chap. IV).							
α-isomorphine-6-methyl ether (heteroisocodeine)	206–207	EtOH	..	−185·5	22	MeOH	446
— methiodide	227–228	EtOH	..	−105·4	22	H_2O	446
α-isomorphine-3-ethyl ether	128–130	..	..	−143·7	23	EtOH	446
— methiodide	243	EtOH	..	−91·6	21	H_2O	446
α-isomorphine-6-ethyl ether	161–162	Distilled	..	−205·1	22	MeOH	446
— hydrochloride	247–248	..	..	−164·2	24	H_2O	446
— hydrobromide	255–258	H_2O	..	−150·2	24	H_2O	446
— hydriodide	264	H_2O	..	−132·7	24	H_2O	446
— methiodide	229–231	EtOH	..	−131·3	24	H_2O	446
Dihydro-α-isomorphine	224–226	..	..	−125·8	19	MeOH	612
—hydrochloride	..	..	..	−112·0	23	H_2O	612
— hydrobromide	..	..	..	−97·9	..	H_2O	612
— binoxalate	..	..	..	−91·9	22	H_2O	612
— methiodide	..	..	..	−80·4	23	H_2O	612
Dihydro-α-isomorphine-3-methyl ether: *see* dihydroisocodeine (Chap. IV).							
Dihydro-α-isomorphine-6-methyl ether	198–200	..	..	−118·1	25	EtOH	446
— hydrochloride	273–275	H_2O	..	−111·1	24	H_2O	446
— hydriodide	287–288	H_2O	..	−85·2	24	H_2O	446
— methiodide	245–248	EtOH	..	−77·9	24	H_2O	446
Dihydro-α-isomorphine-3-ethyl ether	86–91	EtOAc	..	−110·0	24	MeOH	446
— acid tartrate·H_2O	109–112	acetone	..	−66·0	23	H_2O	446
— methiodide	277	80% EtOH	..	−76·2	23	H_2O	446
Dihydro-α-isomorphine-6-ethyl ether	210–212	EtOH	..	−128·0	24	EtOH	446
— hydrochloride	300	..	..	−125·7	24	H_2O	446
— hydriodide	287	..	..	−99·5	24	H_2O	446
— methiodide	256–258	EtOH	..	−86·1	24	H_2O	446
β-isomorphine·½EtOH	182	EtOH	..	−216·2	17	MeOH	463, 609
—hydrochloride	..	H_2O	needles	−200·8	11	H_2O	609
— methiodide	250	H_2O	..	−146·1	23	H_2O	609
β-isomorphine-3-ethyl ether	..	..	oil	..	..	..	446
— perchlorate	264–266	H_2O	..	−113·2	25	40% EtOH	446
— acid sulphate	195–198	H_2O	..	−136·3	24	H_2O	446
— fumarate	172–175	..	..	−100·3	24	EtOH	446
β-isomorphine-6-ethyl ether	209–211	EtOH	..	−60·1	24	EtOH	446
Dihydro-β-isomorphine·H_2O	202–203	..	..	−104·0	22	MeOH	612
— hydrochloride	..	..	..	−98·7	23	H_2O	612
— hydrobromide	..	..	..	−87·0	23	H_2O	612
— acid fumarate	..	..	..	−81·8	22	H_2O	612
Dihydro-β-isomorphine-3-ethyl ether	..	..	oil	..	..	..	446
— perchlorate	231–234	H_2O	..	−64·3	25	H_2O	446
— picrate	187–189	50% EtOH	..	−64·8	25	EtOH	446
Tetrahydro-β-isomorphine	245–247d.	..	..	−60·4	22	10% HOAc	612

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
γ-isomorphine·EtOH	278	EtOH	..	−94·0	15	EtOH	453–4, 463–4
— hydrochloride	314	..	..	−76·0	15	H_2O	463
— hydrobromide	298	..	..	−71·0	15	H_2O	463
— methiodide	293	..	..	−50·0	15	H_2O	463
Diacetyl-γ-isomorphine	..	..	not cryst.	..	..	..	463
— methiodide	267	EtOH	needles	−24·0	15	H_2O	463
γ-isomorphine-3-methyl ether: *see* ψ-codeine (Chap. IV).							
γ-isomorphine-6-methyl ether (hetero-ψ-codeine)	239–241	EtOH	..	−79·5	23	MeOH	446
— hydrochloride	274–276	H_2O	..	−48·6	22	H_2O	446
— hydriodide	185–188	H_2O	..	−48·7	21	H_2O	446
γ-isomorphine-3-ethyl ether	183–184	EtOH	..	−75·0	22	MeOH	446
— hydrochloride	298–300	..	..	−62·7	24	H_2O	446
— methiodide	252–253	70% EtOH	..	−40·8	21	H_2O	446
γ-isomorphine-6-ethyl ether	215–220	EtOH	..	−43·5	23	MeOH	446
— hydrochloride·$2H_2O$	287–290	H_2O	..	−30·5	23	H_2O	446
— hydriodide·H_2O	276–277	H_2O	..	−23·2	22	H_2O	446
Dihydro-γ-isomorphine	127 and 221	..	..	−35	25	95% EtOH	616
— hydrochloride	300–302	..	plates	−27·4	28	H_2O	616
— hydriodide	285–288	..	needles	−21·7	25	H_2O	616
— perchlorate	..	..	needles	−24·0	25	H_2O	616
— salicylate	131·5–132·5	..	..	−22·8	27	H_2O	616
— methiodide	255–257	..	plates	−21·0	27	H_2O	616
Dihydro-γ-isomorphine-3-methyl ether: *see* dihydro-ψ-codeine-A (Chap. IV).							
Dihydro-γ-isomorphine-6-methyl ether	235–237	EtOH	..	−83·4	25	EtOH	446
— hydrobromide	256–258	H_2O	..	−55·4	25	H_2O	446
— hydriodide	185–187	H_2O	..	−52·8	25	H_2O	446
Dihydro-γ-isomorphine-3-ethyl ether	158–159	EtOAc	..	−36·2	23	MeOH	446
— fumarate	180–192	EtOH	..	−23·7	23	H_2O	446
— methiodide	252–253	70% EtOH	..	−40·8	21	H_2O	446
Dihydro-γ-isomorphine-6-ethyl ether	220–223	EtOH	..	−20·2	25	EtOH	446
— hydriodide	277–281	H_2O	..	−9·1	25	H_2O	446
— methiodide	250–252	80% EtOH	..	−7·2	25	H_2O	446
Tetrahydro-γ-isomorphine	..	..	not cryst.	..	..	..	..
— hydrochloride	278–280	HOAc	needles	−8·0 −35·0	24 27	H_2O H_2O	703 616
— hydriodide	280–290	H_2O	..	−1·8	27	H_2O	616
— perchlorate	215–220	H_2O	..	0	25	H_2O	616
Neomorphine: *see* Chapter VII.							

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III

PSEUDOMORPHINE

In an investigation of the alkaloids obtained from opium Pelletier [1–3] reported the isolation of a base, pseudomorphine, that has since been prepared by the gentle oxidation of morphine under a variety of conditions, especially in alkaline solution. The various agents that effect the change are:

(*a*) alkaline potassium ferricyanide [4–8];
(*b*) mercurous chloride [8];
(*c*) potassium persulphate, copper, and pyridine [8];
(*d*) nitrous acid [9–12];
(*e*) ammoniacal copper [4, 13–14] or silver [4] salts;
(*f*) potassium permanganate and alkali carbonates [15];
(*g*) atmospheric oxygen and ammonia [16];
(*h*) potassium cupricyanide and hydrogen peroxide [17–19];
(*i*) electrolytic oxidation in dilute sulphuric acid [20];
(*j*) enzymes present in extracts of *russula delica* [18, 21–24] and in gum arabic [25].
(*k*) Pseudomorphine is also formed in small quantity during the bromination of morphine with hydrobromic acid and hydrogen peroxide [26], and
(*l*) in the sterilization of solutions of morphine hydrochloride in sealed tubes [27], but a trace of acid or reducing agent hinders this change [28].

Of these oxidations (*a*) and (*b*) are reported to give yields of 90 per cent. [8]; (*c*) 75 per cent. [8]; (*h*) 20–25 per cent. [17]. It is not known whether pseudomorphine is actually present in opium or whether it is formed from morphine during the process of extraction [29]; the amounts obtained from this source are in any case very small (about 0·02 per cent. of opium): the method of extraction is described by Hesse [30]. Pseudomorphine has also been called oxymorphine [10], oxydimorphine [5, 6, 11, 15–16], dehydromorphine [31], and phormin [29].

Physical Properties

Pseudomorphine is sparingly soluble in most organic solvents, the best being benzyl alcohol, pyridine, and guaiacol [19]. The rotatory power of the hydrochloride has been given as $[\alpha]_i = -114{\cdot}76°$ [32]; $[\alpha]_D = -103{\cdot}13°$ [31]; $-109{\cdot}6°$, $-107{\cdot}7°$ [33] (in water). The rotatory power of the base in alkali is variable [23], the rotation being the same

for a given ratio of base:alkali whatever the actual concentrations, and is determined by the equation $M(fa/c+10)^{0.435}$ = a constant, where M is the rotation, f the activity coefficient of the potassium hydroxide of molar concentration a, and c is the molar concentration of pseudomorphine. The constant is approximately −572 [34].

Detection and Estimation

The following colour tests have been recorded for the detection of pseudomorphine.

Reagent	*Colour*	*References*
conc. H_2SO_4	olive-green $\xrightarrow{\text{dilute}}$ rose red	30–31
conc. H_2SO_4, dilute add. oxidn. agt.	deep violet	30–31
conc. H_2SO_4+H·CHO	reddish (green when impure)	35–37
conc. H_2SO_4+H·CHO+$K_3Fe(CN)_6$	emerald green	36
conc. H_2SO_4+glyoxylic acid	green-blue → emerald green	38
conc. H_2SO_4+ammonium selenite	violet	23
conc. H_2SO_4+sucrose	dark groen → brown	29
conc. H_2SO_4+sucrose+ferric salts	blue → dark green	29
conc. H_2SO_4 or conc. HCl at 100° C.+*p*-dimethylaminobenzaldehyde	emerald green	38
conc. HCl+vanillin, 100° C.	green	39
conc. HNO_3	orange-red	30
ferric chloride	blue	30
chlorine water	green $\xrightarrow{NH_3}$ yellow-green to brown	40

The reaction between pseudomorphine, concentrated hydrochloric acid, and vanillin may be used to detect the base in presence of morphine [41], and pseudomorphine and concentrated sulphuric acid may be used as a specific reagent for the detection of the —CHO group in a large number of substances [42]. Microprecipitation reactions for pseudomorphine with many reagents are given by van Itallie and Toorenberg [43], and the detection of the base in presence of morphine by precipitation with potassium cyanide and sodium acetate is discussed by Grimbert and Leclére [36]. Pseudomorphine can be estimated either as free base or as silicotungstate [19, 44].

Composition

A monomolecular formula $C_{17}H_{18}O_4N$ was first postulated for pseudomorphine [30], the dimolecular $(C_{17}H_{18}O_3N)_2$ being later suggested by Broockmann and Polstorff [11] on the grounds that nitric oxide is evolved when morphine hydrochloride is oxidized by silver nitrite, though this was questioned by Hesse [12]. The dimolecular composition was finally verified by the oxidation of morphine with an

equimolecular quantity of potassium ferricyanide, when pseudomorphine resulted in 70–88 per cent. yield according to the equation

$$2C_{17}H_{19}O_3N+2KOH+2K_3Fe(CN)_6$$
$$= (C_{17}H_{18}O_3N)_2+2K_4Fe(CN)_6+2H_2O. \quad [6\text{–}7]$$

The formula was later confirmed by molecular weight determination [33, 45–46].

Structure

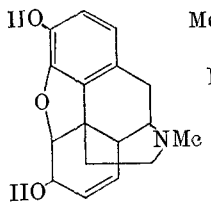
Concerning the structure of pseudomorphine little is known with certainty. The two morphine units were originally believed to be joined in the 2:2′ positions as this was assumed to be the reactive position in the morphine molecule [I], and bromomorphine, believed to have the bromine in position 2, cannot be oxidized in this way [47]. However, the bromine atom in bromomorphine is now known to be in position 1 [48], which is presumably the most reactive position, and pseudomorphine may be 1:1′-dimorphine. An attempt to reduce 1-bromomorphine to a dimolecular derivative by heating in alcoholic alkali with palladium on strontium carbonate and hydrazine (method of Busch [49]) failed, only amorphous coloured substances being obtained [50].

Bertrand and Meyer [46], following a study of the optical properties of pseudomorphine, suggested that in this base the two morphine units are not symmetrically arranged, and indeed the two halves react differently. Although a tetra-acetyl derivative can be prepared by heating the base with acetic anhydride [12] or acetyl chloride [51], only a monomethyl ether results when the base is treated with methyliodide and alkali, and this is alkali-insoluble [52], though it can be converted to a triacetyl- and a tribenzoyl-derivative [52]. A di-methiodide can be formed by heating the methyl ether with methyl iodide under pressure at 110° C., and this is converted to a basic methiodide-methohydroxide by ammonia, indicating that the nitrogen atoms differ in some way [52]. Also oxidation of morphine methiodide with alkaline potassium ferricyanide gives pseudomorphine methiodide-methohydroxide, which yields the di-methiodide on treatment with hydriodic acid [53].

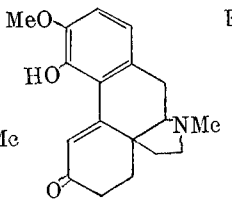
Goto and Kitasato [54–55] degraded the methiodide-methohydroxide by heating with sodium acetate and acetic anhydride to what they claimed was bis-(2:2′)-3:4-diacetylmorphol, which they methylated to 'bis-(2:2′)-3:4-dimethylmorphol' (morphol is 3:4-dihydroxyphenanthrone). At the same time α- and β-dimetathebainone (prepared by the silver nitrate oxidation of metathebainone [II] and almost certainly bis-1:1′ compounds [54]) were degraded to what was assumed to be bis-(1:1′)-3-methyl-4-acetylmorphol [54–55], but the crucial hydrolysis

and methylation of this to bis-(1:1′)-3:4-dimethylmorphol for comparison with the substance derived from pseudomorphine was apparently not attempted.

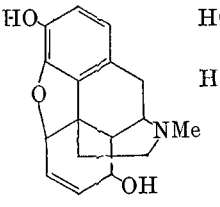
The oxidation of morphine to pseudomorphine bears an analogy to the oxidation of naphthols to dimolecular compounds, and, as would be expected from this, neither codeine nor diacetylmorphine can be oxidized in this way [52]. However, a simple 1:1′ or 2:2′ union of two molecules does not explain the apparent loss of phenolic function of one of the hydroxyl groups nor the difference in behaviour of the two nitrogen atoms.



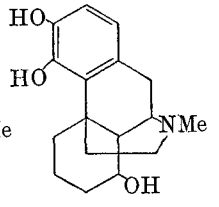
[I]



[II]



[III]



[IV]

Pseudomorphine is not reduced to morphine by sodium amalgam, zinc, and hydrochloric acid or tin and hydrochloric acid [31]. Catalytic hydrogenation affords tetrahydropseudomorphine, which is also obtainable by the oxidation of dihydromorphine [56]. Oxidation of morphine-6-methyl ether (heterocodeine) leads to pseudomorphine-6:6′-dimethyl ether [56].

Isomers

Four isomers of pseudomorphine have been prepared, namely α-pseudomorphine, prepared by the oxidation of α-isomorphine (the C-6 epimer of [I]); β- and γ-pseudomorphine, from the oxidation of β- and γ-isomorphine (a C-8 epimeric pair [III]); morphine-γ-isomorphine obtained by the oxidation of an equimolecular mixture of morphine and γ-isomorphine [56]. Like pseudomorphine, γ-pseudomorphine gives a tetra-acetyl derivative, but gives only a monomethyl-ether monomethiodide under conditions under which morphine yields dimethylmorphine methiodide. The basic γ-pseudomorphine methiodide-methohydroxide results from the oxidation of γ-isomorphine methiodide [56].

Reduction of γ-isomorphine [III] affords a monophenolic dihydrocompound and a diphenolic tetrahydrocompound [IV] [57] (see Chap. II). In the same way reduction of γ-pseudomorphine hydrochloride in glacial acetic acid using a platinum oxide catalyst yields tetrahydro-γ-pseudomorphine (which can be prepared by the oxidation of dihydro-γ-isomorphine), whilst reduction of the base in dilute acetic acid affords

octahydro-γ-pseudomorphine. Morphine-γ-isomorphine is reduced with the absorption of three moles of hydrogen [56].

Oxidation of dihydrodesoxymorphine-D (see Chap. IX) leads to tetrahydrodidesoxypseudomorphine [56].

It has been claimed that pseudomorphine is a product of the degradation of morphine in the body [58], but this has been challenged [59].

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Pseudomorphine·$3H_2O$	D. c. 327	NH_4OH	plates	..	..	..	5
— hydrochloride·xH_2O	D. c. 350	..	..	−103·18	24	H_2O	32, 60
— basic hydrochloride·xH_2O	..	..	..	..	..	..	12
— hydrobromide	..	..	prisms	..	..	..	60
— hydriodide·$2H_2O$	..	..	yellow cryst.	..	..	.. ..	30, 12
— sulphate·$8H_2O$	..	H_2O	plates	..	..	..	5, 12
— dichromato·$6H_2O$	..	..	prisms	..	..	..	12, 60
— platinichloride·$8H_2O$	..	..	..	..	..	..	12
— mercurichloride	..	..	prisms	..	..	..	30
— oxalate·$8H_2O$	..	..	..	..	..	..	12, 30
— bitartrate·$6H_2O$	..	..	needles	..	..	..	12, 30
— dimethiodide·$4H_2O$	..	H_2O	yellow cryst.	..	..	..	53
— methiodide-methohydroxide	294d.	H_2O	plates	..	..	..	53, 54
— dimethohydroxide·$7H_2O$	..	..	..	..	..	..	53
— methosulphate·$4H_2O$	..	H_2O	yellow plates	..	..	..	53
Tetra-acetylpseudomorphine·$8H_2O$	276	Et_2O	prisms	..	..	..	12, 51
— hydrochloride	..	..	..	..	..	..	12, 51
— platinichloride·$6H_2O$	..	..	..	..	..	..	12
Di and tribenzoylpseudomorphine	not crystalline			..	..	..	52
Pseudomorphine methyl ether·$7H_2O$	> 280	pptd.	needles	..	..	..	52
— hydrochloride·$4H_2O$	..	..	plates	..	..	..	52
— sulphate·xH_2O	..	..	needles	..	..	..	52
— platinichloride	..	pptd.	..	..	..	..	52
— dimethiodide·$4H_2O$	..	H_2O	prisms	..	..	..	52
— methiodide-methohydroxide·$6H_2O$	..	H_2O	plates	..	..	..	52
— tribenzoyl derivative	..	..	amorph.	..	..	..	52
— triacetyl derivative	..	..	..	..	..	..	52
Tetrahydropseudomorphine	300–302	..	..	−85·9	26	*N*·HCl	56
— monotartrate·$5H_2O$	..	..	..	−54·4	25	H_2O	56
Pseudomorphine-6:6′-dimethyl ether	250–252	..	..	−192	27	10% HOAc	56
α-pseudomorphine	276	..	..	+6·2	24	*N*·HCl	56
β-pseudomorphine	272	..	..	−77	25	*N*·HCl	56
γ-pseudomorphine·$3H_2O$	282–283	conc. NH_4OH	prisms	+44·8	24	*N*·HCl	56
— dihydrochloride·$2\frac{1}{2}H_2O$	..	H_2O	..	+46·4	23	H_2O	56
— dihydrobromide·$2H_2O$	..	H_2O	..	+39·0	23	H_2O	56
— dihydriodide·H_2O	..	H_2O	..	+35·3	24	H_2O	56
— diperchlorate·$2H_2O$	..	EtOH/H_2O	..	+49·4	23	H_2O	56
— monosulphate·$3H_2O$	..	70% EtOH	..	+29·6	25	H_2O	56
— dibenzoate	..	..	..	+42·5	23	H_2O	56
— disalicylate	..	..	..	+40·4	23	60% EtOH	56
— monotartrate	..	H_2O	..	+43	23	H_2O	56
— dimethiodide·$3H_2O$	..	H_2O	..	+31·1	24	H_2O	56
— methiodide-methohydroxide·$5H_2O$	..	H_2O	..	+45·7	25	H_2O	56
Tetra-acetyl-γ-pseudomorphine	189–191	iso Pr_2O	prisms	+57·5	26	EtOH	56
— dihydrobromide·$4H_2O$	..	..	..	+72·6	22	H_2O	56
— dihydriodide·$3H_2O$	..	..	..	+62·4	22	H_2O	56
— diperchlorate·$3H_2O$	..	..	..	+57·7	25	H_2O	56
— dimethiodide	..	..	..	+61	21	H_2O	56
γ-pseudomorphine methyl ether	..	..	..	..	..	..	56
— dioxalate	..	..	needles	−5·6	23	H_2O	56
— monomethiodide	..	..	..	+113·1	25	H_2O	56
Tetrahydro-γ-pseudomorphine	254	NH_4OH	..	+134·3	26	*N*·HCl	56

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Tetrahydro-γ-pseudomorphine sulphate	..	H_2O	..	+20·9	..	H_2O	56
Octahydro-γ-pseudomorphine	..	..	..	..	..	..	56
— dihydrochloride	..	H_2O	..	+8·9	25	H_2O	56
— dihydrobromide	..	H_2O	..	+8·2	23	H_2O	56
— diperchlorate	..	H_2O	..	+6·3	23	H_2O	56
Morphine-γ-isomorphine	268–269	NH_4OH	..	−26·4	24	N·HCl	56
Tetrahydrodidesoxypseudomorphine $2H_2O$	318	..	..	−13·4	27	N·HCl	56

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IV

CODEINE AND ITS ISOMERS

CODEINE

Occurrence

Codeine, first isolated by Robiquet in 1832 [1–2], occurs in opium, of which it forms 0·2–0·8 per cent. [3], a higher figure (2–4 per cent.) being recorded for Manchurian opium [4]. It appears in the plant thirty days after the sprouting of the seed and is the second alkaloid to be formed [5]. The codeine content of the poppy-seed capsules seems to be equal to, or greater than, that of opium [6]. Kerbosch [5] states that poppy seeds contain no codeine, but patents have been granted covering the extraction of the alkaloid from them [7–8].

Isolation

Codeine may be isolated from opium by the 'Gregory process' [9], in which the concentrated aqueous opium extract is treated with a concentrated solution of calcium chloride, when calcium meconate, lactate, and sulphate are precipitated and removed, when the filtrate on concentration deposits the 'Gregory salt', a mixture of the hydrochlorides of morphine and codeine. This is purified, dissolved in water, and the morphine precipitated by ammonia, when the codeine remains in solution from which it is extracted by benzene, or the solution concentrated to the point at which a mixture of codeine hydrochloride and ammonium chloride separates. Other procedures for the isolation of codeine are available [7, 8, 10–22 inc.], critical summaries of which are given by Kanewskaja [23] and Barbier [24]. Codeine may be separated from neopine (see Chap. VII) through the sulphate [25] and from morphine by chromatography [26–29]. Most of the codeine used commercially is prepared by the methylation of morphine (see below).

Physical Properties

Crystallized from ether or benzene codeine is obtained as prisms, from water or aqueous alcohol as rhombic prisms (hydrated) [30] or octahedra [31], and as rhombohedra from carbon disulphide. Gaubert [32] claimed that above 60° C. it crystallizes as rhombic hemihedra, but below 60° C. as four kinds of spherulites, but the cooling curve gives no evidence of the existence of the latter four forms [33]. The hydrated base effloresces to some extent and melts under boiling water.

Crystal measurements [34–38], density [38–39], and refractive indices [38, 40–41] have been determined. Codeine is readily soluble in alcohol [42], chloroform [42], acetone [42], amyl alcohol [43], warm anisole [44–45], less soluble in benzene [42], ether [42], and sparingly soluble in carbon tetrachloride [46], and water [2, 47–48]. A table of solubilities is given by Small and Lutz [49].

Codeine may be purified by recrystallization from benzene or aqueous alcohol, by distillation or vacuum sublimation [50–55], by adsorption of its salts on alumina, when elution provides the base [56], and by filtration of its solution in benzene and chloroform through a layer of sodium sulphate over calcium hydroxide [57]. The adsorption of codeine on active charcoal has been studied by Drevon [58].

The specific rotation of the base has been variously reported as $(\alpha)_D^{15} = -135{\cdot}9°$ (90 per cent. EtOH); $-137{\cdot}75$ (80 per cent. EtOH) and $-111{\cdot}5°$ ($CHCl_3$) [59]; $(\alpha)_D = -118{\cdot}2°$ (EtOH) [60, 61]; $(\alpha)_D = -133{\cdot}18°$, $-130{\cdot}34°$ [62]. The rotations of numerous salts have been measured by Tykociner [63]. Codeine hydrochloride has been reported to exhibit mutarotation in water and in alcohol [64].

Codeine is a strong mono-acid base and its solutions turn litmus blue, phenolphthalein pink, and helianthin yellow [65]; it is incompletely precipitated from its salts by ammonia. The neutral point of a codeine-hydrochloric acid titration is at p_H 4·93, so methyl red can be used as indicator [66–67]; potentiometric titrations can also be used [68–72].

DETECTION

The following colour tests for codeine have been recorded.

Reagent	*Colour*	*References*
conc. H_2SO_4 + $FeCl_3$	blue $\xrightarrow{150°\,C.}$ dirty green	73–75
conc. H_2SO_4 + conc. HNO_3	pale green → violet-green	76
conc. H_2SO_4 + $KReO_4$	yellow-green → violet	77
conc. H_2SO_4 + *p*-dimethylaminobenzaldehyde	blood red	78
conc. H_2SO_4 + sodium arsenite	green or blue $\xrightarrow{NaOH}$ yellow	79–80
conc. H_2SO_4 + ammonium selenite	brilliant green	81–82
conc. H_2SO_4 + 30% H·CHO	red-violet → blue-violet	83–85
conc. H_2SO_4 + sodium arsenate	dark blue	86
conc. H_2SO_4 + 10% KBr, 100° C.	yellow → brown → green	87
conc. H_2SO_4 + *ammonium molybdate*	green → red-brown	88
conc. H_2SO_4 + $(NH_4)_2S_2O_8$	orange	88
conc. H_2SO_4 + benzidine	yellow → brown → dark green	89
conc. H_2SO_4 + benzidine add to water	violet (extracted by $CHCl_3$)	89
conc. H_2SO_4 + NaOCl solution	sky-blue	90
conc. H_2SO_4 + ammonium uranate	blue	91
mannitol oxidized by Br/H_2O then conc. H_2SO_4	violet-rose	92
moisten with conc. sucrose solution, then add conc. H_2SO_4	purple $\xrightarrow[\text{min.}]{80}$ red	93–94

Reagent	*Colour*	*References*
vanillin + 0·5N·H_2SO_4 evaporate	blue-violet	95–96
basic magnesium hypochlorite in HOAc layered on to conc. H_2SO_4	pale green stripe over lilac layer, over green-brown	97
boil + PbO_2/HOAc, filter	pale yellow	98
boil + PbO_2/HOAc, filter, add conc. H_2SO_4	intense blue-violet	98
HNO_3 then alcoholic KOH	brick red	99–100
solarized uranium salts	intense blue	101–2
Br/H_2O added to slightly acid soln. of base until faint yellow, then add excess NH_4OH	rose	103
Antimony trichloride	pale green	104–5

Colour tests are also given by Fulton [106]. Precipitation tests are given by references [107–14 inc.], microprecipitation tests by references [5, 114–20 inc.], and other methods of detection and identification of codeine by references [121–42 inc.].

Estimation

Codeine has been estimated by volumetric titration with mercuric salts [143–5], potentiometric methods [146–7], iodimetrically [148], colorimetrically [149], as silico-tungstate [150] and in other ways [29, 42, 151–9 inc.].

Composition

Numerous empirical formulae were initially suggested for codeine [76, 160–4], the correct composition corresponding to $C_{18}H_{21}O_3N \cdot H_2O$ for the hydrated base finally being determined by Gerhardt [165–6] and Anderson [167–8]. It was subsequently suggested by Wright [169–70] that the formula be doubled, but no necessity for this has ever been revealed.

Codeine is a tertiary base, readily forming quaternary salts [171–7 inc.], that with ethylene dibromide being dimolecular [172–3]. The molecule also contains one alcoholic group and one methoxyl group, and was eventually recognized as the methyl ether of morphine [178–80], as was finally proved by Grimaux [181–6] and by Hesse [187].

Preparation from Morphine

Most of the codeine used commercially is prepared by the methylation of morphine, for which the following methods have been used:

(*a*) Methylation of morphine or its alkali salts by salts of methyl-sulphuric acid [188–9].

(*b*) Methylation with methyl sulphite and alkali [190].

(*c*) Methylation with sodium alkoxides and methyl sulphate [191].

(*d*) Methylation with sodium methoxide and trimethylphosphate [192], methyl nitrite [193], or methyl esters of sulphonic acids [194].

(*e*) Methylation of morphine-N-oxide followed by reduction [195].

(*f*) Methylation with diazomethane [196–8] and modifications of this [199–200].

(*g*) Methylation by aryltrimethylammonium hydroxides [201–8 inc.].

Of these the most satisfactory is (*g*) as no quaternary salts are formed and the aromatic amine produced during the reaction is easily removed by steam distillation. The process may be used on a manufacturing or laboratory scale. Rodionov gives the following details for a laboratory preparation [202].

Dimethylaniline (18 g.) and methylbenzenesulphonate (25 g.) are heated together and allowed to cool. A solution of sodium (4·5 g.) in alcohol (45 ml.) is added to the resulting quaternary salt (55 g.), the solution filtered, and anhydrous morphine (45 g.) added. The alcohol is removed at 110° C. and the mixture maintained at this temperature for one hour, acidified with 15 per cent. acetic acid and dimethylaniline removed by steam distillation. Codeine is recovered from the solution by adding sodium hydroxide and extracting with benzene.

Demethylation

Codeine cannot be demethylated to morphine chemically.† If it is heated with hydriodic acid no methyl iodide is evolved [169, 209–11], but the latter is evolved copiously when codeine is heated with hydriodic acid and red phosphorus [169, 211–212], the other products being intractable, varnish-like substances obtainable in the same way from morphine [213] and supposed to consist of polymers of morphine and codeine. These so-called polymers were also obtained during the action of hydrochloric and hydrobromic acids on the bases, and were the subject of an inconclusive series of investigations by Wright [169, 170, 213–14 inc.]. There is no real evidence for the existence of the polymers. Biological demethylation of codeine by various enzymes and by the glycerol extract of the mould *Polyporus hispidus* in nine to twelve days at 25–37° C. has been reported [225].

Esters

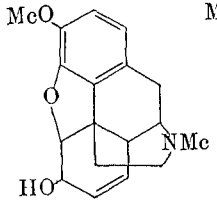
The alcoholic hydroxyl group of codeine can be acetylated by glacial acetic acid or acetic anhydride [226] to give acetylcodeine, the nitrogen ring being stable [227]. Numerous other esters have been prepared [223, 228–33].

The Halogenocodides

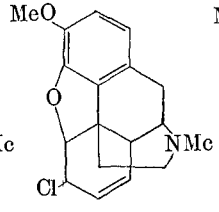
When codeine [I] [234] is heated with concentrated hydrochloric acid [235–6], treated with phosphorus pentachloride and/or oxychloride [237] or thionyl chloride [238–40], the hydroxyl group is replaced by chlorine and α-chlorocodide [II] is formed. The structure of this has

† This has now been accomplished—see Chap. XXVII.

been elucidated by its reduction to 6-chlorodihydrocodide [III, R = Cl] [240], identical with the substance obtained by the action of phosphorus pentachloride on dihydrocodeine [III, R = OH] [241]. α-Chlorocodide can be isomerized on heating alone [242], in an inert solvent [238], or with concentrated hydrochloric acid [243] to β-chlorocodide, believed to be [IV]. Bromocodide, believed to be analogous to [IV], results from the action of concentrated hydrobromic acid [214, 216–17, 221], phosphorus tribromide [244–5], or thionyl bromide [246] on codeine, and iodocodide is formed by the action of potassium iodide on bromo- or α-chlorocodide [247–8].



[I]



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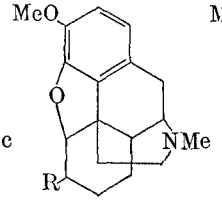
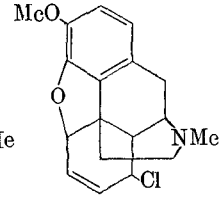
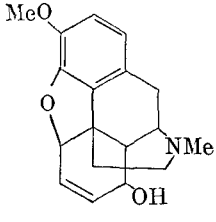


[III]

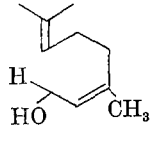


[IV]

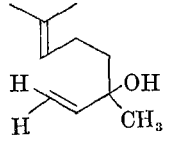
Hydrolysis of iodo and α- and β-chlorocodide gives a mixture of three isomers of codeine, isocodeine, ψ-codeine, and allo-ψ-codeine, the last two named having the alcoholic group at C-8 [V], whilst isocodeine has it, like codeine, at C-6 [237, 243–7, 249–50]. Bromocodide on hydrolysis apparently affords only isocodeine and allo-ψ-codeine [243–5, 251–3]. The conversion of codeine to ψ- and allo-ψ-codeine in this way is analogous to the conversion of geraniol [VI] to linalool [VII] [234, 254]. The halogenocodides are discussed in Chapter VIII.



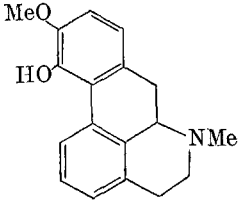
[V]



[VI]



[VII]



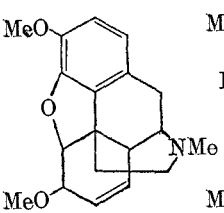
[VIII]

APOCODEINE

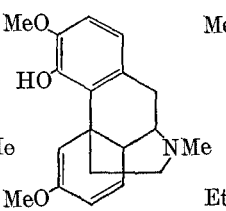
Apocodeine [VIII], the 3-methylether of apomorphine, is formed when codeine is heated with zinc chloride [209–10, 219, 225], anhydrous oxalic acid [256–9], or phosphoric acid [240]. (Cf. the preparation of apomorphine from morphine, Chapters II and XXII.) A substance given the name apocodeine was prepared by treating bromo- and α-chlorocodides with alkaline reagents [172, 260], but this is not an analogue of apomorphine and is probably a complex mixture [261].

Codeine Methyl Ether

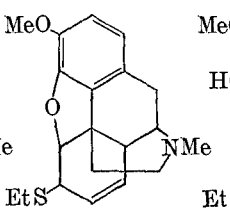
Methylation of the alcoholic group of codeine may be accomplished by cold methyl sulphate or iodide and alkali, the product being the quaternary salt of codeine methyl ether [262], conversion of which to the methochloride followed by dry distillation affords the base [263], which may be obtained also by methylation and reduction of codeine (or morphine)-N-oxide [263] and by sodium amalgam reduction of methylcodeine benzyl iodide [264]. Codeine methyl ether [IX] undergoes rearrangement to thebainone-A enol methyl ether [X] on heating with sodium ethoxide [265]. Codeine, isocodeine methyl ether, and dihydrocodeine methyl ether are recovered unchanged under the same conditions [265], but α-ethylthiocodide [XI] readily undergoes a similar rearrangement to β-ethylthiocodide [XII] [242, 266] (see Chap. XVII). The driving force of this reaction is doubtless the tendency to achieve a conjugated system. Codeine undergoes a similar transformation under the influence of noble metal catalysts (see below).



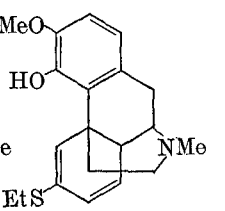
[IX]



[X]



[XI]



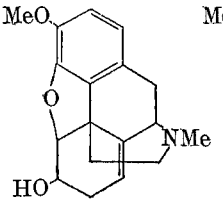
[XII]

Reduction of Codeine

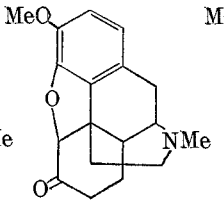
(*a*) Catalytic hydrogenation of codeine proceeds rapidly with saturation of the 7:8 double bond and formation of dihydrocodeine [III, R = OH] [267–9], also obtainable by the electrolytic reduction of codeine [270], the catalytic reduction of neopine [XIII] [271], the methylation of dihydromorphine [272], and the catalytic reduction of dihydrocodeinone [XIV] [273]. By the latter method the optical antipode of dihydrocodeine may be prepared from the sinomenine series [274–5] (see Chap. XXVII). Both enantiomorphs can be demethylated to the corresponding dihydromorphines [269, 274–5]. Dihydrocodeine methyl ether is identical with tetrahydrothebaine [276–8] (see Chap. XIII).

(*b*) Reduction of codeine with sodium and alcohol was reported to be ineffective by Vongerichten [279], but Knorr in this way obtained high-melting phenolic substances that he believed to be dimolecular [280]. Codeine is an allylic alcohol, and sodium and alcohol reduction could proceed by elimination of the alcoholic group to give desoxycodeine-C [XV], which is known to be reduced in this way to a mixture of dihydrodesoxycodeine-B [XVI] and dihydrodesoxycodeine-C [XVII] [248, 281].

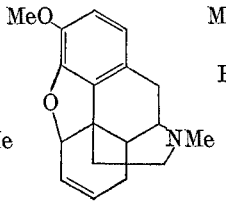
This type of reduction would be expected to proceed more readily with sodium, liquid ammonia, and alcohol, but so far only codeine has been recovered from this reaction [282]. Under the same conditions, however, codeine methiodide is reduced to a phenolic base, m.p. 156° C., the analytical data for which are consistent with structures [XVIII] and [XIX]. This reaction is being investigated further [282].



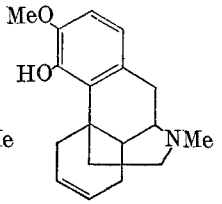
[XIII]



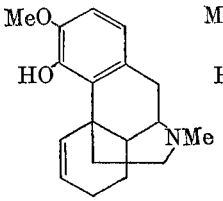
[XIV]



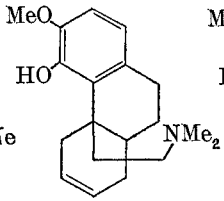
[XV]



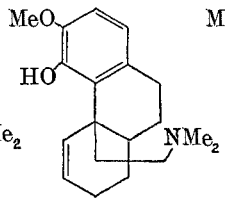
[XVI]



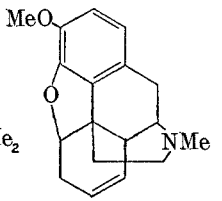
[XVII]



[XVIII]



[XIX]



[XX]

(*c*) Desoxycodeine-E [XX] is obtained by the reduction of *p*-toluenesulphonylcodeine with lithium aluminium hydride [283–4] (see Chap. IX).

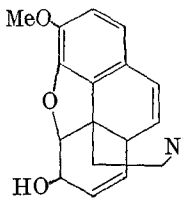
Hofmann Degradation

Alkaline degradation of codeine methiodide affords α-codeimethine [XXI] [185, 285], which can be isomerized by alcoholic alkali to β-codeimethine [XXII] [187, 286–7], also obtainable by the degradation of neopine [XIII] methiodide [271]. The degradation of codeine ethiodide follows a similar course [288]. These bases suffer dehydration and loss of the basic side-chain when heated with acetic anhydride and sodium acetate (when acetylmethylmorphol [XXIII] is formed [187, 289–90]), and when subjected to further Hofmann degradation (which leads to methylmorphenol [XXIV] [290–2]). The resulting aromatic phenanthrene derivatives are of considerable importance in the elucidation of the basic structure of the morphine alkaloids and are discussed in detail in Chapter XXVII.

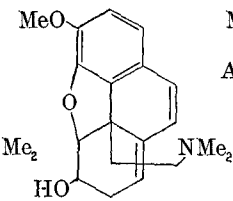
Codeine methyl ether affords α-codeimethine methyl ether on Hofmann [262–3] or Emde [294] degradation.

Dihydrocodeine [III, R = OH] can be degraded to dihydrocodeine methine [XXV] [241, 293, 295–6], which in turn can be degraded to

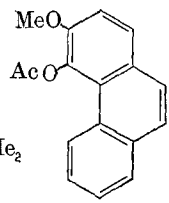
a mixture of 6-hydroxy-13-vinylhexahydromorphenol methyl ether [XXVI, R = H] and 6-methoxy-13-vinylhexahydromorphenol methyl ether [XXVI, R = Me] [293, 295].



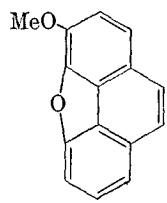
[XXI]



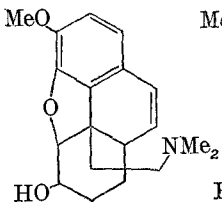
[XXII]



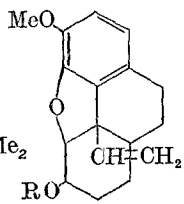
[XXIII]



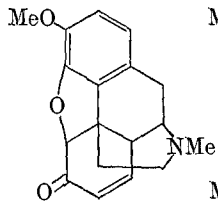
[XXIV]



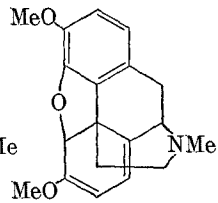
[XXV]



[XXVI]



[XXVII]



[XXVIII]

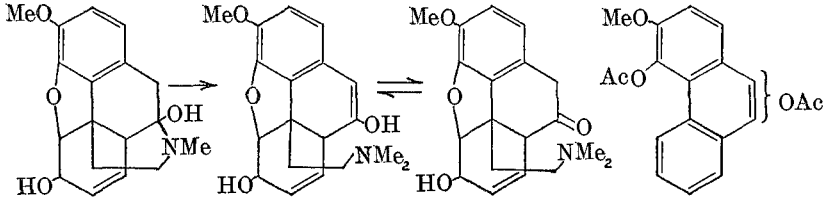
The codeimethines and their derivatives are discussed in detail in Chapter VI.

Oxidation

(*a*) Oxidation of codeine with potassium permanganate in acetone [297], chromic acid in sulphuric [297] or acetic acid [298–9], and the oxidation of codeine methyl ether [300] yields the ketone codeinone [XXVII] which is also formed in small amount during the hydrolysis of thebaine [XXVIII] [301–2]. Hydrogenation of codeinone gives dihydrocodeinone [XIV] [269, 295, 299], which, contrary to a statement by Merck and Co. [303], is not accessible by the oxidation of dihydrocodeine with chromic acid or permanganate [241, 269], but can be prepared from this base by Oppenauer oxidation [304]. Acetic anhydride degradation of codeinone yields 3-methoxy-4:6-diacetoxyphenanthrene with loss of the basic side-chain, thus enabling the position of all three oxygen atoms in codeine to be determined [305]. Codeinone and its derivatives are discussed in Chapter X.

(*b*) Oxidation of codeine with chromic and sulphuric acids also yields a small amount (5–10 per cent.) of a hydroxycodeine [297, 306] containing two alcoholic hydroxyl groups, one as in codeine at C-6, and the other either at C-9 [XXIX] or C-10 as is shown by its degradation to a methoxydiacetoxyphenanthrene [XXXII] [307] that loses an acetoxy-group on oxidation to a quinone [308]. As a hydroxyl group is situated at C-9 or C-10, the fact that hydroxycodeine methiodide can be degraded to a methine base that is a ketone [XXXI] [307, 309–10] clearly

shows that the nitrogen atom in hydroxycodeine and therefore in codeine is attached to position 9 or 10 of the phenanthrene nucleus.

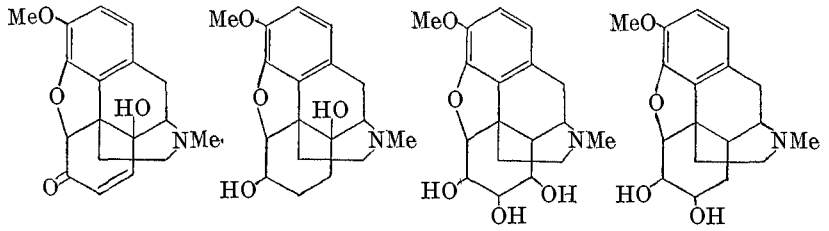


[XXIX] [XXX] [XXXI] [XXXII]

The precise location of the new hydroxyl group in hydroxycodeine remains uncertain; against the 9-hydroxy structure [XXIX] may be cited the fact that it does not show the properties of a carbinolamine [306]. 3:4:9-trimethoxyphenanthrene has been prepared by synthesis [311], but [XXXII] has not been converted to a trimethoxyphenanthrene for comparison.

A hydroxycodeine has been prepared by the zinc and acetic acid reduction of 14-hydroxycodeinone [XXXIII] [312–14], but its structure is uncertain, as on further reduction it gives hydroxydihydrocodeine-A, which is not identical with either 14-hydroxydihydrocodeine-B or C [XXXIV] obtained by the catalytic hydrogenation of [XXXIII] [315] (see Chap. XVIII).

(*c*) Cold 1 per cent. potassium permanganate oxidizes the double bond of codeine giving dihydroxydihydrocodeine [XXXV], which is readily soluble in water by virtue of its three hydroxyl groups and can be acetylated to a triacetyl-derivative [316]. In a similar manner (+) and (−) desoxycodeine-C [XV] can be oxidized to 7-hydroxydihydrocodeine [XXXVI] [317].

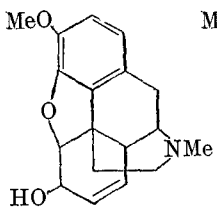


[XXXIII] [XXXIV] [XXXV] [XXXVI]

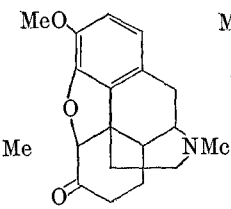
(*d*) Oxidation of codeine with mercuric acetate in aqueous solution proceeds slowly in the cold, rapidly on heating, the optical rotation rising first to a maximum and then falling. The product contains mercury, which cannot be removed except by treatment with formic acid, when 80 per cent. of the original codeine is regenerated. Dihydrocodeine is only oxidized in this way in hot solution, whilst codeine methiodide resists oxidation altogether [318].

Catalytic Rearrangement

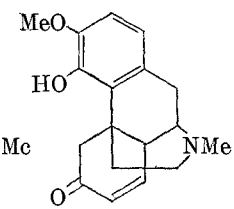
Codeine [I] on heating in alcohol with [319–23] or without [324] acid, with [319–21] or without [322–4] hydrogen, in the presence of noble metal catalysts, undergoes rearrangement to dihydrocodeinone [XIV]. The yields claimed for the transformation are up to 95 per cent. [323], but Rapoport [304] was unable to obtain yields in excess of 50 per cent. Thebainone-A [XXXVII] is a by-product in this reaction, and can be made the main product by modifying the conditions [325] (cf. the conversion of codeine methyl ether to thebainone-A enol methyl ether by sodium ethoxide).



[I]



[XIV]



[XXXVII]

Substitution in the Aromatic Nucleus

(*a*) Bromination of codeine can be effected by bromine water [167–8, 237, 326] or hydrobromic acid and hydrogen peroxide [327], the product being 1-bromocodeine, identical with the substance obtained by the methylation of 1-bromomorphine [328]. The position of the bromine atom was demonstrated by the degradation of 1-bromocodeine through 1-bromo-α-codeimethine and 1-bromo-3-methoxy-4-acetoxyphenanthrene to 1-bromo-3:4-dimethoxyphenanthrene, identical with an authentic specimen [328].

Chlorination of codeine with gaseous chlorine or chlorine water gives resinous substances [167–8], but 1-chlorocodeine can be prepared by the action of hydrochloric acid and potassium chlorate on codeine [167–8] or of 30 per cent. hydrogen peroxide and formic acid on codeine hydrochloride [327].

Both 1-chloro and 1-bromocodeine give the corresponding dihydrocompounds on catalytic reduction; further reduction involves loss of the halogen [327].

With iodine chloride codeine gives a very unstable di-iodocompound [112, 329], and highly coloured superiodides with iodine [330–4].

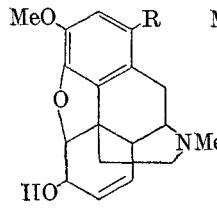
(*b*) Nitration of codeine to 1-nitrocodeine can be accomplished by dilute nitric acid [116–17, 335]. Reduction of the nitrocompound affords 1-aminocodeine, which can be converted through the diazonium salt to 1-hydroxycodeine [336–9]. When 1-nitrocodeine is allowed to

stand with concentrated nitric acid at 20° C. for four days and at 60° C. for ten hours, nitrocodeinic acid is formed. The same compound can be prepared from 1-nitro-ψ-codeine. When heated with hydrochloric acid at 140° C., nitrocodeinic acid $C_{16}H_{18}O_9N_2$ is converted to nitronorcodeinic acid $C_{15}H_{16}O_9N_2$, and with hydriodic acid it gives aminonorcodeinic acid $C_{15}H_{18}O_7N_2$. Esterification of nitronorcodeinic acid by diazomethane yields $C_{18}H_{20}O_8N_2$, containing three methoxyl groups, and this on heating with hydrochloric acid gives $C_{18}H_{20}O_8N_2 \cdot HCl$ containing two methoxyls [340].

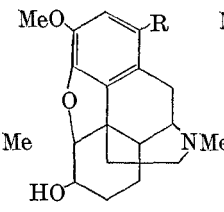
An isomer of 1-nitrocodeine, α-nitrocodeine can be prepared from codeine-N-oxide sulphonic acid. It gives 1-aminocodeine on reduction. Nitration of dihydrocodeine [241] and dihydrocodeine sulphonic acid [341] gives 1-nitrodihydrocodeine.

(*c*) 2-Nitrocodeine results from methylation [342] of the substance obtained when nitrous fumes are passed into morphine hydrochloride solution at about —2° C. (originally thought to be 2-nitrosomorphine [337], but subsequently shown to be a nitro-compound [343]). 2-Nitrocodeine can be reduced to 2-aminocodeine, which can be converted through the diazonium salt to 2-bromocodeine, all these compounds being different from the 1-substituted isomers [342].

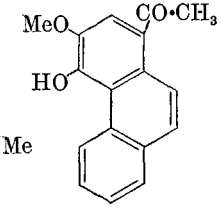
(*d*) 1-Acetocodeine [XXXVIII, R = $CO \cdot CH_3$] is obtained as its acetyl ester by the action of acetic anhydride and concentrated sulphuric acid on codeine [344–5]. (Causse [346], believing codeine to contain a carbonyl group, heated it with zinc-dust, sodium acetate, and acetic anhydride, thereby claiming to have reduced the C=O to CH—OH and produced a diacetyl-derivative. Under these conditions Knorr [345] obtained only 6-acetylcodeine.) 1-Acetocodeine cannot be nitrated. The following reduction products have been prepared, free or as deri-



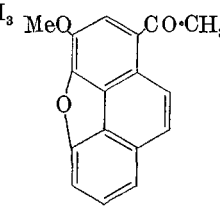
[XXXVIII]



[XXXIX]



[XL]



[XLI]

vatives: 1-acetodihydrocodeine [XXXIX, R = $CO \cdot CH_3$]; 1-(1′-hydroxyethyl)-codeine [XXXVIII, R = $CH \cdot (OH) \cdot CH_3$], 1-(1′-hydroxyethyl)-dihydrocodeine [XXXIX, R = $CH \cdot (OH) \cdot CH_3$), and 1-ethyldihydrocodeine [XXXIX, R = Et] [347]. 1-Acetocodeine has been degraded to 1-acetyl-3-methylmorphol [XL] [345] and to 1-acetyl-3-methylmorphenol [XLI] [347].

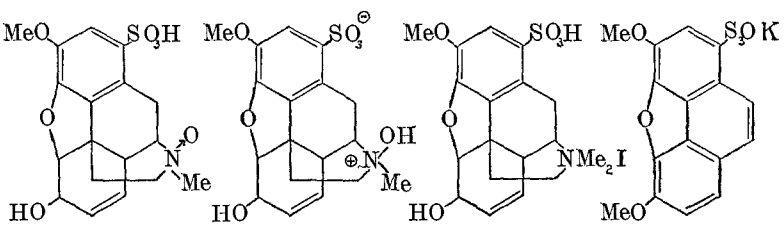
Codeine-N-Oxide and its Derivatives

Like other tertiary amines, on heating with 30 per cent. hydrogen peroxide codeine is converted to an N-oxide; this is reduced to codeine by sulphurous acid [348]. A dimolecular oxide $C_{36}H_{44}O_9N_2 \cdot 7H_2O$ is obtained from the not too prolonged treatment of the base with 1·5 per cent. hydrogen peroxide on the water-bath; it is transformed to a monomolecular oxide by heating with alcohol and concentrated hydrochloric acid [349].

When codeine-N-oxide is sulphonated, two isomeric codeine-N-oxide sulphonic acids, α- and β-, are obtained; the former being transformed to the latter by alkali. Both yield the same codeine sulphonic acid on reduction with sulphurous acid. α- and β-Codeine-N-oxide sulphonic acids and codeine sulphonic acid are converted to codeine by superheated steam and to β- and γ-codeine sulphonic acids by cold concentrated sulphuric acid [339, 350].

Nitration of codeine sulphonic acid affords 1-nitrocodeine [339, 350], whilst nitration and sulphurous acid reduction of α-codeine-N-oxide sulphonic acid gives α-nitrocodeine, which can be reduced to 1-aminocodeine [339, 350, 341]. Bromination of the α-N-oxide sulphonic acid gives a perbromide of unknown constitution [339, 350] that is reduced to 'bromocodeine dibromide' $C_{18}H_{20}O_3NBr_3$ [295].

Catalytic reduction of α-codeine-N-oxide sulphonic acid affords α-dihydrocodeine sulphonic acid, which with water at 100° C. gives dihydrocodeine, and with nitric acid gives 1-nitrodihydrocodeine. Catalytic reduction of β-codeine-N-oxide sulphonic acid and of codeine sulphonic acid gives β-dihydrocodeine sulphonic acid, which gives the same products as the α-isomer with superheated steam and with nitric acid [341]. Dihydrocodeine-N-oxide gives only one sulphonic acid [295, 341], and this is reduced by sulphurous acid to β-dihydrocodeine sulphonic acid [341]. With bromine the N-oxide sulphonic acid gives a substance $C_{18}H_{22}NO_3Br$, presumably 1-bromodihydrocodeine [295].



[XLII] [XLIII] [XLIV] [XLV]

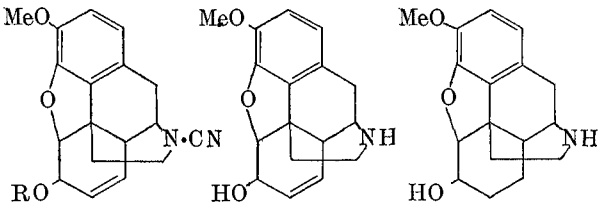
The isomeric codeine-N-oxide sulphonic acids are not derived from ψ-codeine, as ψ-codeine-N-oxide sulphonic acid is different from both [341]. It has been suggested that their structures are [XLII] and [XLIII] [330].

Hofmann degradation of codeine sulphonic acid methiodide [XLIV] affords tetramethylethylenediamine and a substance $C_{16}H_{11}SO_6K$, possibly [XLV] [339, 350], whilst degradation of β-dihydrocodeine sulphonic acid methohydroxide affords tetramethylethylenediamine, but the nitrogen-free product was not isolated [341].

β-Codeine-N-oxide sulphonic acid on heating with potassium chromate is converted to norcodeine sulphonic acid, which yields norcodeine on heating with superheated steam [352]; (the nature of this change was not at first appreciated [339, 350]). Codeine-N-oxide likewise yields norcodeine and formaldehyde when oxidized with potassium chromate [352].

Norcodeine and its Derivatives

The action of cyanogen bromide on acetylcodeine involves replacement of the N·Me group by N·CN, the product being acetylcyanonorcodeine [XLVI, R = Ac], hydrolysis of which affords cyanonorcodeine [XLVI, R = H] and norcodeine [XLVII] [353–5]. Acetyldihydrocodeine can be converted in the same way to dihydronorcodeine [XLVIII] [353–4], also obtainable by the catalytic reduction of norcodeine [356]. Nitration of cyanonorcodeine gives nitrocyanonorcodeine which can also be prepared from nitrocodeine; it can be reduced to aminocyanonorcodeine and hydrolysed to nitronorcodeine. The latter cannot be prepared by the nitration of norcodeine. Stannous chloride reduction of nitronorcodeine affords aminonorcodeine, which suffers a rearrangement of unknown nature on warming in dilute acid [356].



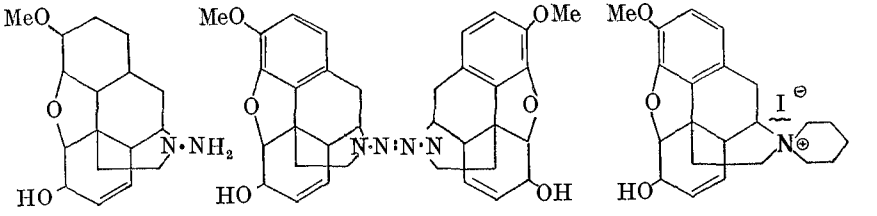
[XLVI] [XLVII] [XLVIII]

Norcodeine can be prepared, as already stated, by the oxidation of codeine-N-oxide by potassium chromate [352].

Codeine reacts with ethylazodicarboxylate to give a yellow addition compound that on warming with N hydrochloric acid yields norcodeine, formaldehyde, and ethyl *s*-hydrazinedicarboxylate [357]. This is a general method for de-alkylating amines [358–9].

Codeine and dihydrocodeine are converted to N-nitrosonorcodeine and N-nitrosodihydronorcodeine respectively on treatment with nitrous acid, and these compounds yield norcodeine and dihydronorcodeine when heated with dilute hydrochloric acid [360]. This is probably the most convenient way of preparing norcodeine.

N-nitrosonorcodeine can also be prepared from norcodeine; on reduction with zinc-dust and acetic acid it yields norcodylhydrazine [XLIX], which forms crystalline derivatives with aldehydes and ketones [356]. Norcodylhydrazine can be oxidized to the tetrazone [L], $C_{34}H_{36}O_6N_4$, by mercuric acetate [356].



[XLIX] [L] [LI]

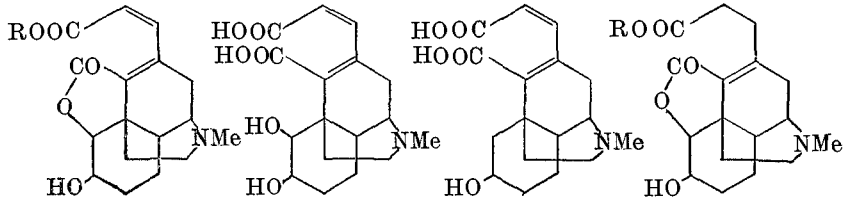
Numerous N-alkylnorcodeines have been prepared, and these can be nitrated, acetylated and chlorinated like codeine [361]. Other N-substituted norcodeines have also been prepared [362–7], and of these N-allylnorcodeine and other $\beta:\gamma$-unsaturated derivatives have an action antagonistic to that of morphine [364, 368]. A dimolecular derivative results from the interaction of norcodeine and *trans* $\Delta^{2:3}$-1:4-dibromobutene [369]. Spirocyclic quaternary salts such as [LI] result from the treatment of norcodeine with pentamethylene iodide, *o*-xylyldibromide, and $\beta:\beta'$ di-iododiethyl ether, and these suffer degradation in alkaline solution with fission of the codeine heterocyclic ring [370] (see Chap. VI).

Ozonolysis

When ozone is passed through a solution of dihydrocodeine in formic acid, α-ozodihydrocodeine [LII, R = Me] is formed. This, on hydrolysis, affords dihydromorphinic acid [LIII], which is also obtained by the hydrolysis of α-ozodihydroethylmorphine [LII, R = Et], the product of ozonolysis of dihydroethylmorphine, showing that ozonolysis involves cleavage of the aromatic nucleus between carbon atoms 3 and 4 [371].

Electrolytic reduction of α-ozodihydrocodeine yields an acid (hydrolysis by the sulphuric acid used as solvent), originally called 5-desoxydihydromorphinic acid [LIV], whilst catalytic reduction gives the corresponding methyl ester [371]. The course of reduction has recently been reinterpreted, and it is now known that catalytic hydrogenation involves saturation of a double bond giving methyl tetrahydromorphilactonate [LV, R = Me], whilst hydrolysis and hydrogenation affords tetrahydromorphilactonic acid [LV, R = H] which can be esterified with the introduction of only one methyl group to [LV, R = Me]. The position of the double bond in [LV] is assumed [246]. Catalytic reduction of dihydromorphinic acid [LIII] had earlier been shown to involve the

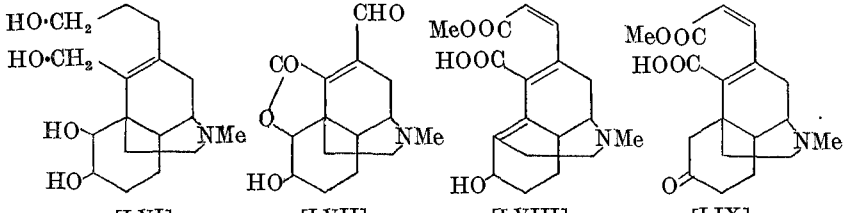
saturation of a double bond [371]. With hydrogen peroxide or ozone [LV, R = Me] gives an amine oxide [372].



[LII] [LIII] [LIV] [LV]

Lithium aluminium hydride reduction of methyl tetrahydromorphilactonate [LV, R = Me] yields tetrahydromorphitetrol [LVI], an isomer of which, tetrahydro-α-isomorphitetrol, differing only in the spatial arrangement of the vicinal diol system, can be prepared from dihydroisocodeine. Oxidation of tetrahydromorphitetrol with lead tetraacetate proceeds three times faster than the oxidation of its isomer, indicating that in the former the vicinal hydroxyl groups are *cis* and in the latter *trans* relative to each other, and hence the 4:5 oxygen bridge and 6-hydroxyl group are in the *cis* configuration in morphine and codeine, and in the *trans* configuration in α-isomorphine and isocodeine [246].

Further ozonolysis of α-ozodihydrocodeine involves rupture of one of the double bonds and loss of methyl glyoxylate, the product being dihydrocodinal [LVII], which can be formed in the same way from α-ozodihydroethylmorphine [373]. β- and γ-ozodihydrocodeines yield β-dihydrodiconal on further ozonolysis [372].



[LVI] [LVII] [LVIII] [LIX]

When α-Ozodihydrocodeine is heated with sodium methoxide and reesterified with hydrochloric acid and methyl alcohol, β- and γ-ozodihydrocodeines are formed. Sodium methoxide causes a change in the lactone bridge and, in addition, hydrolysis of the ester group, so that the products are only isomeric with the original material if esterification is carried out with methyl alcohol, ethyl alcohol giving β- and γ-ozodihydroethylmorphine. The change was interpreted on the Wieland formula for morphine and the isomers allotted *cis* and *trans* forms of [LVIII] [372], but this is reinterpreted on the basis of the Gulland–Robinson formula as [LIX].

Miscellaneous Reactions

(*a*) Codeine is unaffected by Grignard reagents [374], but codeine methyl ether forms simple addition complexes with ethyl- and phenyl-magnesium halides; these are readily decomposed with liberation of the unchanged base [375].

(*b*) Codeine condenses with benzaldehyde in the presence of sodium ethoxide to give a product of unknown constitution [376].

(*c*) Treatment of codeine with formaldehyde and concentrated hydrochloric acid affords an ill-defined varnish-like substance of unknown nature to which the name dicodeylmethane has been given [377]. Codeine has also been reported to react with hydrogen sulphide in the presence of oxygen, but the nature of the product has not been determined [378].

(*d*) With *p*-nitrosodimethylaniline in alcohol codeine condenses to give an intensely coloured substance, codeine violet. This compound, which is soluble in alcohols to give dichroic solutions, will dye silks and wool directly, but the dye is not fast to light. The platinichloride has the composition $Me_2N \cdot C_6H_4 \cdot N \cdot G_7H_{18}Me \cdot NO_4 \cdot H_2PtCl_6$, but the constitution is unknown [379].

(*e*) Codeine reacts with ethyl chloroformate in chloroform in the presence of potassium hydroxide to give a carbethoxy-derivative isolated as bitartrate. In general ethyl chloroformate appears to react with tertiary amines in the same way as does cyanogen bromide, but its sphere of activity is more limited [380].

(*f*) Codeine will form an addition compound with carbon suboxide, in the proportions 1:5, which is stable to oxygen and water [381], with phenolphthalein [382], and with *p*-acetamidophenol [383]. Codeine forms double salts with narcotine [384–5], and salts with numerous barbituric acid derivatives [386–92], of therapeutic interest.

(*g*) Sodium and potassium derivatives of codeine are reported to result from boiling the alkaloid and the metals in benzene [393].

Thermochemical studies have been made by Leroy [394–5]. The absorption spectrum of codeine in the visible [396–7] and in the ultra-violet [398–9] has been determined. The ultra-violet absorption curve, compared with those of morphine and thebaine is given in Fig. 1. That of ethylmorphine is closely similar [400].

Alkyl and Other Substituted Codeine Derivatives

(*a*) Treatment of codeinone [XXVII] with methyllithium affords 6-methylcodeine [LX], which can be degraded to α- and β-methine bases and to 3-methoxy-6-methyl-4:5-phenanthrylene oxide. It gives only a poor yield of a 6-methylchlorocodide with phosphorus pentachloride,

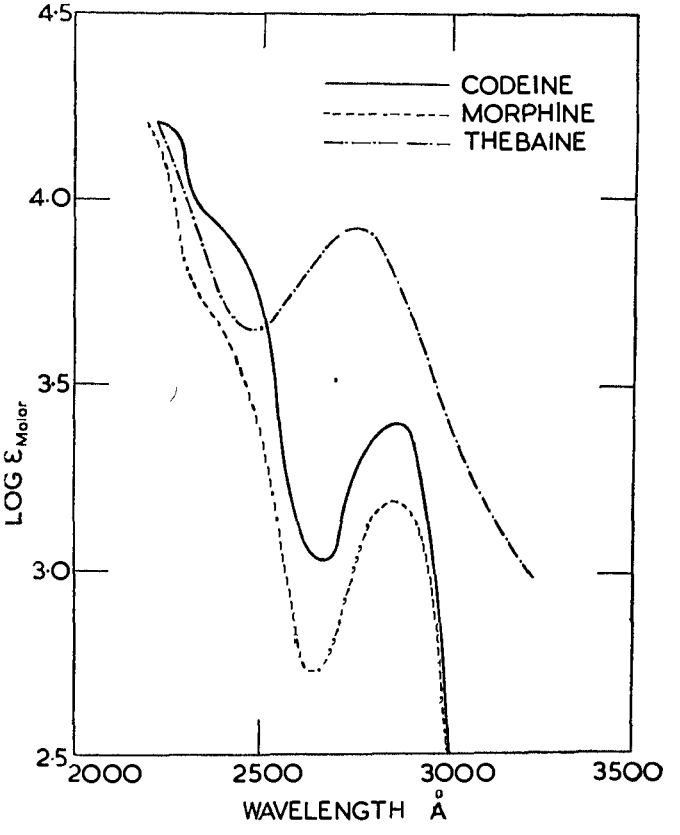
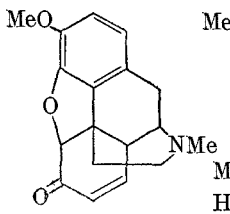


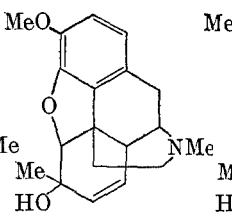
FIG. 1.

which is not remarkable as the alcoholic group of [LX] is both allylic and tertiary [401]. 6-Methyl-, 6-ethyl-, 6-*n*-amyl-, and 6-phenyl dihydrocodeine can be prepared from dihydrocodeinone and the corresponding organo-lithium compound; 1-chloro- and 1-bromodihydrocodeinone react with methyl lithium without elimination of halogen. 6-Methyldihydrocodeine [LXI] can be degraded to a methine base and nitrogen-free product (see Chap. VI) and is dehydrated to 6-methyldesoxycodeine-C [LXII] by boiling with thionyl chloride in chloroform (1-chloro-6-methyldesoxycodeine-C is formed if phosphorus pentachloride is used) [402].

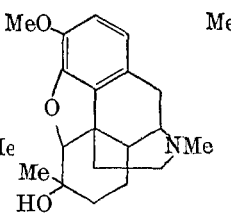
(*b*) When dihydrothebaine [LXIII, R = Me] and dihydrocodeinone enol acetate [LXIII, R = Ac] react with Grignard reagents alkyldihydrothebainones ([LXIV] and/or [LXV]?) are formed, and these can be converted to alkyldihydrocodeinones which can be reduced catalytically to alkyldihydrocodeines [273, 403]. The location of the alkyl groups in these compounds is uncertain; they are discussed in detail in Chapter XIX.



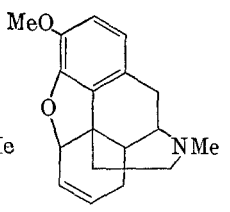
[XXVII]



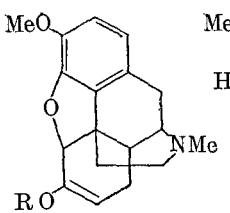
[LX]



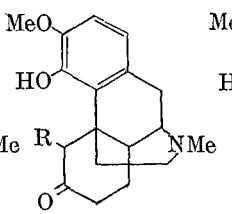
[LXI]



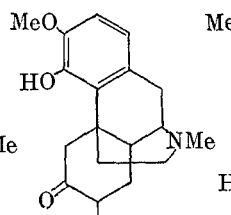
[LXII]



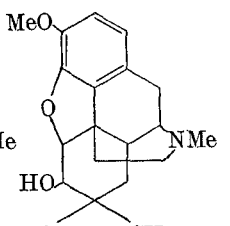
[LXIII]



[LXIV]



[LXV]



[LXVI]

(*c*) 7:7-Bis-[hydroxymethyl]-dihydrocodeine [LXVI] results from the interaction of dihydrocodeinone [XIV], formaldehyde, and calcium oxide in methyl alcohol, when aldol condensation and reduction occur [404].

ISOCODEINE

Isocodeine is one of the products of hydrolysis of α-chlorocodide [244–5], β-chlorocodide [238, 243, 250], bromocodide [244, 252], and iodocodide [247]. (The name was applied to the product of mineral acid hydrolysis of dihydrothebaine-φ by Freund [405], but this was a misnomer, see Chap. XIV.) It is also obtained by the methylation of α-isomorphine [245, 252]. There was some initial confusion regarding the identity of isocodeine [245, 252, 406–7], which forms a molecular compound [m.p. 145–146° C.] with allo-ψ-codeine [244–5, 253], but this was clarified by Lees [245].

That isocodeine differs from codeine only in the spatial arrangement of the —CH·OH— group was shown by the oxidation of both bases to the same ketone, codeinone [XXVII] [305].

Although isocodeine is formed by the hydrolysis of both α- and β-chlorocodide, only the latter can be obtained from the reaction of isocodeine with thionyl chloride [238].

Catalytic reduction of isocodeine affords dihydroisocodeine [408], which is conveniently prepared directly from the mixture of products resulting from the hydrolysis of bromocodide [246]; it also results from

the methylation of dihydro-α-isomorphine [409]. Dihydroisocodeine is resistant to Oppenauer oxidation, yielding only 3 per cent. of dihydrocodeinone, in marked contrast to dihydrocodeine, which gives 80 per cent. of the ketone [304]. No dihydroisocodeine is obtained by the catalytic reduction of dihydrocodeinone, which yields exclusively dihydrocodeine [273–5].

Whereas dihydrocodeine can be converted to 6-chlorodihydrocodide [241], dihydroisocodeine gives only phosphorus-containing products on treatment with phosphorus pentachloride or tribromide, whilst thionyl chloride only effects nuclear chlorination, presumably in position 1, the product giving dihydroisocodeine on reduction with sodium and alcohol [240].

Hofmann degradation of isocodeine follows the same course as the degradation of codeine, giving in the first step γ-codeimethine the C-6 epimer of [XXI], which can be isomerized to δ-codeimethine, the C-6 epimer of [XXII], and in the second step methylmorphenol [XXIV] [252, 410] (see Chap. VI). Dihydroisocodeine can be degraded to a methine base and a nitrogen-free substance [295].

Isocodeine methyl ether, prepared from the methyl ether methiodide [411] or by methylating isocodeine-N-oxide and reducing the product [265], cannot be isomerized to thebainone methyl enolate by heating with sodium ethoxide [265]. On degradation it yields γ-codeimethine methyl ether [411].

Ozonolysis of dihydroisocodeine follows the same course as ozonolysis of dihydrocodeine, giving ozodihydroisocodeine, which can be converted to methyl tetrahydro-α-isomorphilactonate, tetrahydro-α-isomorphilactonic acid, and tetrahydro-α-isomorphitetrol [246] (see above under the ozonolysis of codeine).

Isocodeine-N-oxide can be sulphonated to two sulphonic acids, which give 'bromoisocodeine dibromide' on bromination and reduction of the perbromide [295].

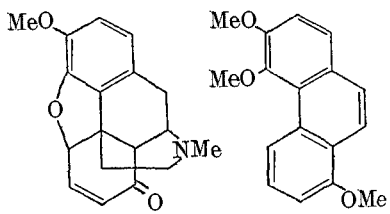
ψ-CODEINE

PREPARATION

ψ-Codeine is obtained by the hydrolysis of α-chlorocodide [249–50]. β-chlorocodide [238, 250], and iodocodide [247], but it has apparently not been isolated from the products of hydrolysis of bromocodide (see Chap. VIII). It is also obtained when codeine is heated with oxalic acid during the preparation of apocodeine [256, 412] and is identical with the 'amorphous codeine' resulting from the action of moderately concentrated sulphuric acid on codeine [167–8, 172, 413–14]. Methylation of γ-isomorphine also gives ψ-codeine [245, 407, 415].

STRUCTURE

The relationship of ψ-codeine to codeine was demonstrated by the oxidation of the former to ψ-codeinone [LXVII] [305, 416] and the degradation of this to 3:4:8-trimethoxyphenanthrene [LXVIII] [305, 406, 416–17], indicating that the hydroxyl group, at C-6 in codeine [LXIX, R = OH], has moved to C-8 in ψ-codeine [LXX].



[LXVII] [LXVIII] [LXIX] [LXX]

When the chlorine of α-chlorocodide [LXIX, R = Cl] is replaced by groups other than hydroxyl, the new substituent appears at C-8 (see Chap. VIII) and ethers of ψ-codeine can be prepared by heating α-chlorocodide with alcohols or with the sodium salts of phenols [353, 403, 418–20]. ψ-codeine methyl ether methiodide can also be prepared by direct methylation of ψ-codeine [411].

REDUCTION

The reduction of ψ-codeine is complicated by the presence in the same molecule of an allylic ether and an allylic alcohol. Catalytic reduction generally proceeds with opening of the cyclic ether system and production of phenolic bases, but this can be suppressed by hydrogenating the hydrochloride over platinum oxide.

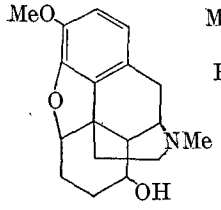
(*a*) Reduction of ψ-codeine hydrochloride in glacial acetic acid over a platinum oxide catalyst gives 80 per cent. of the non-phenolic dihydro-ψ-codeine-A [LXXI] [421]. This can be demethylated with hydriodic acid to dihydro-γ-isomorphine [421–2].

(*b*) Hydrogenation of the base in dilute acetic acid using a colloidal palladium catalyst gives the phenolic dihydro-ψ-codeine-B [LXXII] together with a small amount of an isomer [421].

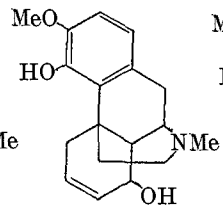
(*c*) Electrolytic reduction gives dihydro-ψ-codeine-B [295, 423].

(*d*) Sodium and alcohol reduction of ψ-codeine follows a different course giving dihydro-ψ-codeine-C [LXXIII] and the constant proportion mixture of dihydrodesoxycodeines B [LXXIV] and C [LXXV] known as dihydrodesoxycodeine-A (see Chap. IX) [423].

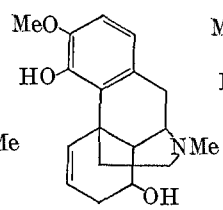
(*e*) Complete catalytic reduction of ψ-codeine in dilute acid and of dihydro-ψ-codeines B and C gives tetrahydro-ψ-codeine [LXXVI] [295, 408, 421, 423].



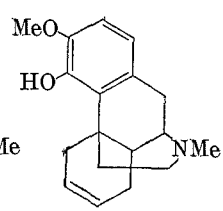
[LXXI]



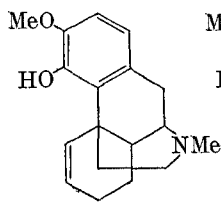
[LXXII]



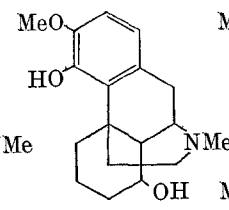
[LXXIII]



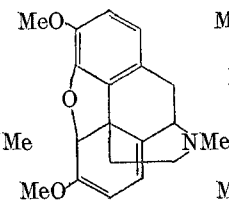
[LXXIV]



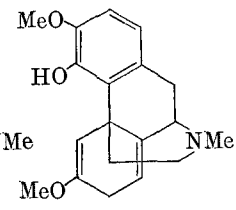
[LXXV]



[LXXVI]



[LXXVII]



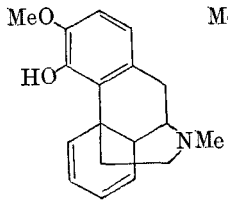
[LXXVIII]

Dihydro-ψ-codeine-B is allotted the structure [LXXII] by analogy with the electrolytic reduction of desoxycodeine-C [XV] to dihydrodesoxycodeine-B [LXXIV], and dihydro-ψ-codeine-C the structure [LXXIII] by analogy with the sodium and alcohol reduction of desoxycodeine-C to dihydrodesoxycodeine-C [LXXV]; sodium and alcohol reductions have a known tendency to effect 1:4 addition of hydrogen to an allylic ether [248, 281, 423]. (Cf. the reduction of thebaine [LXXVII] to dihydrothebaine-ϕ [LXXVIII] [265, 405, 424].)

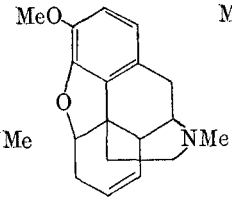
The loss of the hydroxyl at C-8 during the sodium and alcohol reduction must occur before or during the opening of the cyclic ether link as both [LXXII] and [LXXIII] are stable under these conditions. The process doubtless proceeds by 1:6-addition of hydrogen to the system $\overset{1}{\text{—O—}}\overset{2}{\text{CH—}}\overset{3}{\text{CH}}\overset{4}{\text{=CH—}}\overset{5}{\text{CH—}}\overset{6}{\text{OH}}$ to give desoxycodeine-A [LXXIX], which is known to give [LXXIV] and [LXXV] on sodium and alcohol reduction [281, 425]. (5:6-addition is improbable as it would involve an activating influence of the double bond not found in codeine, and 3:6-addition would yield desoxycodeine-E [LXXX] in which the double bond occupies a position that precludes reduction by sodium and alcohol [423].)

Catalytic reduction of ψ-codeine methyl ether [LXXXI] hydrochloride in acetic acid over platinum oxide gives 77 per cent. dihydro-ψ-codeine-A methyl ether and 16 per cent. tetrahydro-ψ-codeine methyl ether; sodium and alcohol reduction affords almost 100 per cent. dihydro-ψ-codeine-C methyl ether, and only traces of dihydrodesoxycodeines [426]. Loss of the group at C-8 is also observed during the sodium and alcohol reduction of δ-ethylthiocodide [LXXXII] [427] (see Chap. XVII).

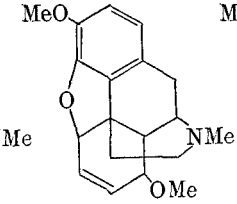
Unlike dihydrocodeine and dihydroallo-ψ-codeine-A (q.v.) but like dihydroisocodeine, dihydro-ψ-codeine-A is resistant to Oppenauer oxidation from which only unchanged alcohol can be recovered [304].



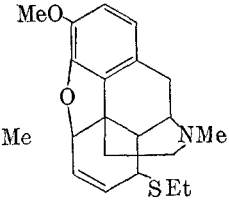
[LXXIX]



[LXXX]



[LXXXI]



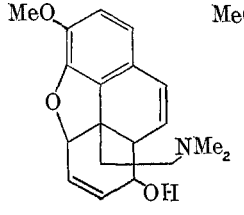
[LXXXII]

Replacement of Hydroxyl

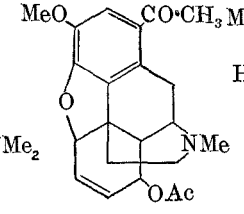
When ψ-Codeine is treated with phosphorus pentachloride or thionyl chloride allylic rearrangement occurs and α-chlorocodide is formed [238, 428]. β-Chlorocodide results when ψ-codeine is heated under pressure with concentrated hydrochloric acid, but this doubtless arises by rearrangement of the α-isomer first formed [243]. Bromocodide is produced by the interaction of ψ-codeine and phosphorus tribromide [428]. With phosphorus pentachloride dihydro-ψ-codeine-A gives 8-chlorodihydrocodide, with thionyl chloride chlorination only occurs in the aromatic nucleus, and with phosphorus tribromide a poor yield of 8-bromodihydrocodide is obtained [240]. Tetrahydro-ψ-codeine gives tetrahydro-ψ-chlorocodide with phosphorus pentachloride [295].

Hofmann Degradation

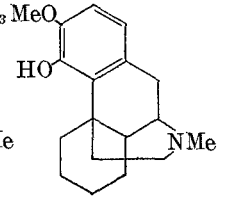
Alkaline degradation of ψ-codeine methiodide affords ϵ-codeimethine [LXXXIII], which resists isomerization [415, 428–9], and this on further degradation gives morphenol and acetylmethylmorphenol [428] (see Chap. VIII). Methine bases have also been prepared from ψ-codeine methyl ether [411, 419], dihydro-ψ-codeine-A [421] and its methyl ether [426], dihydro-ψ-codeine-B [421, 423], dihydro-ψ-codeine-C [295, 423] and its methyl ether [426], tetrahydro-ψ-codeine [295] and its methyl ether [426].



[LXXXIII]



[LXXXIV]



[LXXXV]

1-Chloro-ψ-codeine is obtained by the action of potassium chlorate

and hydrochloric acid on ψ-codeine, and 1-bromo- and 1-nitro-ψ-codeine by direct bromination and nitration respectively [428]. Treatment of the base with acetic anhydride and concentrated sulphuric acid gives 1-aceto-8-acetyl-ψ-codeine [LXXXIV] [430].

Two sulphonic acids are obtained by the sulphonation of ψ-codeine-N-oxide [295, 341] and bromination of these, followed by decomposition of the perbromide with sulphurous acid, gives bromo-ψ-codeine dibromide, $C_{18}H_{20}O_3NBr_3$, which can be reduced catalytically to tetrahydro-ψ-codeine [295].

ψ-Codeine methyl ether readily reacts with methylmagnesium iodide, yielding a compound, methyldihydro-ψ-codeine methyl ether, that strongly resists hydrogenation. The reaction in *iso*propyl ether also affords a compound giving analytical data for, and no melting-point depression with, tetrahydro-ψ-codeine methyl ether, but differing from this in certain physical properties [403].

ALLO-ψ-CODEINE

Allo-ψ-codeine is the third product of hydrolysis of α-chlorocodide [244–5, 250], β-chlorocodide [238, 243, 250], bromocodide [243–4, 251, 253, 407], and iodocodide [247]. It differs from ψ-codeine only in the spatial arrangement of the —CH·OH— group, as is shown by the production of ψ-codeinone when it is oxidized [305, 407, 416]. It is related to β-isomorphine, from which it can be prepared by methylation [245, 253]. Though it is formed by the hydrolysis of α-chlorocodide it yields β-chlorocodide exclusively when treated with phosphorus pentachloride [238, 305].

REDUCTION

The reduction of allo-ψ-codeine in general follows the same pattern as the reduction of ψ-codeine, though elimination of the 8-hydroxyl group is more facile, and occurs even during catalytic hydrogenation.

(*a*) Hydrogenation of the hydrochloride in glacial acetic acid over platinum oxide affords 80 per cent. dihydroallo-ψ-codeine-A (epimer of LXXI) together with small amounts of tetrahydroallo-ψ-codeine (epimer of LXXVI) and tetrahydrodesoxycodeine [LXXXV] [431].

(*b*) Hydrogenation of the base in alcohol with palladized calcium carbonate gives equal amounts of dihydroallo-ψ-codeine-A and tetrahydroallo-ψ-codeine [431].

(*c*) Hydrogenation of the base in dilute acetic acid with colloidal palladium as catalyst yields exclusively tetrahydroallo-ψ-codeine [295, 431].

(*d*) Sodium and alcohol reduction yields the constant-proportion mixture of dihydrodesoxycodeines B [LXXIV] and C [LXXV] and dihydroallo-ψ-codeine-C (the epimer of LXXIII) [431].

Tetrahydroallo-ψ-codeine and dihydroallo-ψ-codeine-A can be prepared by the demethylation of the corresponding derivatives of β-isomorphine [409].

Dihydro-ψ-codeinone is obtained in 40 per cent. yield by the Oppenauer oxidation of dihydroallo-ψ-codeine-A [304]. The latter on treatment with phosphorus pentachloride gives 8-chloro- and 1:8-dichlorodihydrocodide, which are also produced in the same way from dihydro-ψ-codeine-A; thionyl chloride effects chlorination in the aromatic nucleus only. With phosphorus tribromide it apparently suffers replacement of the hydroxyl group by bromine, loss of hydrogen bromide, and demethylation, as the product is desoxymorphine-D [240] (see Chap. VIII).

Degradation of the quaternary salts of allo-ψ-codeine affords ζ-codeimethine (the epimer of LXXXIII) [407] which cannot be isomerized [428], and methine bases have also been prepared from dihydroallo-ψ-codeine-A [431] and tetrahydroallo-ψ-codeine [295, 431].

1-Aceto-8-acetylallo-ψ-codeine results from the action of acetic anhydride and concentrated sulphuric acid on allo-ψ-codeine [430].

Two sulphonic acids result from the sulphonation of allo-ψ-codeine-N-oxide, and these on bromination and reduction of the perbromide are converted to 'bromoallo-ψ-codeine dibromide' [295].

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Codeine	156–157	Benzene	prisms	−111·5 −137·75	15 15	$CHCl_3$ 80% EtOH	59
— hydrochloride·$2H_2O$	287	H_2O	prisms	−108·2	22·5	...	59 432–3
— hydrochloride (anhyd.)	264	..	..	..	..	..	434
— hydrobromide·$2H_2O$	..	H_2O+ EtOH	needles	−96·6	22	H_2O	434
— hydrobromide (anhyd.)	190–192	..	..	..	..	..	435-6
— hydriodide·$2H_2O$	266	H_2O	..	..	..	..	167–8, 172
— perchlorate	explodes	..	needles	..	..	..	437
— sulphate·$5H_2O$	..	..	needles	−101·2	..	H_2O	59, 167, 172, 123
— thiosulphate·$5H_2O$	..	H_2O	prisms	..	..	..	438
— nitrate	..	H_2O	prisms	..	..	..	167–8
— phosphate·$2H_2O$	..	..	needles	..	..	..	167–8
— chromate·$5H_2O$	..	H_2O	needles	..	..	..	172
— thiocyanate	100	H_2O	needles	..	..	..	167–8
— platinichloride·$4H_2O$	..	..	needles or granules	..	..	..	167–8
— aurichloride	..	..	amorph.	..	..	..	172
— mercurichloride·H_2O	..	..	needles	..	..	..	172
— mercuriiodide	..	..	cryst.	..	..	..	439–41
— stibnichloride	..	..	red-brown plates	..	..	..	442
— superiodide (tri-iodide)	..	EtOH	violet crystals	..	..	..	331–2
— penta-iodide	..	..	needles	..	..	..	333
— tetrachloro-iodide	..	HOAc	orange needles	..	..	..	443
— hydrazone·$2H_2O$	D. 100	..	needles	..	..	..	444
— hydroferrocyanide	..	..	cryst.	..	..	..	104
— hydroferricyanide	..	..	cryst.	..	..	..	104

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Codeine iodozincate	..	..	..	..	..	..	445
— fluorocolumbate	..	..	..	−94	..	..	446
— 'Reineckate'	..	..	..	..	..	..	447
— acetate·$2H_2O$	D. 100	..	..	..	..	..	172
— monochloracetate	153–154	..	..	..	..	..	452
— dichloracetate	156	..	..	..	..	..	452
— trichloracetate	93	..	..	..	..	..	448
— benzoate	79	..	..	..	..	..	449
— o-chlorobenzoate	134	..	..	..	..	..	449
— *m*-chlorobenzoate	96	..	..	..	..	..	449
— *p*-chlorobenzoate	162	..	..	..	..	..	449
— o-bromobenzoate	139	..	..	..	..	..	449
— *m*-bromobenzoate	99	..	..	..	..	..	449
— *p*-bromobenzoate	166	..	..	..	..	..	449
— o-hydroxybenzoate	121	..	..	..	..	..	449–50
— *m*-hydroxybenzoate	148	..	..	..	..	..	449
— *p*-hydroxybenzoate	162	..	..	..	..	..	449
— o-nitrobenzoate	185	..	..	..	..	..	449
— *m*-nitrobenzoate	173	..	..	..	..	..	449
— *p*-nitrobenzoate	189	..	..	..	..	..	449
— camphorsulphonate	256	..	..	−62·7	..	H_2O	451
— dibromopyruvate	70	..	..	..	..	..	452
— oxalate·$3H_2O$	..	..	..	..	..	..	167–8, 434
— picrate	196–197	50% EtOH	..	..	..	..	453
— shikimate	173–174	..	..	..	..	..	454
— styphnate	115	..	..	..	..	..	455
— trichlorobutyrate	173	..	..	..	..	..	452
— tris-(*p*-hydroxyphenyl)-arsenate	D.245–246	..	..	..	..	..	456
— o-guaiacolsulphonate	164–165	H_2O	cubes	..	..	..	457–8
— *p*-toluenethiosulphonate	..	EtOH	leaflets	..	..	..	459
— α-naphthalenethiosulphonate	..	EtOH	..	..	..	..	459
— β-naphthalenethiosulphonate	..	EtOH	..	..	..	..	459
— diethylbarbiturate	c. 85	..	..	..	..	..	386
— dipropylbarbiturate	59·5	..	..	..	..	..	391
— diallylbarbiturate	105	..	..	..	..	..	387, 389
— phenylethylbarbiturate	80	..	..	..	..	..	388
— *p*-acetamidophenate	c. 125	H_2O	..	..	..	..	383
— methochloride·H_2O	..	H_2O	..	..	..	..	187
— methobromide	261	Acetone $+H_2O$	prisms	..	..	..	175–7
— methiodide·$2H_2O$	..	H_2O	needles	..	..	..	187
— methiodide	D. 270	EtOH	..	−98·8 −81·9	27 17	H_2O 99% EtOH	461 460
— methomethylsulphate·$4H_2O$	..	H_2O	rhombs.	−130·1	15	H_2O	187
— methomethylsulphite	..	..	..	..	..	..	177
— methohydroxide	..	..	not cryst.	..	..	..	..
— methoplatinichloride·$3H_2O$	..	..	orange cryst.	..	..	..	187
— ethobromide·$5H_2O$	..	..	..	..	..	..	176
— ethiodide	..	H_2O	crystals	..	..	..	171
— benzyliodide	..	..	..	..	..	..	264
— iodomethochloride	235–238	..	needles	..	..	..	174
— iodomethiodide	214–216	..	needles	..	..	..	174
Dicodeine ethylene dichloride·$4H_2O$	182–192	H_2O	needles	..	..	..	173
Dicodeine ethylene dibromide·$4H_2O$	177–179	..	rhombs.	−97·1	20	H_2O	173
— platinichloride	..	..	..	..	..	..	172–3
— aurichloride	..	..	..	..	..	..	172–3
Codeine-narcotine hydrochloride	D. 200	..	prisms	..	..	..	384–5
Formylcodeine	180	EtOH	needles	..	..	..	229–31
hydrochloride	..	..	needles	..	..	..	229–31
Acetylcodeine	133·5	Et_2O	prisms	..	..	..	237, 187, 226
hydrochloride·$2H_2O$	..	..	cryst.	..	..	..	187, 226
methochloride	..	..	cryst.	..	..	..	187
methiodide	250–252d.	H_2O	needles	..	..	..	326
ethiodide·$\frac{1}{2}H_2O$	..	..	cryst.	..	..	..	187
o-guaiacolsulphonate	..	H_2O	prisms	..	..	..	457
Propionylcodeine	..	..	not cryst.	..	..	..	187
— hydrochloride·$2H_2O$	..	H_2O	needles	..	..	..	187

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Propionylcodeine hydriodide·H_2O	..	H_2O	needles	..	..	..	187
— platinichloride	..	..	yellow cryst.	..	..	..	187
— oxalate·$3H_2O$	..	..	cryst.	..	..	..	187
Butyrylcodeine	..	..	not cryst.	..	..	..	224, 228
— hydrochloride·$3H_2O$	..	..	cryst.	..	..	..	224, 228
— ethiodide·$\frac{1}{2}H_2O$	..	..	cryst.	..	..	..	224, 228
Succinylcodeine·$5H_2O$	..	80% EtOH	..	..	..	..	223
— hydrochloride·H_2O	..	..	..	..	..	..	223
Benzoylcodeine	..	Et_2O	..	..	..	..	228
— hydrochloride·H_2O	..	..	..	..	..	..	228
— methiodide	254	..	needles	..	..	..	462
— ethiodide·$\frac{1}{2}H_2O$	..	85% EtOH	..	..	..	..	224
Tartrylcodeine	..	..	amorph.	..	..	..	223
Camphorylcodeine·$4H_2O$	..	EtOH	..	..	..	..	223
— hydrochloride·$3H_2O$	..	..	cryst.	..	..	..	223
p-toluenesulphonylcodeine	121–121·5 126–128	butanone	..	−209·0	25	dioxane	283–4
— picrate	153–155	..	..	..	..	..	283
— hydrochloride·H_2O	154–156	..	..	..	..	..	283
Codeine 9-hydroxyfluorene-9-carboxylate (ester)	D. 258	..	..	..	..	..	233
Codeine phenylurethane	141	..	prisms	..	..	..	462
— methiodide	255–260	EtOH	needles	..	..	..	462
Carbethoxycodeine	77–78	..	..	−202·8	..	EtOH	380
— bitartrate	120	EtOH	needles	..	..	..	380
— bitartrate (hydrated)	137–140	..	..	−120·3	..	H_2O	380
Codeine methyl ether	140–141	MeOH	prisms	−194	22	EtOH	263
— methochloride	208	EtOH	prisms	..	..	..	263, 294
— methiodide	257	80% EtOH	prisms	−109·7	15	H_2O	262, 294
— methoplatinichloride	D. 215	..	needles	..	..	..	263
— methopicrate	211–212	H_2O	needles	..	..	..	263
— benzyl iodide	181	..	..	..	..	..	264
— N-oxide hydriodide	253	..	..	..	..	..	263
Dihydrocodeine·H_2O	62–63	H_2O	octahedra	..	..	..	267–8, 296
Dihydrocodeine·$2H_2O$·(2 forms) (*a*)	55	..	..	−118·0	..	96% EtOH	269
Dihydrocodeine·$2H_2O$·(2 forms) (*b*)	82–87	H_2O	..	..	..	..	313, 241, 269
Dihydrocodeine (anhydrous)	112–113	..	..	..	..	..	269, 271, 296
— hydrochloride	256	..	..	..	..	..	296
— acid tartrate·H_2O	192d.	..	..	−66·0	25	H_2O	463
— diethylbarbiturate	..	..	..	..	..	..	390
— diallylbarbiturate	95	H_2O	..	..	..	..	386–7
— methiodide	257	EtOH	..	..	..	..	241
— chromate	..	..	..	..	..	..	299
Racemate with antipode from sinomenine series	105	..	prisms	0	..	..	275
— methiodide	257	MeOH	.	0	..	..	275
(+) dihydrocodeine·$2H_2O$	87–88	..	..	..	..	..	275
(+) dihydrocodeine (anhydrous)	110	..	..	+146·4	30	EtOH	275
— methiodide	257	EtOH	..	+80·1	30	H_2O	275
Acetyldihydrocodeine	120	Et_2O+ petrol	..	..	..	..	353–4
Dihydrocodeine methyl ether	83	Et_2O or petrol	..	−153·4	18	EtOH	263, 276–8
— hydrochloride·$3H_2O$	115–116	H_2O+ acetone	needles	..	..	..	276
— picrate	222	EtOH+ toluene	needles	..	..	..	282
— methiodide	135–140 and 212	H_2O	..	..	..	..	276
1-chlorocodeine·$1\frac{1}{2}H_2O$	175–176	EtOH	needles	−147·2	16	EtOH	327, 167–8
— hydrochloride	..	..	needles	..	..	..	327
— sulphate·$4H_2O$	..	..	prisms	..	..	..	327
— platinichloride	..	..	amorph.	..	..	..	327

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
1-chlorodihydrocodeine	196	EtOH	octahedra	..	..	..	327
1-bromocodeine·½ or ·1H_2O	161–162	H_2O+EtOH	prisms	..	..	..	167–8, 237, 327
— hydrochloride	..	..	needles	..	..	..	237
— hydrobromide·H_2O	..	H_2O	prisms	..	..	..	237
— platinichloride	..	..	yellow amorph.	..	..	..	167–8
— picrate	D. 235	H_2O+EtOH	..	..	..	..	464
— methochloride·2½H_2O	..	H_2O	needles	..	..	..	326
— methiodide·H_2O	242–244	H_2O	prisms	..	..	..	326
— ethiodide	..	..	..	..	..	..	288
— N-oxide·H_2O	200–201d.	H_2O	..	..	..	..	464
— N-oxide hydrobromide	D. 242	EtOH+Et_2O	rods	..	..	..	464
1-bromodihydrocodeine	190	EtOH	octahedra	..	..	..	327
'Bromocodeine dibromide'	200	..	..	..	..	..	295
2-bromocodeine	160–161	..	needles	..	..	..	342
Tribromocodeine	..	..	amorph.	..	..	..	167–8
Diiodocodeine	..	..	yellow cryst.	..	..	..	329
1-nitrocodeine	221–222	EtOH	..	..	.	..	167–8, 339–40
— hydrochloride	..	..	amorph.	..	..	..	167–8
— sulphate	..	..	needles	..	..	..	167–8
— platinichloride·4H_2O	..	..	..	..	..	..	167–8
— oxalate	..	..	prisms	..	..	..	167–8
— methiodide	..	..	..	..	..	..	336
6-acetyl-1-nitrocodeine	203	..	leaflets	..	..	..	356
α-nitrocodeine	197	EtOH	plates	..	..	..	339, 350
2-nitrocodeine·H_2O	116–117	..	prisms	..	..	..	342
— hydrochloride	D. 249	..	..	..	..	..	342
1-aminocodeine	226	EtOH	plates	..	..	..	337, 339, 336, 338
— hydrochloride	D. c. 290	..	..	..	..	..	339
Diacetylaminocodeine	120	MeOH	needles	..	..	..	336
— methiodide	251–252	..	..	..	..	..	336
2-aminocodeine	95–96·5	..	prisms	..	..	..	342
— perchlorate	D. 170	..	..	..	..	..	342
1-nitrodihydrocodeine	221	EtOH	double pyramids	..	..	..	241, 341
α-nitrodihydrocodeine	180	EtOH	needles	..	..	..	341
1-hydroxycodeine·H_2O	176 234	EtOH	needles	..	..	..	337 339
- -hydrochloride·2H_2O	..	..	cryst.	..	..	..	337 338
1-acetocodeine·H_2O	150	..	..	−141	21	$CHCl_3$	344–5, 347
oxime	D. c. 100	..	amorph.	..	..	..	345
methiodide	D. c. 235	H_2O	needles	−64	15	H_2O	345
6-acetyl-1-acetocodeine·½H_2O	125–126	EtOH	..	−208	20	$CHCl_3$	347
2 forms	146–147	EtOH	..	−207	20	$CHCl_3$	345, 347
oxime·½EtOH	176–178	EtOH	..	..	..	..	344–5
6-acetyl-1-acetodihydrocodeine	166–167	EtOAc	..	−105	20	acetone	347
1-acetodihydrocodeine	138–140	EtOAc	..	−101	20	EtOH	347
1-(1′-hydroxyethyl)-codeine	222–224	H_2O	..	−101	20	EtOH	347
6-acetyl-1-(1′-hydroxyethyl)-codeine	185–187	60% EtOH	..	−212	20	$CHCl_3$	347
acid tartrate·H_2O	165–170	H_2O	..	−115	20	H_2O	347
1-(1′-hydroxyethyl)-dihydrocodeine	225–227	60% EtOH	rods	−82	20	10% HOAc	347
6-acetyl-1-(1′-hydroxyethyl)-dihydrocodeine	251–252	EtOH	..	−91·2	..	$CHCl_3$	347
6-acetyl-1-ethyldihydrocodeine	104–105	..	..	−126	20	EtOH	347
acid tartrate·H_2O	160–170	H_2O	..	..	..	..	347
6 (or 10)-hydroxycodeine	207–208	Benzene or HOAc	..	..	..	..	297, 306 .307
hydrochloride	..	H_2O	cryst.	..	..	..	307
picrate	166	H_2O	..	..	..	..	307
- *picrolonate*	170	EtOH	..	..	..	..	307

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
9 (or 10)-hydroxycodeine methiodide ·MeOH	240–250	MeOH	..	..	..	..	307
9 (or 10)-hydroxycodeine methine, i.e. 9 (or 10)-ketodihydrocodeimethine	50–60	Et_2O	..	..	..	..	307–9
— hydrochloride	D. c. 246	..	..	..	..	..	307
— hydriodide	220	..	..	..	..	..	307
— picrate	211	..	..	..	..	..	307
— picrolonate	D. 140	..	..	..	..	..	307
— methiodide·1½H_2O	220	..	..	..	..	..	307
— oxime hydrochloride	279	..	..	..	..	..	310
— oxime methiodide	270	..	..	..	..	..	310
— semicarbazone	106–107	..	..	..	..	..	309
Acetyl-9 (or 10)-ketodihydrocodeimethine	81	..	..	..	..	..	310
— hydrobromide	280–285	..	..	..	..	..	310
— hydriodide	270	..	..	..	..	..	310
— methiodide	D. 260	..	..	..	..	..	310
Diacetylhydroxycodeine	160–161	EtOH	..	..	..	..	297, 310
— hydriodide	230	..	..	..	..	..	297, 310
— methiodide	248–255	..	..	..	..	..	310
1-nitro-9 (or 10)-hydroxycodeine	D. 232	MeOH	..	..	..	..	340
7-hydroxydihydrocodeine	225	..	..	..	..	..	317
Dibenzoyl-7-hydroxydihydrocodeine	2	..	..	..	..	..	317
7:8-dihydroxydihydrocodeine	208–209	EtOH	plates	..	..	..	316
Triacetyl-7:8-dihydroxydihydrocodeine	200	MeOH	plates	..	..	..	316
— perchlorate	281	H_2O	needles	..	..	..	316
14-hydroxycodeine and derivatives: *see* Chap. XVIII.							
Codeine-N-oxide	230–231 [1]	H_2O	tablets	..	..	..	348
— hydrochloride	..	..	cryst.	..	..	..	348
— hydrobromide	196	..	..	..	..	..	348
— nitrate	187	..	..	..	..	..	348
— acetate	..	..	cryst.	..	..	..	348
Codeine-N-oxide (dimolecular)·7H_2O	200–202	..	..	−97·6 −107·2	20 19	H_2O EtOH	349
N-oxide (monomolecular) from the dimolecular oxide	215	..	..	−97·1	18	H_2O	349
— hydrochloride·H_2O	219–220	..	..	−105·8	20	H_2O	349
α-codeine-N-oxide sulphonic acid	..	..	..	..	..	..	339, 350
β-codeine-N-oxide sulphonic acid	272	..	..	−115·4	20	2N-KOH	339, 350
Nitro-α-codeine-N-oxide sulphonic acid	D.167–170	..	..	..	..	..	339, 350
Codeine sulphonic acid	D. > 300	..	needles or prisms	−136·3	20	2N-KOH	339, 350
— methohydroxide	D. 284	H_2O	needles	−63·2	20	H_2O	339, 350, 465
β-codeine sulphonic acid	D. c. 243	..	plates	−190·1	20	v. dil. KOH	339
γ-codeine sulphonic acid	D. c. 280	50% EtOH	plates	..	..	..	339
Dihydrocodeine-N-oxide	D. 225	..	rhombs.	..	..	..	341
— hydrochloride	217	..	..	..	..	..	341
— picrate	161–162	..	..	..	..	..	341
Dihydrocodeine-N-oxide sulphonic acid	273–275	..	prisms	..	..	..	341
α-dihydrocodeine sulphonic acid	315–320d.	..	cryst. powder	−88	20	H_2O	341
β-dihydrocodeine sulphonic acid	D.330–340	H_2O+EtOH	prisms and leaflets	−76·7	20	v. dil. alkali	341
— methohydroxide	D.280–285	H_2O+EtOH	plates	..	..	..	341
Norcodeine	185	EtOAc or acetone	plates or needles	..	..	..	352–3, 357, 360
— hydrochloride·3H_2O	309	..	..	..	..	..	354
— hydriodide·2H_2O	257	..	..	..	..	..	354
— platinichloride	230	..	..	..	..	..	354
— picrate	..	..	non-cryst.	..	..	..	354
— thiocarbamide	210	MeOH	..	..	..	..	354
Hexahydrocodeine	170–178	MeOH	..	..	..	..	357
Acetyloxycodeine	**184**	MeOH	..	..	..	..	353–5

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Cyanonorcodeine	262	..	powder	..	..	..	353–5
N-ethylnorcodeine	203	..	..	..	..	..	361
N-propylnorcodeine	..	..	oil	..	..	..	361
— hydrochloride	185	..	..	..	..	..	361
— platinichloride	216	..	..	..	..	..	361
N-*n*-butylnorcodeine	100	..	..	..	..	..	361
— platinichloride	205	..	..	..	..	..	361
N-*iso*amylnorcodeine	..	..	oil	..	..	..	361
— platinichloride·$3H_2O$	207	..	..	..	..	..	361
— picrate	100	..	..	..	..	..	361
N-(β-hydroxyethyl)-norcodeine	197	..	needles	..	..	..	361–2
N-benzylnorcodeine	< 60	..	..	..	..	..	361
N-phenylethylnorcodeine	114	..	..	..	..	..	354
— hydrochloride	277	..	scales	..	..	..	354
— platinichloride	216–217	..	..	..	..	..	354
N-(γ-hydroxypropyl)-norcodeine	133	..	..	..	..	..	366
— picrate	120–121	..	plates	..	..	..	366
N-(γ-benzoyloxypropyl)-norcodeine	47	..	..	..	..	..	366
— picrate	118–119	..	..	..	..	..	366
— methiodide	169–170	..	..	..	..	..	366
N-allylnorcodeine	95	..	..	..	..	..	361
— hydrochloride	125	..	..	..	..	..	361
— platinichloride	214	..	..	..	..	..	361
— allyliodide	D. 208	..	..	..	..	..	361
N-(γ-chloroallyl)-norcodeine	54–56	..	..	..	..	..	367
— hydrochloride	120	..	..	..	..	..	367
— picrate	124	..	..	..	..	..	367
— methiodide	115	..	..	..	..	..	367
N-(γ-bromoallyl)-norcodeine	68–70	..	..	..	..	..	367
— picrate	127	..	..	..	..	..	367
N-dibromoallylnorcodeine	c. 60	..	..	..	..	..	367
N-β-butenylnorcodeine	44	..	..	..	..	..	363
— hydrochloride	128	..	..	..	..	..	363
- platinichloride	198–208	..	..	..	..	..	363
N-cyclopropylmethylnorcodeine	..	..	amorph.	..	..	..	364
— hydrochloride	250–252	..	..	..	..	..	364
- platinichloride	11.199–200	..	..	..	..	..	364
N-cyclobutylmethylnorcodeine	..	..	not cryst.	..	..	..	364
— hydrochloride	150	..	..	..	..	..	364
- platinichloride	D. 217	..	..	..	..	..	364
N-cyclopentylmethylnorcodeine	50	..	..	..	..	..	364
- picrate	125–128	..	..	..	..	..	364
- hydrochloride	171–174	..	..	..	..	..	364
N-cyclohexylmethylnorcodeine	55–60	..	..	..	..	..	364
- hydrochloride	171–176	..	..	..	..	..	364
picrate	132–135	..	..	..	..	..	364
N-cycloheptylmethylnorcodeine	59–61	..	..	..	..	..	364
- picrate	139	..	..	..	..	..	364
N-(β-cyclopropylethyl-)norcodeine	..	..	not cryst.	..	..	..	364
hydrochloride	D. 160	..	..	..	..	..	364
N-α-thienylnorcodeine	76	..	..	..	..	..	364
hydrochloride	D. 200	..	..	..	..	..	364
picrate	c. 145	..	..	..	..	..	364
N-cyclopentenylnorcodeine	..	..	..	..	..	..	365
hydrochloride	188	..	..	..	..	..	365
N-cinnamylnorcodeine	78	..	..	..	..	..	369
platinichloride	D. 208	..	..	..	..	..	369
N-propargylnorcodeine	95	..	..	..	..	..	364
(anhydrous)	137	..	..	..	..	..	364
methiodide	D. 172	..	..	..	..	..	364
N-*p*-nitrophenylnorcodeine	212	..	..	..	..	..	366
N-2:4-dinitrophenylnorcodeine	265	..	..	..	..	..	366
N-2:4-diaminophenylnorcodeine	233	..	..	..	..	..	366
Triacetyl-N-2:4-diaminophenylnorcodeine	144–146	..	..	..	..	..	366
cyanogen bromide	148–149	..	..	..	..	..	366
N-propargyl-1-bromonorcodeine?	100–102	..	..	..	..	..	364
1:4-dibromocodeyl-β-butone	132	..	..	..	..	..	369
N-nitrosonorcodeine	246	EtOH $+H_2O$	pyramids or plates	..	..	..	354, 360
Norcodylhydrazine	174	MeOH	..	+136	20	$CHCl_3$	356
hydrochloride·$2H_2O$	135	..	..	..	..	..	356

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Norcodylhydrazine hydrochloride (anhyd.)	182–185	..	..	+116	20	EtOH	356
Tetrazone	232	..	..	..	..	..	356
1-aminonorcodeine	221	EtOH	..	..	..	..	356
— hydrochloride	D. 235	..	..	..	..	..	356
— platinichloride	..	..	leaflets	..	..	..	356
Triacetyl-1-aminonorcodeine	160–162	..	..	..	..	..	356
1-aminocyanonorcodeine	288	..	needles	..	..	..	356
— hydrochloride	> 300	..	..	..	..	..	356
— platinichloride	..	..	cryst.	..	..	..	356
1-nitronorcodeine	185	..	yellow cryst.	..	..	..	353, 356
— hydrochloride	..	..	cryst.	..	..	..	356
Diacetyl-1-nitronorcodeine	251	..	..	..	..	..	356
1-nitro-N-*iso*amylnorcodeine	90	..	..	..	..	..	361
Acetyl-1-nitro-N-*iso*amylnorcodeine	62	..	..	..	..	..	361
1-nitro-N-nitrosonorcodeine	236	..	..	..	..	..	356
Norcodeine sulphonic acid	D. 335	..	..	..	..	..	352, 339
Dihydronorcodeine	194	EtOH	..	..	..	..	353–4, 356
— hydrochloride	295	..	..	..	..	..	356
— platinichloride	D. 245	..	red needles	..	..	..	356
Cyanodihydronorcodeine	213–214	..	..	..	..	..	354
Acetylcyanodihydronorcodeine	227–228	EtOH	needles	..	..	..	354
N-allyldihydronorcodeine	..	..	oil	..	..	..	361
— allyliodide	157	..	..	..	..	..	361
Hofmann degradation product from N-allyldihydronorcodeine allyl iodide	..	..	oil	..	..	..	361
— platinichloride	78	..	..	..	..	..	361
— allyliodide	173	..	..	..	..	..	361
N-nitrosodihydronorcodeine	198	H_2O	..	..	..	..	356, 360
Nordihydrocodeinium-piperidinium iodide	271	..	..	..	..	..	370
Nitrocodeinic acid	Dec.	..	needles	..	..	..	340
— hydrochloride	..	dil. HCl	yellow needles	..	..	..	340
— barium salt·$2H_2O$	..	..	..	..	..	..	340
— potassium salt	..	..	..	..	..	..	340
— methyl ester·2MeOH	..	MeOH	plates	0	..	..	340
— methyl ester hydrochloride	..	..	needles	..	..	..	340
— ethyl ester hydrochloride	..	..	..	..	..	..	340
— +diazomethane → $C_{19}H_{22}O_8N_2$	180	..	..	..	..	..	340
Nornitrocodeinic acid	..	..	needles	..	..	..	340
Aminocodeinic acid hydrochloride	..	..	..	..	..	..	340
Noraminocodeinic acid	..	..	..	..	..	..	340
α-ozodihydrocodeine	..	..	oil	..	..	..	371
— hydrochloride	{ 242 235–236	..	..	+77·6 +78·8	16 20	H_2O H_2O	371 246
— hydriodide	D.248–250	H_2O	..	..	..	..	371
— hydrobromide	D. 238	..	rhombs.	..	..	..	371
— picrate	D.238–239	..	..	..	..	..	371
— methiodide	D. 155	..	..	..	..	..	371
Acetyl-α-ozodihydrocodeine	..	..	oil	..	..	..	371
— picrate	D.208–209	..	..	..	..	..	371
β-ozodihydrocodeine	..	..	oil	..	..	..	372
— hydriodide	D. 229	H_2O	plates and needles	+52·4	20	H_2O	372
Dibromo-β-ozodihydrocodeine	D. c. 222	96% EtOH	leaflets	..	..	..	372
γ-ozodihydrocodeine	..	..	oil	..	..	..	372
— hydriodide	219–220	..	rods	..	..	..	372
α-ozodihydroethylmorphine	..	..	oil	..	..	..	371
— hydriodide	D.255–256	EtOH	needles	+69·1	17	H_2O	371
β-ozodihydroethylmorphine	170·5	H_2O+ EtOH	prisms	+24·4	18	EtOH	372
γ-ozodihydroethylmorphine	175	H_2O+ EtOH	needles	−8·2	18	EtOH	372
6-chloro-α-ozodihydrocodeine	157–158	60% EtOH	needles	..	..	..	371

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
6-chloro-α-ozodihydrocodeine picrate	D.249–250	..	..	..	..	..	371
Dihydromorphinic acid	227	EtOH	needles	+30·9	16	H_2O	371
Tetrahydromorphinic acid	217–218	EtOH	..	..	..	..	371
Tetrahydromorphilactonic acid	245–246	EtOH	..	+29·0	22	EtOH	371, 246
— amide	226–228	..	..	−3·4	19	EtOH	246
Methyl tetrahydromorphilactonate	147–148	EtOAc	..	+6·3	19	EtOH	371, 246
— picrate	228–229	..	..	..	..	..	371, 246
— hydrochloride	247–248	..	plates	+13	18	H_2O	371
— hydriodide	D. 195	..	plates	..	..	..	371
— methiodide	183–184	..	..	..	..	..	371
— N-oxide	D. 183	EtOH	..	+19·7	30	H_2O	372
— N-oxide hydrochloride	D.195–199	..	..	..	..	..	372
— N-oxide picrate	D. 196	..	..	..	..	..	372
Methyl acetyltetrahydromorphilactonate	..	..	oil	..	..	..	371
— methiodide	D. 225	70% EtOH	needles	..	..	..	371
Methyl 6-chlorotetrahydromorphilactonate	143	96% EtOH	..	..	..	..	371
— picrate	213–214	..	..	..	..	..	371
Ethyl tetrahydromorphilactonate	..	..	oil	..	..	..	371
— picrate	D.234–235	..	..	..	..	..	371
Tetrahydromorphitetrol	..	..	oil	..	..	..	246
— picrate	D.178–179	EtOH	..	+25	20	50% acetone	246
— methiodide	192–194	EtOH	..	+36·7	19	H_2O	246
Tetra-acetyltetrahydromorphitetrol methiodide	236–237	EtOH	..	+4·5	19	H_2O	246
Dihydrocodinal phenylhydrazone hydriodide	D. 247	..	yellow rods	..	..	..	373
Dihydrocodinal semicarbazone	D. 278	..	..	..	..	..	373
β-dihydrodiconal	..	..	..	..	..	..	372
— oxime·$2H_2O$	D.268–287	..	..	..	..	..	372
— oxime hydrochloride·H_2O	D. 266	..	..	..	..	..	372
— phenylhydrazone acetate·H_2O	205–206	..	..	..	..	..	372
— semicarbazone	D. 247	..	..	..	..	..	372
Dicyanocodeine	..	EtOH+ Et_2O	..	..	..	..	167–8
Codeine-carbonsuboxide	155–160d.	..	orange powder	..	..	..	381
Dicodeylmethane	..	..	varnish	..	..	..	377
— hydrochloride	D. 140	..	..	..	..	..	377
Sodium codeine	..	..	yellow powder	..	..	..	393
Potassium codeine	..	..	cryst.	..	..	..	393
6-methylcodeine	114·5–116·5	ligroin	..	−163	20	EtOH	401
— perchlorate	139–144	EtOH	..	..	..	..	401
— salicylate	167–169	EtOAc	prisms	..	..	..	401
— methiodide	232–233	MeOH	..	..	..	..	401
6-methyldihydrocodeine	116	Subl.	..	−139	20	EtOH	402
hydrochloride	268–273	Et_2O+ EtOH	..	−112	20	EtOH	402
acid oxalate·$\frac{1}{2}H_2O$	240–241	90% EtOH	..	−99·5	20	EtOH	402
methiodide	251–252	MeOH	..	−86·3	20	EtOH	402
N-acetyl-6-methyldihydrocodeine	124·5–125·5	Subl.	..	−85·1	20	EtOH	402
1-chloro-6-methyldihydrocodeine	..	..	oil	..	..	..	402
hydriodide	260–262	EtOH	..	−73·6	20	EtOH	402
perchlorate	238–239	EtOH	..	−81·4	20	EtOH	402
1-bromo-6-methyldihydrocodeine	..	..	amorph.	..	..	..	402
hydriodide	248–249	H_2O	..	−64·6	20	EtOH	402
— methiodide	235–237	Et_2O+ MeOH	..	−73·1	20	EtOH	402
6-ethyldihydrocodeine	..	..	oil	..	..	..	402
picrate	217–219	75% EtOH	..	−73·0	20	EtOH	402
methiodide	238–240	Et_2O+ MeOH	..	−82·0	20	EtOH	402
6-n-amyldihydrocodeine	..	..	oil	−108	20	EtOH	402
6-phenyldihydrocodeine	..	..	oil	−155	20	EtOH	402

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
6-phenyldihydrocodeine hydrochloride	190–191	Et_2O+EtOH	..	−131	20	EtOH	402
— perchlorate	246–248	..	..	−126	20	EtOH	402
— acid oxalate·½EtOH	126–127	Et_2O+EtOH	..	−117	20	EtOH	402
Other alkyl-dihydrocodeines: *see* Chap. XIX.							
7:7-bis-[hydroxymethyl]-dihydrocodeine: *see* Chap. X.							
Isocodeine	171–172	EtOAc	..	−150·6	..	$CHCl_3$	245
— acid tartrate	185–186	MeOH	plates	−99·4	24	H_2O	421, 463
— binoxalate	235	EtOH	..	..	..	..	243
— acid oleate	..	..	..	..	..	..	463
— methiodide	270	MeOH	leaflets	−102	15	H_2O	243, 252
Isocodeine methyl ether	80–82	..	..	..	..	..	265
— salicylate	158–159	EtOH	..	−122·4	24	EtOH	265
— methiodide	199–200	EtOH	plates	−111·6	22	H_2O	265, 411
Dihydroisocodeine	199–200	EtOH	prisms	..	..	..	408
— acid tartrate·$3H_2O$	*c.* 180	..	..	−62·4	26	H_2O	421
— acid tartrate	192	..	..	−65·3	29	H_2O	463
— picrate	235–237	..	..	..	..	..	408
— methiodide	272	..	..	..	..	..	408
Acetyldihydroisocodeine	166	H_2O+EtOH	..	..	..	..	295, 408
— methiodide	268–269	..	..	..	..	..	295, 408
6-acetyl-1-acetoisocodeine·½EtOH	80–85	EtOH+H_2O	..	..	..	..	430
6-acetyl-1-acetoisocodeine (anhyd.)	105	..	..	−236	14	$CHCl_3$	430
Isocodeine-N-oxide	D. 219	Et_2O+EtOH	prisms	..	..	..	295
α-Isocodeine-N-oxide sulphonic acid	D. 290	H_2O	prisms	..	..	..	295
β-Isocodeine-N-oxide sulphonic acid	D. *c.* 300	H_2O	leaflets	..	..	..	295
'Bromoisocodeine dibromide'	212	H_2O+EtOH	..	..	..	..	295
Ozodihydroisocodeine	..	..	oil	..	..	..	246
— perchlorate	206–208	EtOH	..	+22·6	20	H_2O	246
Tetrahydro-α-isomorphilactonic acid	D.243–245	EtOH	..	0·0	18	H_2O	246
Methyl tetrahydro-α-isomorphilactonate	..	..	non-cryst.	..	..	..	246
— picrate	218d.	EtOH	..	+2·4	22	H_2O	246
Tetrahydro-α-isomorphitetrol	..	..	oil	..	..	..	246
— picrate	168–169	Benzene+EtOH	..	−4·5	22	H_2O	246
Tetra-acetyltetrahydro-α-isomorphitetrol methiodide	203d.	EtOH	..	−8·5	18	..	246
ψ-codeine	181–182	EtOAc	..	−96·8	20	EtOH	245, 407, 463
— hydrochloride	D. > 218	..	rods	−71	25	H_2O	412, 463
— hydrobromide	228–230	..	needles	..	..	..	412
— hydriodide·H_2O	260–265	H_2O	..	−57	15	H_2O	249, 407
— sulphate·$2H_2O$	..	H_2O+EtOH	leaflets	..	..	..	172
— nitrate	D.190–192	..	needles	..	..	..	412
— platinichloride	D. > 214	H_2O	yellow needles	..	..	..	412
— mercurichloride·$1\frac{1}{2}H_2O$	*c.*173–178	..	rods	..	..	..	412
— picrate	D.209–210	..	needles	..	..	..	412
— methiodide	278–279	MeOH	..	−50·6	15	H_2O	407, 415
Acetyl-ψ-codeine	..	..	oil	..	..	..	249
— hydriodide	285	H_2O	..	..	..	..	249
— methiodide	..	..	oil	..	..	..	249
Benzoyl-ψ-codeine	..	..	..	..	..	..	428
— hydrochloride	174–184	..	..	..	..	..	428
— methiodide	206–208	..	..	..	..	..	428
ψ-codoino phenylurethane	..	..	oil	..	..	..	428
— hydrochloride	73–94	EtOH	..	..	..	..	428
— methiodide	243–244	H_2O	..	..	..	..	428
ψ-codoino methyl ether	137	..	..	−80	15	EtOH	403, 418–20
— hydrochloride·½EtOH	278–280	..	..	−53·7	23	H_2O	406
	285	EtOH	..	−60	20	H_2O	410
— hydriodide	238–240	..	..	..	..	..	410

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
ψ-codeine methyl ether sulphate	241	..	..	..	..	..	418
— nitrate	219	..	..	..	..	..	418
— methiodide	D.270–271	..	..	..	..	..	418–19, 411
ψ-codeine ethyl ether	76	..	..	..	..	..	420
— hydrochloride	225	..	..	..	..	..	420
— hydriodide	267–270	..	..	..	..	..	420
ψ-codeine propyl ether	..	..	not cryst.	..	..	..	420
— hydriodide	259	..	..	..	..	..	420
ψ-codeine phenyl ether	187	..	..	..	..	..	420, 418
ψ-codeine o-tolyl ether	189	..	..	..	..	..	420
ψ-codeine *m*-tolyl ether	144	..	..	..	..	..	420
— nitrate	192	..	..	..	..	..	420
ψ-codeine *p*-tolyl ether	165	..	..	−13·7	20	$CHCl_3$	420
— hydrochloride	231	..	..	..	..	..	420
— nitrate	181	..	..	..	..	..	420
ψ-codeine guaiacyl ether	214	..	..	−22·9	20	$CHCl_3$	420
— nitrate	197	..	..	..	..	..	420
— oxalate	197	..	..	..	..	..	421
— tartrate	205	..	..	..	..	..	420
Dihydro-ψ-codeine-A	121–122	EtOAc	plates	−41·4	28	EtOH	421
— hydrochloride	239–240 260–265	EtOH ..	plates ..	−24 −26	28 25	H_2O H_2O	421 463
— hydriodide	287	H_2O	..	−22·5	28	H_2O	421
— methiodide	241–243	H_2O	octa-hedra	−22·1	28	H_2O	421
p-phenylbenzoyldihydro-ψ-codeine-A	191–192	EtOH	..	+44·7	25	dioxane	304
Dihydro-ψ-codeine-A methyl ether	127	EtOH +H_2O	plates	+35	25	EtOH	426
— perchlorate	243–244	H_2O	plates and prisms	−6·5	27	H_2O	426
Dihydro-ψ-codeine-B. 2 forms	196–197 174·5–175·5	Benzene EtOAc	.. prisms	.. ..	.. ..	.. ..	.. 423
Dihydro-ψ-codeine-B·EtOH	125–127	EtOH	needles	−14·1	24	EtOH	295, 423
— methiodide	D. 275	H_2O	leaflets	..	..	..	295
Dihydro-ψ-codeine-C. 2 forms	167·5–168 110–116	..	..	+13	22	95% EtOH	423
Dihydro-ψ-codeine-C methyl ether	..	..	oil	..	..	..	426
— hydriodide	161–162	H_2O	prisms	+48	27	H_2O	426
— perchlorate	252–255	H_2O	plates	+38·7	27	H_2O	426
— methiodide	230–232	MeOH	plates	+43	30	H_2O	426
Tetrahydro-ψ-codeine	114–115	EtOH	prisms	−17·8	21	EtOH	421, 295, 408
— hydrochloride	263 D. 238–240	.. EtOH	.. ..	+ 1·9 ..	25 ..	H_2O ..	421 295
— salicylate·H_2O	165–166	..	..	−1·7	24	EtOH	421
- salicylate·$2H_2O$	135–136	EtOH	..	..	..	..	421
- methiodide	D.249–250	..	..	−0·9	26	H_2O	295, 421
Diacetyltetrahydro-ψ-codeine	137–138	EtOH+H_2O	leaflets	..	..	..	..
Tetrahydro-ψ-codeine methyl ether·$\frac{1}{2}H_2O$	125–130	60% EtOH	plates	−5	30	EtOH	426
— hydriodide	251–252	H_2O	needles	+6	27	H_2O	426
- methiodide	250–255	H_2O	..	+25·5	27	H_2O	426
1-chloro-ψ-codeine	203–204	50% EtOH	needles	−100·8	15	90% EtOH	428
1-bromo-ψ-codeine	190–192	EtOH	needles	−75·2	15	99% EtOH	428
1-nitro-ψ-codeine	235	EtOH	..	−49·9	15	$CHCl_3$	340, 428
8-acetyl-1-aceto-ψ-codeine	170	EtOH	prisms	−126	18	$CHCl_3$	430
ψ-codeine-N-oxide·H_2O	226–228	EtOH	prisms	..	..	..	295, 341
— picrate	166–168	..	..	..	..	..	295, 341
ψ-codeine-N-oxide sulphonic acid. 2 forms	D. *c.* 300	..	..	..	..	..	295, 341
'Bromo-ψ-codeine dibromide'	220	H_2O+EtOH	..	..	..	..	295
Cyanomor-ψ-codeine methyl ether	170–172	EtOH	needles	..	..	..	353
Cyanomor-ψ-codeine phenyl ether	171	..	..	..	..	..	353

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Allo-ψ-codeine	116–117	EtOH	needles	−235·4	21	EtOH	245, 295
— hydrochloride	256–257	..	prisms	−199	25	H_2O	463
— hydriodide	D.280–285	H_2O	..	−153	15	H_2O	407
— methiodide	215–216	EtOH	..	−142	15	H_2O	243, 245, 253, 407
Acetylallo-ψ-codeine	194–195	EtOH	needles	..	..	..	407
— methiodide	260	..	..	..	..	..	407
Dihydroallo-ψ-codeine-A	78–79	EtOAc+ petrol	..	−105	25	EtOH	431
— hydriodide	255d.	EtOH	..	−70	26	H_2O	431
— perchlorate	265–270	H_2O	..	−83·0	30	H_2O	431
— acid tartrate	124–125 and 160–163	H_2O	..	−50	25	H_2O	431, 463
Dihydroallo-ψ-codeine-C	.	..	oil	..	.	.	431
— perchlorate	145–147	H_2O	..	−16	25	H_2O	431
— methiodide	247–248d.	EtOH	..	−5 5	27	H_2O	431
Tetrahydroallo-ψ-codeine·EtOAc	113–118	EtOAc	scales	−52	25	EtOH	431
Tetrahydroallo-ψ-codeine (anhyd.)	145·5	subl.	..	−58	25	EtOH	295, 431
— hydrochloride	245–248	..	..	+1·8	24	H_2O	467
— perchlorate	102–104	H_2O	..	−35	23	H_2O	431
— methiodide	252	H_2O	needles	..	..	..	295
	241–242	MeOH	..	−22	27	H_2O	431
Diacetyltetrahydroallo-ψ-codeine	115	..	..	..	..	..	295
Allo-ψ-codeine-N-oxide sulphonic acid (2 forms)	271	..	..	..	..	..	295
	D. 280	..	..	..	..	..	295
'Bromoallo-ψ-codeine dibromide'	206–207	EtOH	..	..	..	..	295
8-acetyl-1-acetoallo-ψ-codeine	..	..	oil	..	..	..	430
Molecular compound isocodeine+ allo-ψ-codeine	145–145·5	..	..	−205	..	..	244, 253

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V

PORPHYROXINE

MERCK [1] in 1837 and Robertson [2] later isolated from Bengal opium a substance they named porphyroxine, but this was clearly not a single compound and was believed by Hesse [3] to be a mixture of rhoeadine, meconidine, and other alkaloids, and indeed it resembles rhoeadine in its properties and method of preparation [4]. Dey [5] also reported the preparation from opium of a substance that gave a violet colour with mineral acid, a reaction cited by Merck [1] as characteristic of porphyroxine.

In 1919 Rakshit [6] isolated a substance that he claimed was pure porphyroxine, and that he believed was the main component of Merck's preparation. The substance was obtained as pale yellow or colourless prisms, m.p. 134–135° C., and gave the following colour reactions:

Reagent	*Colour*
conc. H_2SO_4	red
conc. H_2SO_4 + trace $K_2Cr_2O_7$.	grass green
conc. HNO_3	pale yellow
conc. HCl	orange
iodine solns. + base . . .	orange-red ppt.
iodine solns. + base in dil. HCl .	brick red ppt.

Samples of numerous preparations were analysed, one of which corresponded to $C_{19}H_{23}O_4N$.

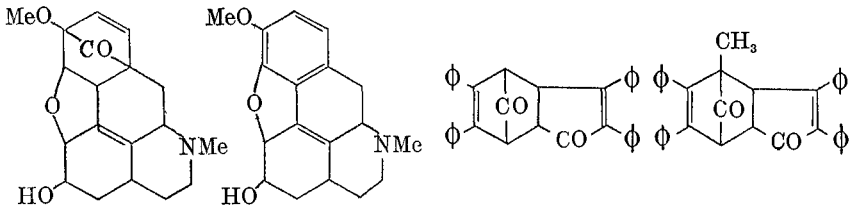
Further analysis indicated that porphyroxine contained one —OMe group, and that it was a tertiary base readily giving quaternary salts [7]. An acetyl-derivative was prepared showing the alkaloid to be an alcohol as the free hydroxy-compound was alkali-insoluble. The presence of a carbonyl group in the molecule was demonstrated by the preparation of an oxime, semicarbazone, and phenylhydrazone. Methylporphyroxine was obtained by treating the quaternary salts with alkali, and methyltetrahydroporphyroxine by sodium amalgam reduction of porphyroxine methomethylsulphate. These derivatives also yielded oximes [7].

The most important reaction of porphyroxine from a structural point of view is its reported conversion to codeine and formic acid on boiling with hydrogen peroxide in weakly alkaline solution, represented by Rakshit as:

$$C_{19}H_{23}O_4N = C_{18}H_{21}O_3N + 2H + CO \xrightarrow{H_2O_2} C_{18}H_{21}O_3N + H_2O + H\cdot COOH,$$

and it was argued that since the carbonyl group and two additional

atoms of hydrogen are removed simultaneously they are attached to the same ring of codeine. Accordingly Rakshit [7] proposed the structure [I] for porphyroxine, basing it on that suggested by Pschorr for codeine [II] [8], a return to which is now inconceivable and was even then (1926) highly improbable. Porphyroxine was in addition reported to give phenanthrene, ammonia, and trimethylamine on distillation with zinc-dust [7].



[I] [II] [III] [IV]

The evidence for the existence of porphyroxine as a chemical individual has been critically examined by Rajagopalan [9], who cited the following facts:

(*a*) Attempts to isolate the base from the mother liquors of the preparation of codeine from Bengal opium failed [10].

(*b*) In the separation of alkaloids from Japanese opium, Machiguchi obtained a mixture of codamine, laudanine, and meconidine, identical in melting-point and other characteristics with Rakshit's porphyroxine [11].

(*c*) Rakshit's distinctive specific colour test for porphyroxine, red with hot dilute hydrochloric acid [12], is not distinctive for Indian opium [13].

(*d*) There is no parallel in nature for carbonyl-bridged compounds such as [I], but compounds of this type have recently been prepared synthetically (e.g. [III] [14] and [IV] [15]), and their behaviour towards alkaline hydrogen peroxide is quite different from that reported for porphyroxine. For example, [III] on treatment with hydrogen peroxide and cold alkali gives a peroxide containing four atoms of oxygen, and this explodes on heating, reverts to [III] on treatment with hydrogen bromide or iodide, halogen being liberated, and is converted to an isomer of [III] with liberation of oxygen on warming in acetic acid [16].

(*e*) When codeine is heated with hydrogen peroxide codeine-N-oxide is formed [17] together with a dimolecular oxide [18], and Rakshit made no mention of finding these in the products of the action of hydrogen peroxide on porphyroxine.

A careful investigation of the components of Bengal opium by Rajagopalan [9] failed to reveal any substance corresponding to

porphyroxine and led him to suggest that the latter was in fact only impure codeine, and to draw attention to the fact that Rakshit did not report having found codeine during the isolation of porphyroxine.

It must be concluded, therefore, that it is very likely that no such alkaloid as porphyroxine exists and that whilst the preparations of Merck [1] and Robertson [2] are clearly mixtures, the so-called pure alkaloid isolated by Rakshit was very probably a mixture of bases [11] containing a considerable amount of codeine [9].

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Porphyroxine	134–135	..	prisms	−139·9	32	$CHCl_3$	6
— hydrochloride	155	H_2O	needles	−118·8	32	H_2O	6
— hydrobromide	148–150	H_2O	needles	−90·6	32	H_2O	6
— hydriodide	115	..	powder	−77·8	32	EtOH	6
— aurichloride	..	..	amorph.	..	..	..	6
— platinichloride	D. 204	H_2O	powder	..	..	..	6
— nitrate	122	H_2O	tablets	−115·4	32	H_2O	6
— sulphate	193	H_2O	plates	−111·4	32	H_2O	6
— phosphate	117	H_2O	powder	−98·2	32	H_2O	6
— oxalate	182	H_2O	prisms	−114·2	32	H_2O	6
— citrate	82–85	..	amorph.	−108·6	32	H_2O	6
— tartrate	116–118	..	..	−95·5	32	H_2O	6
— picrate	198	..	..	−49·9	32	H_2O	6
— methochloride	c. 171	..	..	−90·4	34	H_2O	7
— methiodide	150–152	..	amorph.	−82·5	25	MeOH	7
— methomethylsulphate	205	MeOH	needles	−74·6	25	MeOH	7
— methohydroxide	112–115	EtOH	cubes	−71·8	34	EtOH	7
— oxime	c. 198	Et_2O	..	..	..	..	7
— phenylhydrazone	150d.	acetone	..	..	..	..	7
— semicarbazone	D. 244	..	..	..	..	..	7
Acetylporphyroxine	125	benzene	..	−187·2	34	EtOH	7
— hydrochloride	126	H_2O	needles	−123·4	30	H_2O	7
— hydrobromide	c. 155d.	H_2O	needles	−98·8	35	H_2O	7
— hydriodide	104–107d.	EtOH	needles	..	..	..	7
— sulphate	D. c. 190	H_2O	needles	−150·2	34	EtOH	7
— platinichloride	230d.	..	..	..	..	..	7
Methylporphyroxine	125–126	benzene	needles	−131·8	28	$CHCl_3$	7
— oxime	185–186	MeOH	..	..	..	..	7
— phenylhydrazone	189d.	..	amorph.	..	..	..	7
— semicarbazone	217d.	..	..	..	..	..	7
Methyltetrahydroporphyroxine	150	MeOH	plates	..	..	..	7
— oxime	234–235	..	..	..	..	..	7
— phenylhydrazone	126	..	..	..	..	..	7
— semicarbazone	D. c. 210	..	..	..	..	..	7

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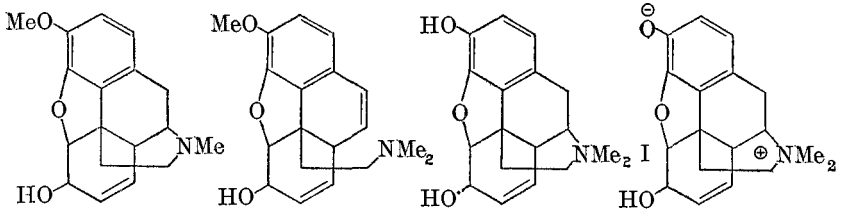
VI

THE CODEIMETHINES AND THEIR DERIVATIVES

THE quaternary salts of codeine and its isomers can be degraded to unsaturated bases to which the general term 'methylmorphimethine' has hitherto been applied, but here the less cumbersome and more systematic term 'codeimethine' [1] will be used, the term methylmorphimethine being reserved for the derivatives obtained from nuclear methylated morphines. The term dihydromethine will be applied to bases in which the double bond introduced by degradation has been saturated. In this way a convenient and unambiguous system of nomenclature is available.

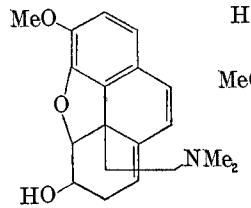
The reaction between silver oxide and the quaternary salts of morphine and codeine was first investigated, inconclusively, by How [2]. Grimaux, by heating codeine [I] methiodide with silver oxide or potassium hydroxide, obtained α-codeimethine [II]; dionin methine likewise could be prepared from dionin (ethyl morphine) methiodide [3–4]. The reaction presumably proceeds by elimination of water from the methohydroxide, and Hesse found that evaporation of codeine methohydroxide solutions over concentrated sulphuric acid affords α-codeimethine [5].

Morphine methiodide [III] cannot be induced to degrade in this way owing to formation of the phenol betaine [IV], from which water cannot be eliminated [6].

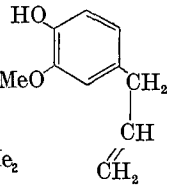


[I] [II] [III] [IV]

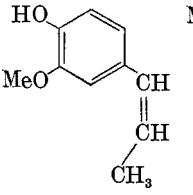
α-Codeimethine [II] when heated alone [7], with water, 50 per cent. alcohol, or, best, alcoholic potassium hydroxide [8] is converted into an isomer, β-codeimethine [V], by migration of the 7:8 double bond into conjugation with that at 9:10. These structures [II] and [V] for the α- and β-isomers receive support from the ultra-violet absorption spectra of the bases, shown in Fig. 2 in comparison with those of codeine [I], eugenol [VI], and *iso*eugenol [VII], and in Fig. 3 in comparison with



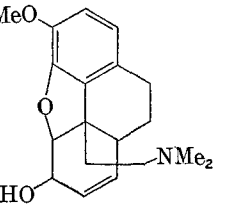
[V]



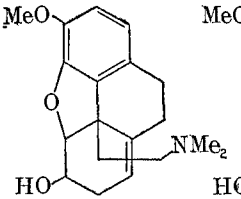
[VI]



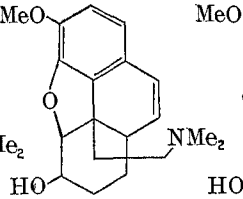
[VII]



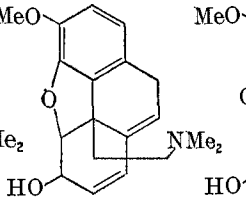
[VIII]



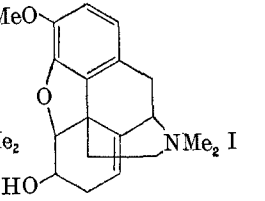
[IX]



[X]



[XI]



[XII]

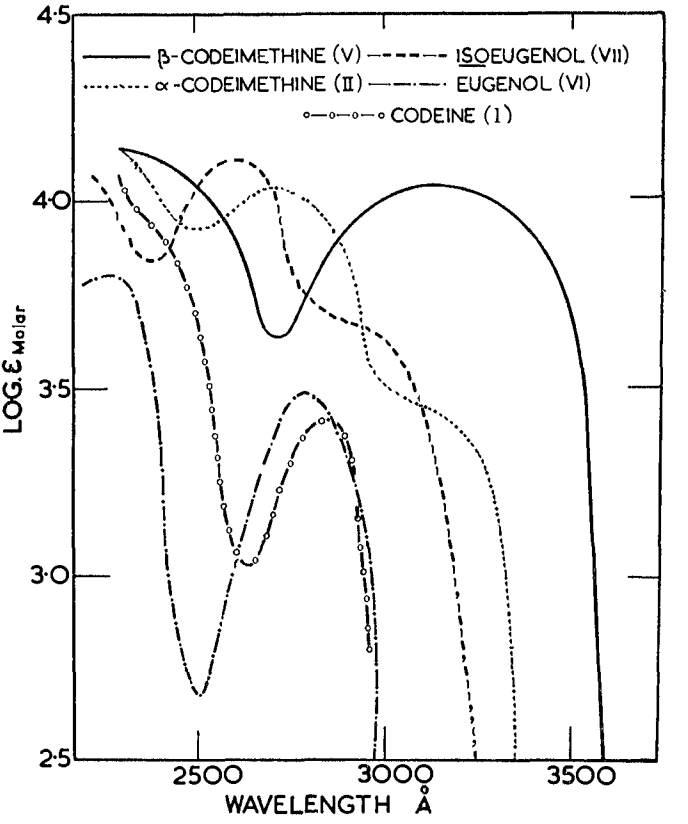


FIG. 2.

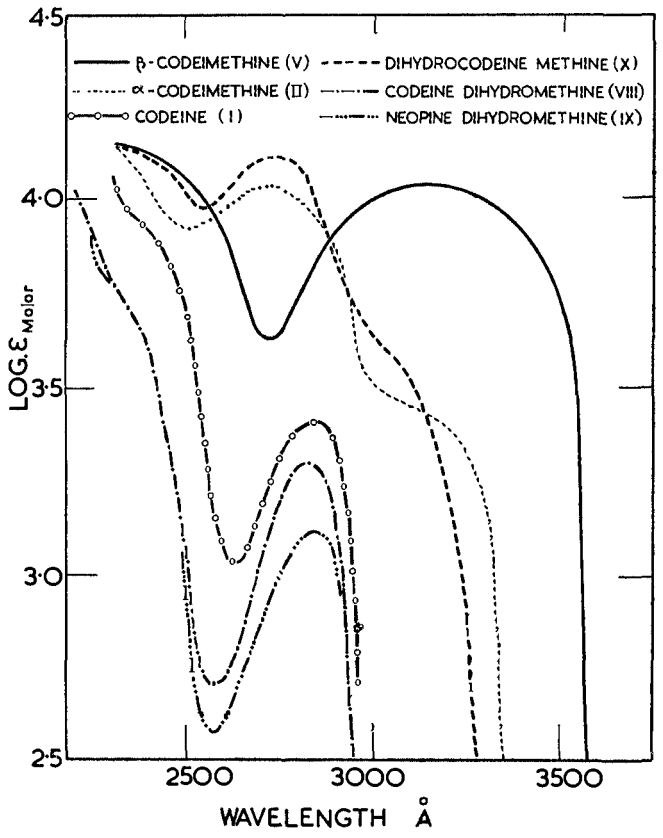


FIG. 3.

those of codeine, codeine dihydromethine [VIII], neopine dihydromethine [IX], and dihydrocodeine methine [X] [9]. The absorption spectrum of α-codeimethine was at one time thought not to be consistent with structure [II], and [XI] was tentatively proposed [10–11], but this is no longer necessary. β-Codeimethine [V] also results directly from the degradation of neopine methiodide [XII], and it was in this way that the structure of neopine was elucidated [12–13]. It is also formed in small amount during the acetic anhydride degradation of α-codeimethine [14] (see below).

OTHER ISOMERS

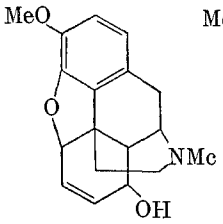
Isocodeine can be degraded to γ-codeimethine, the C-6 epimer of α-codeimethine [15], and like the latter this undergoes isomerization in hot alcoholic alkali, δ-codeimethine, epimeric with the β-isomer, being formed [16]. ψ-Codeine [XIII] can be degraded to ε-codeimethine [XIV] [17–18], the epimer of which, ζ-codeimethine, is obtained by the degradation of allo-ψ-codeine [19]. The last two methines cannot be

isomerized [20] as there is no possibility of an increase in double bond conjugation.

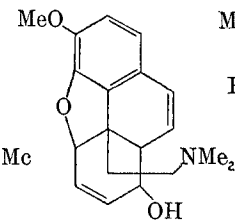
Further Degradation

Further degradation of the methines leads to fully aromatic phenanthrene derivatives of two types: derivatives of 3:4-dihydroxyphenanthrene, and derivatives of 3-hydroxy-4:5-phenanthrylene oxide.

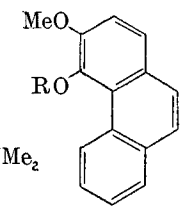
(*a*) When α-codeimethine is heated above 120° C. with acetic anhydride acetylmethylmorphol [XV, R = Ac] is formed [5, 21–22], and this results also from ε-codeimethine and acetic anhydride at 180° C. [20]. β-Codeimethine is stable under these conditions [14]. The basic products of these degradations are β-dimethylaminoethanol [20, 22–23], together with a small amount of dimethylamine [22].



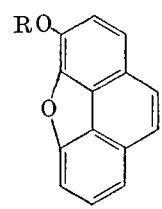
[XIII]



[XIV]



[XV]

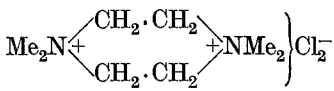


[XVI]

(*b*) Heating with sodium ethoxide at 150° C. converts α-codeimethine to methylmorphol [XV, R = H] and β-dimethylaminoethyl ethyl ether [24].

(*c*) Hydrochloric acid at 180° C. converts α-codeimethine to β-codeimethine, methylchloride, 3:4-dihydroxyphenanthrene, β-dimethylaminoethanol, and tetramethylethylenediamine [24].

Vinyldimethylamine, $CH_2{=}CH \cdot NMe_2$, is probably the initial basic product in these degradations, being subsequently converted to $HO \cdot CH_2 \cdot CH_2 \cdot NMe_2$, $EtO \cdot CH_2 \cdot CH_2 \cdot NMe_2$, or $Cl \cdot CH_2 \cdot CH_2 \cdot NMe_2$ [25], and Knorr has shown that the latter rapidly polymerizes to the piperazine salt [XVII], which is decomposed by alkalis to acetylene, tetramethylethylenediamine, and β-dimethylaminoethanol [26].



[XVII]

(*d*) Hofmann degradation of the codeimethines proceeds with formation of methylmorphenol [XVI, R = Me] [20, 22, 27–30], trimethylamine [5, 20, 22, 28], and ethylene [28]. β-Codeimethine is the most stable, requiring heating of its quaternary salts in cyclohexanol with sodium ethoxide at 120° C. [30] or at 160° C. with alcoholic potassium

hydroxide, when demethylation occurs, the product being morphenol [XVI, R = H] [28]. Mosettig and Meitzner state that β-codeimethine methohydroxide is stable in boiling water, even in the presence of alkali, but its solution on evaporation leaves a lacquer that immediately decomposes to an amine and methylmorphenol on treatment with water, and they suggest that the process of drying changes the methohydroxide to a compound with the side chain so loosely attached that hydrolysis under very mild conditions causes aromatization [30].

The mechanisms of these aromatizing degradations as given by Gulland and Robinson [31] are discussed in Chapter XXVII.

Zinc-dust distillation of α-codeimethine affords 10 per cent. of phenanthrene [14].

Esters and Ethers

The codeimethines can be esterified [5, 32–34, 14, 16–17, 20, 35–37] and methylated. Methylation can be accomplished by methyl sulphate or methyl iodide and cold 1 N. alkali, when quaternary salts of the methyl ethers are obtained [38–39]. The methyl ethers, however, are best prepared by degradation of the corresponding codeine methyl ethers. In this way α- [39–40], γ- [41], and ε- [41–42] codeimethine methyl ethers have been prepared, and the first two named can be converted to the β- and δ-isomers respectively on heating with alcoholic alkali [39, 41]. Emde degradation of codeine methyl ether methochloride affords exclusively α-codeimethine methyl ether [43]. Hofmann degradation of the methiodides of β- [38] and ε- [42] codeimethine methyl ethers affords methylmorphenol [XVI, R = Me], ethylene, trimethylamine, and methanol.

Halogenated Codeimethines

1-Bromocodeine can be degraded to 1-bromo-α-codeimethine [44–45], which can be converted to the β-isomer [46] and degraded to 1-bromomethylmorphenol [32] and 1-bromoacetylmethylmorphol [44–45]. The latter has been converted to 1-bromo-3:4-dimethoxyphenanthrene, identical with an authentic specimen [45].

Bromination of α-codeimethine in chloroform affords 'bromohydroxydihydro-α-codeimethine', $C_{19}H_{24}O_4NBr$, which on acetolysis gives 1-bromo-3-methoxy-4-acetoxyphenanthrene, though the acetyl derivative is reported to give 3-methoxy-4:6-diacetoxyphenanthrene under the same conditions [46]. As an intermediate in the latter degradation 'acetylnorparathebaine methobromide' was obtained and converted to 'norparathebaine methiodide', $C_{19}H_{22}O_3NI$ [47]. Acetyl-α-codeimethine is brominated in the same way in chloroform or dilute acetic acid, but in glacial acetic acid it gives 'acetyldibromodihydro-α-codeimethine', $C_{21}H_{25}O_4NBr_2$, which on boiling with acetic anhydride yields 'acetylbromo*iso*-α-codeimethine', $C_{21}H_{24}O_4NBr$, [46].

Bromination of α-codeimethine methyl ether in chloroform leads to bromohydroxydihydro-α-codeimethine methyl ether, which affords 3:6-dimethoxy-4-acetoxyphenanthrene on acetolysis [48], and in like manner the ε-isomer can be degraded to 3:8-dimethoxy-4-acetoxyphenanthrene [48].

The positions of the bromine atom and additional hydroxyl group in these compounds are unknown but must be such as to allow facile elimination of these in view of the production of halogen-free derivatives of trihydroxyphenanthrene.

Reduction of the Codeimethines

Three α-dihydrocodeimethines have been prepared as follows:

(i) α-**Dihydrocodeimethine-A** (*codeine dihydromethine*) [VIII], which results from the reduction of α-codeimethine by sodium, liquid ammonia, and alcohol. The yield is below 50 per cent. owing to the formation of phenolic substances, presumably of the dihydrodesoxycodeine type. It cannot be prepared by the sodium-ammonia reduction of codeine methiodide, which apparently gives dihydrodesoxycodeine-C dihydromethine [9] (see Chaps. IV and IX).

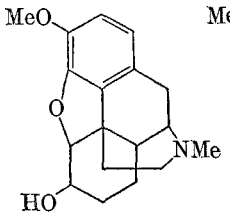
(ii) α-**Dihydrocodeimethine-B** (*neopine dihydromethine*) [IX], obtained by the sodium-alcohol reduction of α-codeimethine [29, 49] which involves prior rearrangement to the β-compound, the mild catalytic [50] or sodium amalgam [51] reduction of β-codeimethine, and the reduction of neopine methiodide [XII] by sodium and liquid ammonia [52]. The latter reduction and its failure to undergo isomerization serve to fix its structure as [IX]. The methyl ether results from the mild catalytic hydrogenation of β-codeimethine methyl ether [53].

(iii) α-**Dihydrocodeimethine-C** (*dihydrocodeine methine*) [X] is formed by the mild catalytic hydrogenation of α-codeimethine [50] and the Hofmann degradation of dihydrocodeine [XVIII] [54–56]. The ultra-violet absorption spectrum shows the presence in [X] of the same conjugated system as in α-codeimethine, whilst the spectra of [VIII] and [IX] show no conjugation in these compounds (Fig. 3). [X] is also obtained when α-codeimethine is boiled with Raney nickel in alcohol, together with dihydrocodeinone methine [XIX] [9], the latter arising from a rearrangement of α-codeimethine similar to the isomerization of codeine to dihydrocodeinone under the influence of noble metal catalysts [57–62] (see Chap. IV). The C-6 epimer of [X], i.e. γ-dihydrocodeimethine-C (dihydroisocodeine methine), results from the Hofmann degradation of dihydroisocodeine [55].

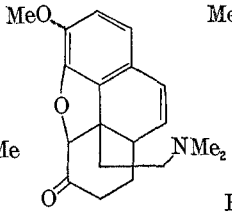
Vongerichten [46] reported the bromination of a dihydrocodeimethine of unspecified origin to α-bromodihydrocodeimethine (m.p. 165° C.) and the isomerization of this to a β-compound (m.p. 169° C.). It seems probable that these two supposed isomers are identical as there is no

reason why [VIII], [IX], or [X] should undergo isomerization. A fourth isomer [XX] is admittedly possible and this should isomerize to [X], but there is no evidence that such a compound has ever been prepared.

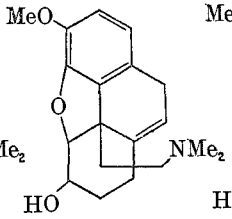
The Hofmann degradation of the dihydrocodeimethines is considered below.



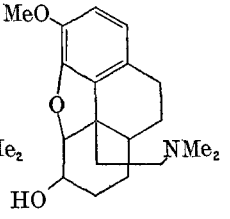
[XVIII]



[XIX]



[XX]



[XXI]

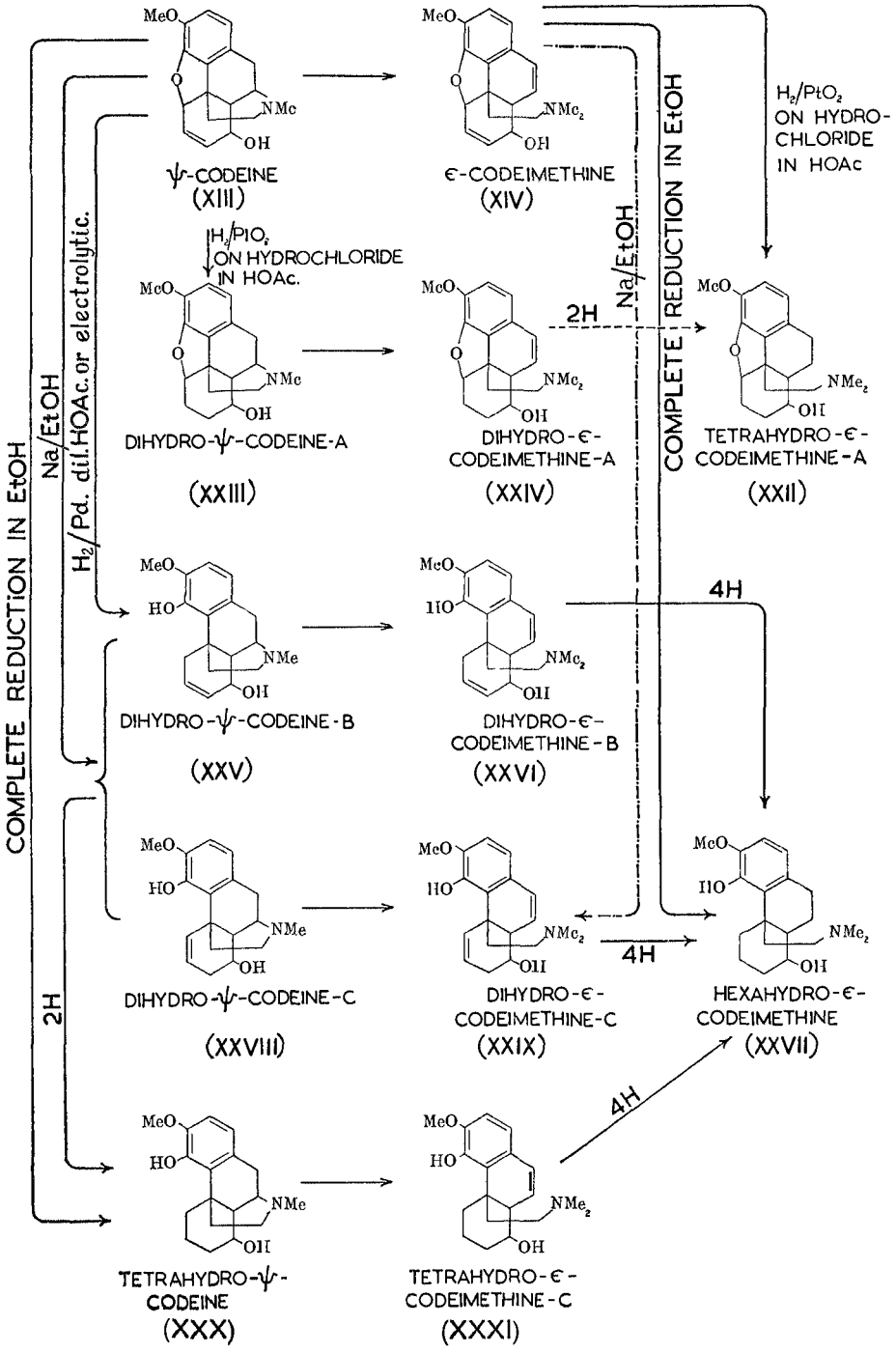
α-**Tetrahydrocodeimethine** [XXI] is the product of further reduction of the α-dihydrocodeimethines and complete reduction of α- and β-codeimethine [40, 51, 53–4, 56, 63–64]. Its acetyl ester [63] and methyl ether [53] are also known. In the same way reduction of γ- and δ-codeimethine affords the epimer of [XXI], i.e. γ-tetrahydrocodeimethine [40, 63]. The —CH·OH— group of [XXI] is oxidized to —CO— by chromic acid, the product being dihydrocodeinone dihydromethine [64].

The Reduction of ε- and ζ-Codeimethines

This is complicated by the fact that these substances are allylic ethers and can suffer reduction with opening of the cyclic ether link in addition to saturation of the double bonds. The reduction of ε-codeimethine runs parallel to the reduction of ψ-codeine, which varies according to the conditions, hydrogenation of the hydrochloride in glacial acetic acid using a platinum oxide catalyst favouring saturation of the double bonds only. In this way ψ-codeine [XIII] is reduced to dihydro-ψ-codeine-A [XXIII] and ε-codeimethine [XIV] to tetrahydro-ε-codeimethine-A [XXII] and hexahydro-ε-codeimethine [XXVII] [65]. The latter is the sole product when ε-codeimethine is hydrogenated in neutral solution [63, 65]; it resembles tetrahydrodesoxycodeine in being alkali-insoluble [65].

Degradation of dihydro-ψ-codeine-A [XXIII] yields dihydro-ε-codeimethine-A [XXIV], which can be reduced only to tetrahydro-ε-codeimethine-A [XXII].

Hydrogenation of ψ-codeine in dilute acetic acid [65] or electrolytic reduction [55] affords dihydro-ψ-codeine-B [XXV] obtained together with dihydro-ψ-codeine-C [XXVIII] by reduction with sodium and alcohol [66]. These two compounds suffer Hofmann degradation in the usual way giving, respectively, dihydro-ε-codeimethine-B [XXVI] [55, 66] and dihydro-ε-codeimethine-C [XXIX] [66], the latter also being


COMPLETE REDUCTION IN EtOH
Na/EtOH
H2/Pd. dil.HOAc. or electrolytic.
2H
ψ-CODEINE
(XIII)
H2/PtO2
ON HYDROCHLORIDE
IN HOAc.
DIHYDRO-ψ-CODEINE-A
(XXIII)
DIHYDRO-ψ-CODEINE-B
(XXV)
DIHYDRO-ψ-CODEINE-C
(XXVIII)
TETRAHYDRO-ψ-
CODEINE
(XXX)
ε-CODEIMETHINE
(XIV)
H2/PtO2
ON HYDRO-
CHLORIDE
IN HOAc
Na/EtOH
COMPLETE REDUCTION IN EtOH
2H
DIHYDRO-ε-
CODEIMETHINE-A
(XXIV)
TETRAHYDRO-ε-
CODEIMETHINE-A
(XXII)
4H
DIHYDRO-ε-
CODEIMETHINE-B
(XXVI)
4H
DIHYDRO-ε-
CODEIMETHINE-C
(XXIX)
HEXAHYDRO-ε-
CODEIMETHINE
(XXVII)
4H
TETRAHYDRO-ε-
CODEIMETHINE-C
(XXXI)

produced in small but significant yield by the reduction of ϵ-codeimethine with sodium and alcohol [66]. Both isomers can be reduced to hexahydro-ϵ-codeimethine [XXVII] [66].

Hydrogenation of ψ-codeine in neutral solution affords tetrahydro-ψ-codeine [XXX] which yields tetrahydro-ϵ-codeimethine-C [XXXI] on degradation, the latter being reducible to hexahydro-ϵ-codeimethine [55, 65].

The methyl ethers of [XIV], [XXIV], [XXIX], and [XXXI] have been obtained by degradation of the corresponding ψ-codeine derivatives. [XIV], [XXIX], and [XXXI] methyl ethers are reduced to hexahydro-ϵ-codeimethine methyl ether, whilst the ether of [XXIV] is reduced to tetrahydro-ϵ-codeimethine-A methyl ether [67].

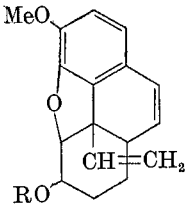
Though the reduction of allo-ψ-codeine shows certain differences from that of ψ-codeine (see Chap. IV), reduced ζ-codeimethines corresponding to [XXIV], [XXII], [XXVII], and [XXXI] have been prepared [55, 63, 68].

HOFMANN DEGRADATION OF THE REDUCED CODEIMETHINES

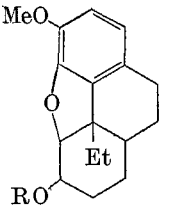
(*a*) Neopine dihydromethine [IX] methiodide is unaffected by boiling with aqueous alkali and is only slowly degraded by sodium *cyclo*hexoxide in boiling cyclohexanol, giving what is clearly a mixture, the separation of which has not been attempted [52]. Trimethylamine and a nitrogen-free substance are reported to result from heating the methohydroxide with alcoholic potash at 160° C. [29], but this salt simply loses methyl alcohol when heated with acetic anhydride [49].

(*b*) Dihydrocodeine methine [X] methiodide was reported initially to suffer degradation to trimethylamine [54, 56] and a nitrogen-free substance $C_{17}H_{18}O_3$ [55], but this degradation has recently been shown to be more complex [39]. Dry-distillation of the methohydroxide yields an oil that can be resolved into three components: 34 per cent. of the original base; 30 per cent. 6-hydroxy-13-vinylhexahydromethyl morphenol [XXXII, R = H], and 30 per cent. 6-Methoxy-13-vinylhexahydromethylmorphenol [XXXII, R = Me], and this was the first case in which methylation of the alcoholic group had been observed during exhaustive methylation of a morphine derivative. These nitrogen-free substances can be hydrogenated to 6-hydroxy- and 6-methoxy-13-ethyloctahydromethylmorphenol, [XXXIII, R = H] and [XXXIII, R = Me], respectively with absorption of two moles of hydrogen. The latter two compounds are also obtained by hydrogenation of 6-hydroxy- and 6-methoxy-13-vinyloctahydromethylmorphenol [XXXIV, R = H] and [XXXIV, R = Me] respectively, which result (together with 40–50 per cent. of undegraded base) from the degradation of α-tetrahydrocodeimethine [XXI]. [XXXIV, R = Me] can also be prepared by the degradation of α-tetrahydrocodeimethine methyl ether, a reaction by which its structure is conclusively proved [39].

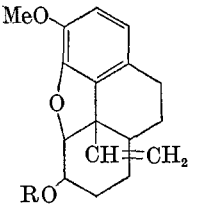
The isocodeine analogue of [X] has also been reported to give a nitrogen-free substance on degradation [55], but the reaction has not been investigated as above.



[XXXII]



[XXXIII]



[XXXIV]

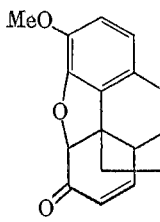
(*c*) The degradation of α-tetrahydrocodeimethine was first reported to give trimethylamine [54, 56] and amorphous products [56], but the reaction has been elucidated as above [39].

(*d*) The further degradation of ε and ζ-codeimethines has been only superficially studied. Tetrahydro-ζ-codeimethine-C [XXIX epimer] methiodide loses trimethylamine in hot alkali [55] and hexahydro-ε-codeimethine [XXVII] has been degraded in the form of its acetyl-derivative methiodide to a substance $C_{19}H_{24}O_4$ [63].

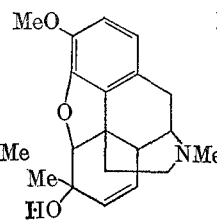
6-Methylcodeimethines

When codeinone [XXXV] is treated with lithium methyl a nearly quantitative yield of one isomer of 6-methylcodeine [XXXVI] is obtained, and this can be degraded to 6-methyl-α-codeimethine [XXXVII], which can be isomerized to 6-methyl-β-codeimethine [XXXVIII]. Dry distillation of the methohydroxide of [XXXVII] affords 6-methylmorphenol methyl ether [XXXIX] [69].

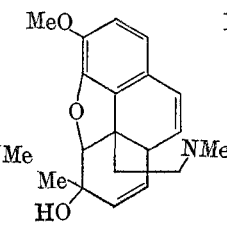
Similarly, treatment of dihydrocodeinone with lithium methyl affords 6-methyldihydrocodeine [XL], which can be degraded to 6-methyldihydrocodeine methine [XLI] and 6-methyl-6-hydroxy-13-vinylhexahydromethylmorphenol [XLII, R = CH=CH_2], the latter giving 6-methyl-6-hydroxy-13-ethyloctahydromethyl morphenol [XLII, 9:10-dihydro, R = Et] on reduction [70].



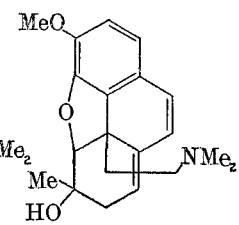
[XXXV]



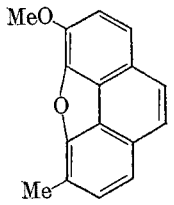
[XXXVI]

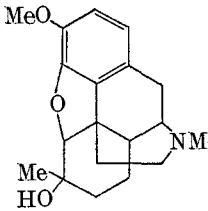


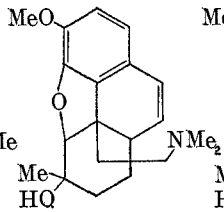
[XXXVII]

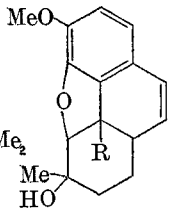


[XXXVIII]


[XXXIX]


[XL]


[XLI]


[XLII]

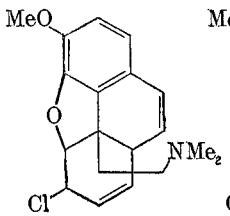
As degradation of 1-bromocodeine yields 1-bromo-α-codeimethine, so degradation of 1-nitrocodeine yields 1-nitro-α-codeimethine [71].

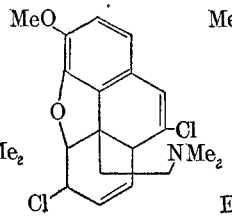
Replacement of the Hydroxyl Group

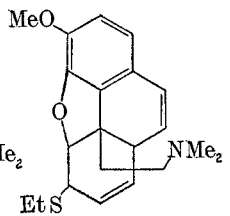
(*a*) Codeimethine derivatives in which the hydroxyl group has been replaced by chlorine can be prepared, but not by degradation of the chlorocodides. A solution of α-chlorocodide methohydroxide is strongly alkaline and gives no silver chloride on addition of silver nitrate, but on boiling the solution becomes neutral and silver chloride is precipitated [44]. However, α-chlorocodeimethine [XLIII] is obtained by the action of phosphorus trichloride on α-codeimethine in chloroform (the reaction in absence of solvent yields the phosphorous ester of α-codeimethine), whilst a dichlorocodeimethine [XLIV ?] results if phosphorus pentachloride is used [37].

α-Chlorocodeimethine is converted by acetolysis to acetylmethylmorphol [XV, R = Ac] and β-methylaminoethanol, β-dimethylaminoethanol, or tetramethylethylenediamine according to the conditions [37], whilst heating the base with ethanol and ether at 100° C. affords methylmorphol [XV, R = H] and the piperazine salt [XVII] [71]. An amorphous substance having the properties of a phenol and the salt of a quaternary base is obtained by heating the base in benzene, and this on successive treatment with methyl iodide, potassium hydroxide, methyl sulphate, and potassium iodide is converted to a substance $C_{19}H_{21}O_2N \cdot MeI$ containing two methoxyl groups [71].

Acetolysis of the dichlorocodeimethine gives the same basic products as acetolysis of [XLIII] and 3-methoxy-4:9 (or 10)-diacetoxyphenanthrene, identical with the product of degradation of 9 (or 10)-hydroxycodeine [37] (see below).


[XLIII]


[XLIV]


[XLV]

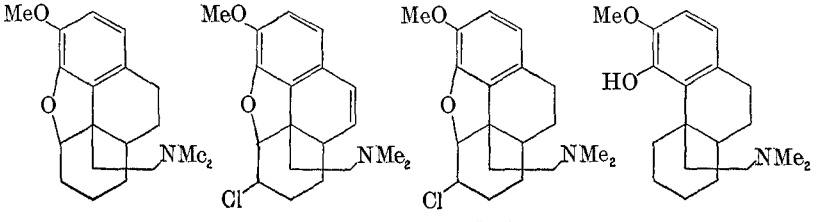
In the same way that hydrolysis of α-chlorocodide gives isomers of codeine with no trace of codeine (see Chap. VIII) hydrolysis of α-chlorocodeimethine gives a mixture of γ-, δ-, and ε-codeimethines, but no α-codeimethine. If the hydrolysis is carried out above 100° C., an additional product is a dihydrate of the ε-isomer in which one molecule of water forms part of the molecular structure; this is also formed from ε-codeimethine by heating a solution of the acetate, and can be converted back to the normal form by heating above 80° C. *in vacuo* [72]. α-chlorocodeimethine is regenerated by the action of phosphorus pentachloride on γ-codeimethine [63].

(*b*) Degradation of α-ethylthiocodide, or of bromocodide in the presence of ethylmercaptan, affords α-ethylthiocodeimethine [XLV], and this is isomerized by heating with sodium ethoxide to the phenolic β-ethylthiocodide methine, also formed by the action of sodium ethoxide and ethylmercaptan on [XLIII]. These compounds, and δ-ethylthiocodeimethine, which is really related to ε- or ζ-codeimethine, are discussed in Chapter XVII [73–74].

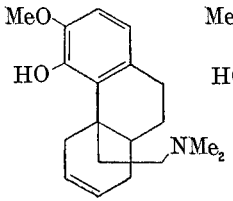
(*c*) Catalytic reduction of α-chlorocodeimethine [XLII] with a palladium catalyst gives a mixture of a crystalline 'desoxytetrahydrocodeimethine' (dihydrodesoxycodeine-D dihydromethine) [XLVI] (which can be degraded to a nitrogen-free substance, $C_{17}H_{20}O_2$) and an oily isomer that resists degradation [63].

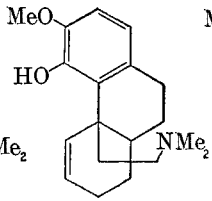
(*d*) α-Chlorodihydrocodeimethine-C [XLVII] results from the degradation of 6-chlorodihydrocodide, and gives α-chlorotetrahydrocodeimethine [XLVIII] on reduction [54], the latter also being formed by the interaction of phosphorus pentachloride and α-tetrahydrocodeimethine [63]. Speyer and Koulen reduced [XLVIII] with sodium and alcohol and obtained a substance they believed to be 'dihydrodesoxytetrahydrocodeimethine' [XLIX] [63], but that was shown by Cahn [75] to be unsaturated, and to be either [L] (dihydrodesoxycodeine-B dihydromethine) or [LI] (dihydrodesoxycodeine-C dihydromethine), to which the name 'dihydrodesoxydihydrocodeimethine' was given. A base believed to be [LI] is produced by the sodium, liquid ammonia, and alcohol reduction of codeine methiodide [9].

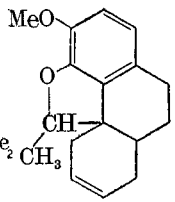
Cahn's 'dihydrodesoxydihydrocodeimethine' was hydrogenated to 'dihydrodesoxytetrahydrocodeimethine' [XLIX] and these two bases

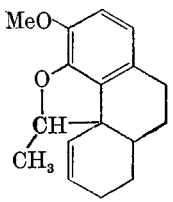


[XLVI] [XLVII] [XLVIII] [XLIX]

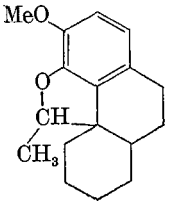

[L]

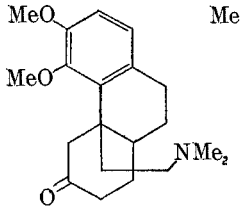

[LI]

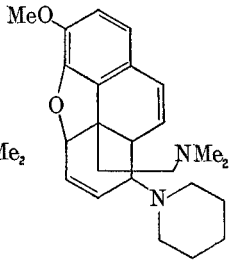

[LII]


[LIII]

were degraded to nitrogen-free substances $\Delta^{6\ 7}$-dehydrothebenane [LII] (or the $\Delta^{5\ 6}$ isomer [LIII]) [63, 75] and thebenane [LIV] [75]. The methyl ether of [XLIX], which resists further degradation, appears to be identical with the product of Clemmensen reduction of dihydrothebainone dihydromethine methyl ether [LV].


[LIV]

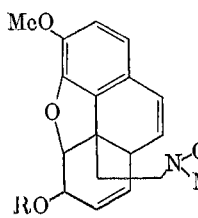

[LV]

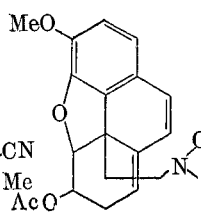

[LVI]

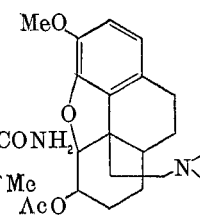
(*e*) Degradation of 8-piperidocodide (see Chap. VIII) gives 8-piperidocodeimethine [LVI], corresponding to either ϵ- or ζ-codeimethine [76–77].

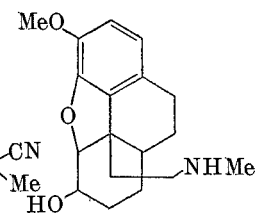
α-Codeimethine and its tetrahydro-derivative behave as typical amines, giving N-oxides on heating with hydrogen peroxide. The tetrahydro-N-oxide on sulphonation yields (like codeine-N-oxide) two sulphonic acids, whilst the N-oxide of α-codeimethine does not yield a sulphonic acid [63].

Cyanogen bromide converts acetyl-α-codeimethine to cyanonoracetyl-α-codeimethine [LVII, R = Ac] [33, 78]; acetyl-β- and γ-codeimethines behave likewise. [LVII, R = Ac] is saponified to α-cyanonorcodeimethine [LVII, R = H], whilst the β-derivative gives the urea [LVIII]


[LVII]


[LVIII]

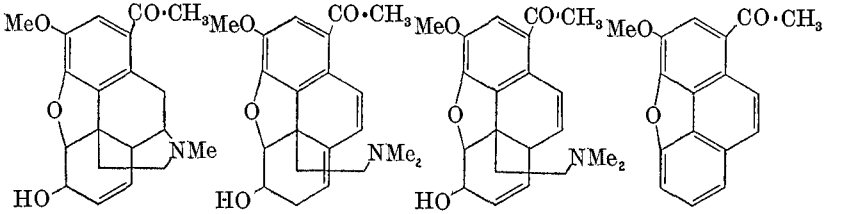

[LIX]


[LX]

on treatment with sodium ethoxide. All three cyanonoracetyl-derivatives can be reduced to the corresponding tetrahydro-compounds [LIX] which can be hydrolysed to nortetrahydro-α (and γ)-codeimethine [LX]; the α-derivative of the latter was re-converted to α-tetrahydrocodeimethine methiodide [50].

ACETOCODEIMETHINES

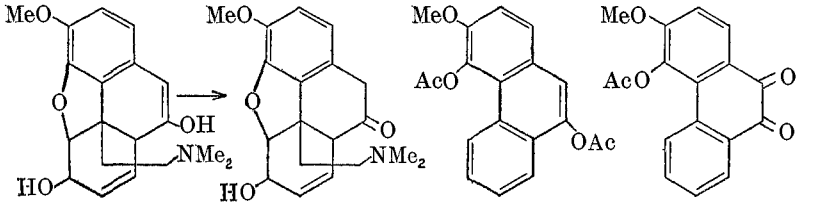
Hofmann degradation of 1-acetocodeine [LXI] (see Chap. IV) leads readily to 1-aceto-β-codeimethine [LXII] [79], the α-isomer [LXIII] only being obtained if the degradation is stopped after five minutes [80]. The β-isomer can be degraded to 1-acetyl-3-methoxy-4-hydroxyphenanthrene by heating with sodium ethoxide at 160° C. [79]; the methohydroxide of [LXII] on dry-distillation affords 1-acetylmethylmorphenol [LXIV], though on heating in *cyclo*-hexanol with sodium cyclohexoxide an undistillable oil giving no semicarbazone is obtained, probably as the result of a polymerization reaction involving the ketone group [80]. Attempts to prepare [LXIII] and [LXII] by the nuclear acetylation of α- and β-codeimethines failed [80].



[LXI] [LXII] [LXIII] [LXIV]

9 (or 10)-KETODIHYDROCODEIMETHINE

Oxidation of codeine with cold chromic acid and sulphuric acid gives rise to a hydroxycodeine [81] (see Chap. IV) in which the new hydroxyl group is at position 9 or 10, as degradation gives a methine base [LXVI] [82] that on acetolysis is converted to 3-methoxy-4:9 (or 10)-diacetoxyphenanthrene [LXVII ?] [82] which loses an acetoxy group on oxidation to a quinone [LXVIII] [83]. As the methine base [LXVI ?] is a ketone [84, 85] the carbonyl group must arise from [LXV] by tautomerization,

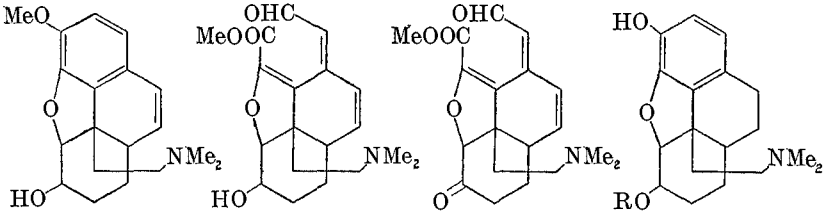


[LXV] [LXVI] [LXVII] [LXVIII]

and a double bond must have appeared at 9:10 during the Hofmann degradation of hydroxycodeine. In this way it was shown that the nitrogen atom in the morphine alkaloids must be attached to position 9 or 10 of the phenanthrene skeleton. The precise location of the hydroxyl group in hydroxycodeine is still uncertain [86].

Ozonolysis of Dihydrocodeine Methine

Rupture of the aromatic nucleus with production of an aldehydo-ester, 7:8-dihydrocodizal-3-methyl ester methine [LXIX], occurs when dihydrocodeine methine [X] is treated with ozonized oxygen in aqueous acid solution. The hydroxyl group of [X] presumably remains intact, as an acetyl ester of [LXIX] can be prepared, and oxidation with chromic acid leads to 6-keto-7:8-dihydrocodizonal-3-methyl ester methine [LXX] which no longer yields an acetyl derivative. [LXIX] can be hydrogenated to a dihydro-derivative [87]. It is surprising that in the ozonolysis of dihydrocodeine methine rupture of the aromatic nucleus at the 2:3 bond occurs, whereas with dihydrocodeine rupture occurs at the 3:4 bond (see Chap. IV).



[X] [LXIX] [LXX] [LXXI]

Derivatives of Morphimethine

As already stated, morphine methiodide cannot be induced to undergo Hofmann degradation owing to the formation of a phenol betaine [6]; nor can a morphimethine derivative be obtained by the demethylation of α- or β-codeimethine, which gives only tars [51]. However, α-dihydrocodeimethine-B (neopine dihydromethine) [IX] can be demethylated by 16 per cent. hydrobromic acid in glacial acetic acid to give the alkali soluble 6-acetyldihydromorphimethine, which can be hydrolysed to dihydromorphimethine. Methylation of the latter, however, does not reproduce [IX], but an isomer that gives α-tetrahydrocodeimethine on reduction, so movement of the double bond must occur during the demethylation.

6-Acetyldihydromorphimethine can be hydrogenated to 6-acetyltetrahydromorphimethine [LXXI, R = Ac], which is insoluble in alkali despite having a free phenolic hydroxyl group. [LXXI, R = Ac] can also be prepared by the demethylation of α-tetrahydrocodeimethine. It can

be hydrolysed to tetrahydromorphimethine [LXXI, R = H], identical with the product of reduction of dihydromorphimethine. The medium of demethylation is important, as attempts to effect the reaction with 48 per cent. hydrobromic acid gave only tars; evidently acetylation precedes demethylation [51].

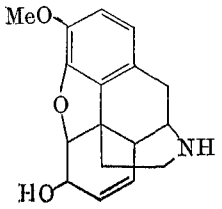
Vongerichten reported the isolation, as a by-product in the preparation of 3:4-diacetoxyphenanthrene by heating diacetyl-morphine with silver acetate and acetic anhydride at 180° C., of a β-morphimethine that could be methylated to β-codeimethine methiodide [88]. Repetition of this work revealed the product to be a monoacetylated β-morphimethine that can be methylated and hydrolysed to β-codeimethine, and reduced to [LXXI, R = Ac] [51].

Stability of the Nitrogen Ring in Codeine

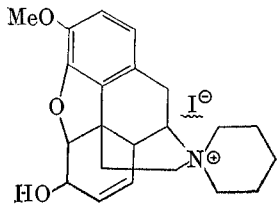
The stability of the nitrogen-containing ring of codeine, compared with that of other cyclic bases, has been investigated by von Braun in an ingenious way [89].

The secondary base norcodeine [LXXII] on treatment with pentamethylene di-iodide gives the salt [LXXIII] in which the nitrogen atom is common to the codeine ring and a piperidine ring. 'Norcodeinium-piperidinium iodide' [LXXIII] suffers degradation to 'codeimethylpiperidine' [LXXIV], the acetate of which is converted by cyanogen bromide to ε-bromoamylcyano-acetylcodeimethylamide [LXXV]. The latter is readily deacetylated and exchanges its bromine for basic residues, ·Oφ, etc. Dihydronorcodeine yields the dihydroderivatives of [LXXIII] and [LXXIV].

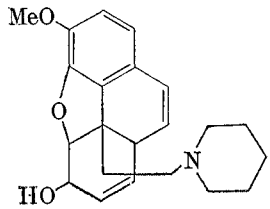
Similarly ω:ω'-dibromoxylene and norcodeine give norcodeinium-dihydro*iso*indolinium bromide [LXXVI] which can be converted to codeimethyldihydro*iso*indole [LXXVII] and ω-bromoxylylcyanoacetyl-codeimethyl-amide [LXXVIII], whilst norcodeinium-morpholinium iodide [LXXIX] (from norcodeine and β:β'-di-iododiethyl ether) can be degraded to codeimethylmorpholine [LXXX]. In all these cases, therefore, the codeine ring was broken in preference to the other heterocyclic ring, presumably owing to the activating influence of the codeine aromatic nucleus.



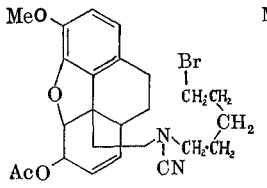
[LXXII]



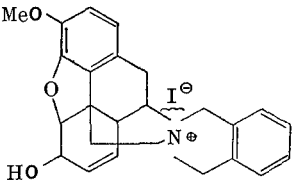
[LXXIII]



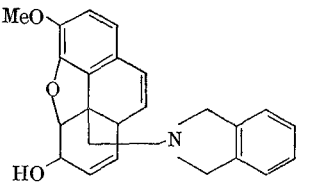
[LXXIV]



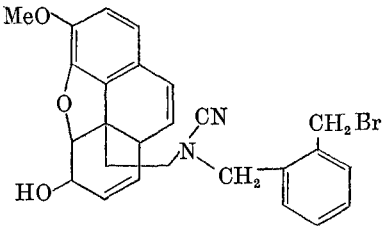
[LXXV]



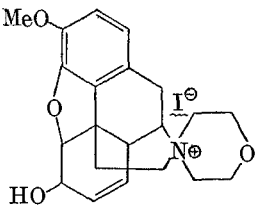
[LXXVI]



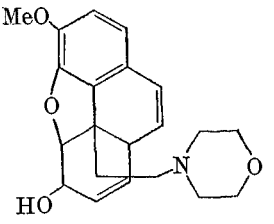
[LXXVII]



[LXXVIII]



[LXXIX]



[LXXX]

X-ray crystallographic studies of α- and β-codeimethines have been carried out by Castelliz and Halla [90] and cryoscopic measurements by von Klobukow [91].

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
α-codeimethine	118·5	EtOH/H_2O	prisms	−212	17	EtOH	4, 5, 14
hydrochloride·2H_2O	105	H_2O	needles	..	..	..	5
perchlorate	183	95% EtOH	prisms	−116·4	20	H_2O	9
dichloride·H_2O	..	..	yellow cryst.	..	..	..	..
benzoate	138	..	..	−112·8	17	H_2O	16
tartrate	165	..	..	..	..	..	14
methiodide	245	..	..	−112	..	99% EtOH	19
				−94·56	17	99% EtOH	14
methochloride	..	..	..	..	..	..	5
N-oxide	D. 188	H_2O	..	..	..	..	63
Acetyl-α-codeimethine	66	H_2O	..	−96·3	17	99% EtOH	5, 14, 33
HCl·$\frac{1}{2}H_2O$	..	..	..	..	..	..	5, 14, 33
methiodide	207	..	..	−73·8	17	EtOH	14
methobromide	207–208	..	..	..	..	..	34
Benzoyl-α-codeimethine	182–183	..	..	..	..	..	37
methiodide	188	..	..	..	..	..	37

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
α-codeimethine methyl ether	94	MeOH petrol	needles	−251·9	24	MeOH	38
— methiodide	256	..	..	−134·4	23	H_2O	38–39
α-codeimethine carbanilide	122–3	..	needles	..	..	..	14
— methiodide	251	..	..	..	..	..	14
β-codeimethine	134–135	EtOH	prisms	+438	17	EtOH	14
— benzoate	157	EtOH	..	+254	17	H_2O	7–8
— methiodide	300–303d.	..	..	+247 +262	19 21	90% EtOH 90% EtOH	7–8 12
Acetyl-β-codeimethine	..	..	amorph.	+413·9	17	EtOH	14
— methiodide	..	..	amorph.	+257·6	17	EtOH	14
Formyl-β-codeimethine	..	..	..	..	..	..	36
β-codeimethine methyl ether	82	petrol	..	+432	17	..	38
— hydriodide	D. 243	..	..	..	..	..	38
— methiodide	318–320	..	..	+268·5 +278·5	22 22	H_2O	38, 39
γ-codeimethine	167–169	..	tablets	+64·3	20	$CHCl_3$	15
— hydrochloride	..	..	cryst.	..	..	..	15
— hydriodide	238–239	..	..	+37	20	H_2O	35
— benzoate	100	..	..	+41·3	15	EtOH	16
— methiodide	265	EtOH	..	+34·7	17	H_2O	15
γ-codeimethine methyl ether	41	..	..	..	..	..	41
— hydriodide·H_2O	192–193	H_2O	..	+20·3	22	H_2O	41
— methiodide	D. 259	..	..	+14	20	H_2O	38–39
δ-codeimethine	111–113	Et_2O	..	+256·6	15	MeOH	16
— benzoate	99–108	H_2O	..	+181·1	15	EtOH	16
— methiodide	282–284	H_2O	..	+150·7	15	EtOH	16
δ-codeimethine methyl ether	71–72	50% MeOH	plates	..	..	..	41
— hydriodide	212	..	..	..	..	..	41
— methiodide	286	..	..	+170·9	28	H_2O	38
ε-codeimethine	129–130	Et_2O	..	−120·1	15	EtOH	20
— hydrochloride·H_2O	150	..	..	−154	15	H_2O	17, 20
— hydriodide	210–213	..	..	−95·6	20	H_2O	35
— methiodide	196–198	..	..	−111	15	H_2O	17, 20
Acetyl-ε-codeimethine	..	..	oil	..	..	..	17
— methiodide	205–210	..	..	−45	15	H_2O	17, 20, 35
ε-codeimethine methyl ether	75	..	..	−92·8	18	EtOH	35, 38
— hydriodide	207	..	..	−85·5	15	H_2O	35, 38
— methiodide	277	..	..	−79·4	20	MeOH	35, 38–9
ζ-codeimethine	..	..	oil	..	..	..	19
— perchlorate	117–118	H_2O	..	−154	28	H_2O	68
— acid tartrate	99–101	H_2O	..	−126	25	H_2O	68
— salicylate	118–120	H_2O	..	−141	25	H_2O	68
— methiodide	c. 180	..	..	−148	15	H_2O	19
α-Dihydrocodeimethine-A (codeine dihydromethine)	..	..	oil	..	..	..	9
— perchlorate	210	90% EtOH	needles	−33·4	20	H_2O	9
— methiodide	265	90% EtOH	prisms	−31·7	20	H_2O	9
α-dihydrocodeimethine-B (neopine dihydromethine)	86–88·5	petrol	prisms	..	..	..	51
— hydrochloride	235–236	H_2O	prisms	−86·3	24	H_2O	51
— perchlorate	216–217	95% EtOH	prisms	−27·7	20	50% EtOH	52
— benzoate	162–164·5	Et_2O	plates	..	..	..	51
— methiodide	263	90% EtOH	prisms	−31·3	19	H_2O	52
— methyl ether	..	..	oil	..	..	..	53
Acetyl-α-dihydrocodeimethine-B	..	..	..	..	..	..	..
— methiodide	265	..	..	+76	22	..	49, 51
α-dihydrocodeimethine-C (dihydrocodeine methine)			oil				50, 54, 56
— perchlorate	201–202	50% EtOH	prisms	..	..	..	9
— methiodide·H_2O	173 160	..	..	..	..	..	54 50, 50

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
α-dihydrocodeimethine-C methiodide (anhyd.)	223–225	..	..	..	..	..	49, 50
γ-dihydrocodeimethine-C	151	EtOH	prisms	..	..	..	55
— methiodide	269	H_2O	needles	..	..	..	55
α-tetrahydrocodeimethine	..	..	oil	..	..	..	54, 63
— hydrochloride·$2H_2O$	94	H_2O	..	−31·9	..	H_2O	54, 63
— hydrochloride (anhyd.)	230·5–232	..	..	..	..	..	51
— hydriodide	251d.	..	..	..	..	..	63, 54
— perchlorate	218–219	..	..	..	..	..	54, 63
— nitrate	174–175	..	..	..	..	..	54, 63
— platinichloride	202	..	..	..	..	..	54, 63
— methiodide	220–221	..	..	..	..	..	54, 63
Acetyl-α-tetrahydrocodeimethine	..	..	oil	..	..	..	63
— hydrobromide	230	..	..	..	..	..	63
— hydriodide	223	..	..	..	..	..	63
— methobromide	225–226	..	..	..	..	..	50
α-tetrahydrocodeimethine methyl ether	43–46	..	..	..	..	..	53
— aurichloride	D. 143	..	..	..	..	..	53
— methiodide	D. 247	..	..	−40	20	Aq/ EtOH	53
α-tetrahydrocodeimethine-N-oxide·$1\frac{1}{2}H_2O$	94	..	..	..	..	..	63
— sulphonic acid α	295	..	..	..	..	..	63
— sulphonic acid β	270	..	..	..	..	..	63
γ-tetrahydrocodeimethine	115	50% EtOH	octa-hedra	−29·2	18	dil. HOAc	63
— hydrochloride·$3H_2O$	D. 273	..	..	..	..	..	63
— hydriodide	D. 265	..	..	..	..	..	63
— sulphate	..	..	cryst.	..	..	..	63
— methiodide	D. c. 300	..	..	..	..	..	63
Acetyl-γ-tetrahydrocodeimethine hydriodide	220	..	..	..	..	..	63
methobromide·$3H_2O$	100–102	..	..	..	..	..	50
Dihydro-ε-codeimethine-A	..	..	oil	..	..	..	65
— hydriodide	232–235	EtOH	..	+99	28	H_2O	65
Dihydro-ε-codeimethine-B	188·5–189·5	EtOAc	..	+28	24	$CHCl_3$	66
Dihydro-ε-codeimethine-C	150	EtOAc	..	+62·5	23	$CHCl_3$	66
Dihydo-ε-codeimethine-A methyl ether	102·5	40% EtOH	needles	+202	27	EtOH	67
— hydrochloride	219–220	EtOH	..	+157	27	H_2O	67
— perchlorate	85–87 155–156	..	..	+136	27	H_2O	67
Dihydro-ε-codeimethine-C methyl ether	140–140·5	acetone	..	+138·5	25	EtOH	67
Tetrahydro-ε-codeimethine-A	..	..	oil	..	..	..	65
— hydrochloride	187	EtOAc	needles	+20	28	H_2O	65
— hydriodide	225–226	H_2O	prisms	+18·6	28	H_2O	65
— salicylate	198	H_2O	needles	+18·1	27	H_2O	65
— acid tartrate	197·5	H_2O	plates	+27	27	H_2O	65
Tetrahydro-ε-codeimethine-C hydriodide	196–197	EtOH	prisms	+192	28	EtOH	65
Tetrahydro-ε-codeimethine-A methyl ether	123–124	H_2O	scales	+156·5	26	$CHCl_3$	65
— hydrochloride	98·5	50% EtOH	plates	+54	27	EtOH	67
Tetrahydro-ε-codeimethine-C methyl ether	251–252	EtOH	needles	+42	27	H_2O	67
	156·5–157	acetone	plates	+199	25	EtOH	67
Hexahydro-ε-codeimethine	155	Et_2O	needles	..	..	..	63
	166·5–167·5	EtOH	prisms	+28	28	EtOH	65
— hydrochloride	213	..	plates	..	..	..	63
	250–254	EtOH	plates	+8·1	28	EtOH	65
— acid tartrate	114–115	..	..	+15·6	27	H_2O	65
Dicetylhexahydro-ε-codeimethine	..	..	oil	..	..	..	63
— methiodide	255	..	..	..	..	..	63
Hexahydro-ε-codeimethine methyl ether	138	EtOAc	..	+17·4	25	EtOH	67
Dihydro-ζ-codeimethine-A	99	EtOAc + ligroin	pyramids	+117	25	EtOH	68
— salicylate	175	MeOH	..	+70	20	H_2O	68

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Tetrahydro-ζ-codeimethine-A	110	EtOAc+ ligroin	needles	−26	25	EtOH	68
—salicylate	175·5	H_2O	..	..	..	..	68
Tetrahydro-ζ-codeimethine-C	..	..	..	..	..	..	..
—hydriodide	249	H_2O+ acetone	..	+46·7	28	H_2O	68
Hexahydro-ζ-codeimethine	174–175	EtOAc	..	..	..	..	63
— hydriodide	279–281d.	H_2O	..	−39·8	28	H_2O	68
6-methyl-α-codeimethine	106·5–107·5	EtOAc	prisms	−222	20	EtOH	69
— methiodide	203·5–205·5	MeOH+ EtOAc	..	..	..	..	69
6-methyl-β-codeimethine	95·5–97	sublim.	..	+357	20	EtOH	69
—methiodide	283–284	..	..	..	..	..	69
6-methyldihydrocodeine methine	..	..	oil	..	..	..	70
— hydrochloride	241–243	Et_2O+ EtOH	..	−6·7	20	EtOH	70
— salicylate	198–200	..	..	−2·3	20	EtOH	70
—methiodide	269–271	..	..	+8·1	20	EtOH	70
6-methoxy-13-vinylhexahydro-methylmorphenol	..	..	oil	+61	20	EtOH	40
6-hydroxy-13-vinylhexahydro-methylmorphenol	102–103	hexane	..	+77·1	20	EtOH	40
— *p*-phenylbenzoate	173–174	EtOH	..	+73·1	20	dioxane	40
6-methoxy-13-ethyloctahydro-methylmorphenol	51–52	sublim.	..	−44	20	EtOH	40
6-hydroxy-13-ethyloctahydro-methylmorphenol	..	..	oil	..	..	..	40
— *p*-phenylbenzoate	170–172	EtOH	..	−3·4	20	dioxane	40
6-methoxy-13-vinyloctahydro-methylmorphenol	47–49	pentane	..	..	..	..	40
6-hydroxy-13-vinyloctahydro-methylmorphenol	..	..	oil	..	..	.	40
— *p*-phenylbenzoate	168–170	EtOH	..	+53·9	20	dioxane	40
6-methyl-6-hydroxy-13-vinylhexahydromethylmorphenol	..	sublim.	cryst.	+24·4	20	EtOH	70
6-methyl-6-hydroxy-13-ethylhexahydromethylmorphenol	98–100	sublim.	..	−29·9	20	EtOH	70
1-aceto-α-codeimethine	188–188·5	EtOH	prisms	+12·6	20	2N·HOAc	80
1-aceto-β-codeimethine	149	EtOH	needles	+150	21	$CHCl_3$	79
6-acetyl-1-aceto-β-codeimethine methiodide	180–182	..	..	..	..	..	79
1-bromo-α-codeimethine	132 and 182–184	..	..	−104·1	15	EtOH	46
— methiodide	..	..	..	−110·7	15	EtOH	46, 47
Acetyl-1-bromo-α-codeimethine	..	..	..	..	..	..	..
— hydrobromide	D. 235	..	..	..	..	..	46
— hydriodide	D. 222	..	..	..	..	..	46
1-bromo-β-codeimethine	184	..	..	+128·2	15	EtOH	46
— methiodide	..	..	amorph.	..	..	..	46
1-bromo-α-dihydrocodeimethine-B ?	169	..	..	..	..	..	46
—methiodide	227	..	..	..	..	..	46
1-nitro-α-codeimethine	215	H_2O+ EtOH	..	..	..	..	44, 71
1-nitro-α-tetrahydrocodeimethine nitrate	220–221	..	..	..	..	..	..
α-chlorocodeimethine	..	..	oil	..	..	..	63
— hydrochloride	177–178	..	..	..	..	..	63, 37
— methiodide	163	..	..	..	..	..	63
α-dichlorocodeimethine	180–181	EtOH	needles	..	..	..	37
— methiodide	153–154	..	..	..	..	..	37
α-chlorodihydrocodeimethine-C	103	MeOH	..	..	..	..	54
— methiodide	272	EtOH	needles	..	..	..	54
α-chlorotetrahydrocodeimethine	..	..	oil	..	..	..	63
— hydrochloride	207	..	..	..	..	..	63
— hydrobromide	236	..	..	..	..	..	63
— hydriodide	280	..	..	..	..	..	63

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Desoxytetrahydrocodeimethine (Speyer & Koulen) = dihydrodesoxycodeine-D dihydromethine.							see Chap. IX.
Desoxytetrahydrocodeimethine (Cahn) = dihydrodesoxycodeine-B dihydromethine.							
Dihydrodesoxytetrahydrocodeimethine = tetrahydrodesoxycodeine dihydromethine.							
9 (or 10)-ketodihydrocodeimethine: *see* Chap. IV.							
α-ethylthiocodeimethine and β- and δ-isomers: *see* Chap. XVII.							
8-piperidocodeimethine	..	..	oil	..	..	..	76
— monomethiodide	248	..	..	..	..	..	76
Acetyldibromodihydro-α-codeimethine hydrobromide	D. 202	..	..	..	..	..	46
Acetylbromo*iso*-α-codeimethine hydrobromide	..	..	..	..	..	..	46
Bromohydroxydihydro-α-codeimethine	170	MeOH	..	..	..	..	44, 46
— methiodide	D. 150	..	..	..	..	..	46
Acetylbromohydroxydihydro-α-codeimethine	118–138d.	..	..	..	..	..	44, 46
Bromohydroxydihydro-α-codeimethine methyl ether	112	..	..	..	..	..	48
Bromoacetoxydihydro-α-codeimethine methyl ether	126	..	..	+108·4	26	..	48
Bromohydroxydihydro-ε-codeimethine methyl ether	127–128	..	..	..	..	..	48
hydriodide	155–156	..	..	..	.	..	48
α-cyanonorcodeimethine	109	..	..	−196	19	..	50
Acetyl-α-cyanonorcodeimethine	108	..	..	−106	16	EtOH	50
β-norcodeimethine urea	130–131	HOAc	..	+364	18	$CHCl_3$	50
Tetrahydro-α-cyanonorcodeimethine	140	MeOH	plates	−51·4	20	$CHCl_3$	50
Tetrahydro-α-norcodeimethine	..	..	oil	..	..	..	50
Chlorotetrahydro-α-cyanonorcodeimethine hydrochloride	267d.	..	..	..	..	..	50
— chloroplatinate	223d.	H_2O	..	..	..	..	50
Acetyltetrahydro-γ-cyanonorcodeimethine	102	..	..	−104	16	$CHCl_3$	50
Tetrahydro-γ-cyanonorcodeimethine	117	H_2O + MeOH	..	−90·7	17	$CHCl_3$	50
6-acetyl-β-morphimethine	183–185	..	needles	.	..	..	51
Dihydromorphimethine	174–176	EtOAc	prisms	+92·8	26	$CHCl_3$	51
hydrochloride	275–278	benzene + petrol	..	..	..	.	51
6-acetyldihydromorphimethine	202–203	Et_2O + EtOH	..	+118·4	24	$CHCl_3$	51
hydrochloride	270–280	sublim.	..	+39·9	24	H_2O	51
3:6-diacetyldihydromorphimethine	..	..	oil	..	..	..	51
α-tetrahydromorphimethine	206–208	EtOH	prisms	..	..	..	51
hydrochloride	243–249	EtOH	needles	−29·6	23	H_2O	51
6-acetyl-α-tetrahydromorphimethine	240–242	sublim.	..	..	..	..	51
hydrochloride	253–262	Et_2O + EtOH	prisms or plates	−48·2	25	H_2O	51
3:6-diacetyl-α-tetrahydromorphimethine	..	..	oil	..	..	..	51
7:8-dihydrocodizal-3-methyl ester methine	205–206	MeOH	prisms	..	..	..	87
hydriodide	250d.	H_2O	rods	..	..	..	87
methiodide	290d.	H_2O	prisms	..	..	.	87
oxime	D. 220	Et_2O	needles	..	..	..	87
acetyl-derivative	234–235	EtOH	plates	..	..	..	87
Tetrahydrocodizal-3-methyl ester methine	175–176	EtOH	plates	..	..	..	87
7:8-dihydrocodizonal-3-methyl ester methine	172	petrol	plates	..	..	..	87
hydrochloride	D. 268	EtOH	needles	..	..	..	87
codelmethylpiperidine	93–94	Et_2O	columns	..	..	..	89
platinichloride	174	..	..	..	..	..	89
Acetylcodelmethylpiperidine	87	..	..	..	..	..	89
α-bromomethylcyanoacetylcodeimethyl-methine	133–134	EtOH	plates	..	..	..	89
codelmethyldihydroisoindole	c. 110	..	..	..	..	..	89
Acetylcodelmethyldihydroisoindole	140	H_2O	plates	..	..	..	89
methiodide	103	H_2O	plates	..	..	..	89
hydrochloride	224	H_2O	plates	..	..	..	89

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
ω-bromoxylylcyanoacetylcodeimethylamide	153	$CHCl_3$ + Et_2O	..	..	..	..	89
codeimethylmorpholine . . .	..	..	oil	..	..	..	89
Acetylcodeimethylmorpholine . .	118–120	..	..	..	..	..	89
chloroplatinate	177	..	..	..	..	..	89

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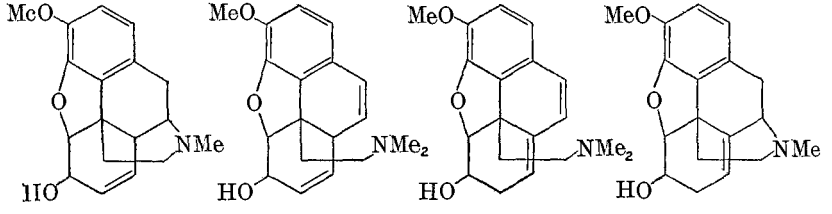
VII

NEOPINE

NEOPINE was first isolated by Dobbie and Lauder from the last mother liquors from the processing of the opium alkaloids after all other bases had been eliminated [1]. This remains the only source of the base. The method of isolation has since been improved and the alkaloid can be separated from codeine through the sulphates [2]. The base was first allotted the formula $C_{18}H_{21}O_4N$ and the name 'hydroxycodeine'; it was shown to contain one —OMe, one —NMe, and to be a tertiary base. Its colour reactions and ultra-violet absorption spectrum are practically identical with those of codeine [1].

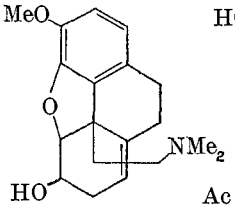
Neopine was later shown to have the composition $C_{18}H_{21}O_3N$, isomeric with codeine [3]. It contains a hydroxyl group, as is evinced by the preparation of an acetyl ester, and on hydrogenation it affords dihydrocodeine, so that it can only differ from codeine in the position of the alicyclic double bond. The nature of the isomerism was elucidated by exhaustive methylation. Codeine [I] methiodide gives α-codeimethine [II] on degradation, and the latter can be isomerized to β-codeimethine [III], with migration of the 7:8 double bond into the 8:14-position, under the influence of alcoholic potassium hydroxide. Neopine methiodide degrades directly to β-codeimethine [III] and therefore neopine must have the structure [IV] with the double bond already in the 8:14-position [3]. The sodium-liquid ammonia reduction of neopine methiodide yields α-dihydrocodeimethine-B (neopine dihydromethine) [V] [4], identical with the product of sodium-alcohol reduction of α- and β-codeimethines (see Chap. VI).



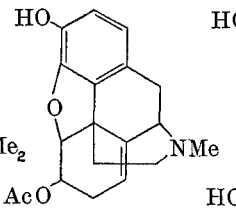
[I] [II] [III] [IV]

In general the double bond seems to be less reactive in neopine than in codeine, e.g. reduction proceeds less readily [3] and oxidation to a dihydroxydihydro-compound cannot be effected with permanganate [5]. Neopine is recovered unchanged from attempts to oxidize it to a ketone with chromic acid [5].

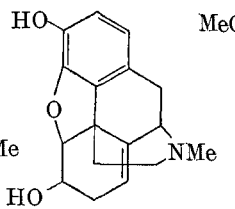
Movement of the double bond does not occur during the methylation of morphine to codeine, from which reaction no neopine can be isolated [2]. Unlike codeine neopine can be demethylated by hydrobromic acid and glacial acetic acid, the product being 6-acetylneomorphine [VI], probably formed by way of the 3:4-diacetyl derivative, which readily loses the 3-acetyl group in dilute acetic acid. Demethylation with 48 per cent. hydrobromic acid alone affords neomorphine [VII], also obtained by the hydrolysis of [VI], but the free dihydroxy-compound is readily soluble in water and difficult to isolate. Neomorphine is converted to neopine by diazomethane. Reduction of 6-acetylneomorphine yields 6-acetyldihydromorphine, which can be hydrolysed to dihydromorphine [6].



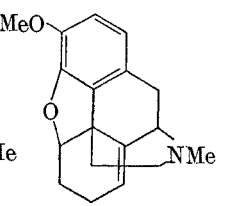
[V]



[VI]



[VII]



[VIII]

An intractable phenolic substance is produced by the prolonged boiling of neopine hydrobromide with Raney nickel in alcohol [7]. Lithium aluminium hydride reduction of *p*-toluenesulphonylneopine gives desoxyneopine (desoxycodeine-D) [VIII] [8] (see Chap. IX).

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Neopine	127–127·5	petrol	needles	−28·1	23	$CHCl_3$	3
— hydrobromide	282–283d.	H_2O	prisms	+17·3	23	H_2O	3
— hydrochloride	.	..	..	+18·2	20	H_2O	6
— sulphate	166–167	EtOH ?	..	+16·4	28	H_2O	2
— methiodide	..	MeOH	prisms	+23·5	20	EOH	1, 6, 8
Acetylneopine	..	.	oil	.	..	..	3
— methiodide	256–257d.	MeOH	needles	..	..	..	3
p-toluenesulphonylneopine	191–192	EtOH	.	−249	20	acetone	8
Neomorphine·$CHCl_3$	107 ± 2	$CHCl_3$	coffin-shaped	.	..	..	6
Neomorphine·(anhyd.)	..	.	.	−18·2	20	$CHCl_3$	..
	240–241	.	.	−9·2	20	EtOH	6
— hydrochloride	295–298	90% EtOH + HCl	granular	+22·6	20	H_2O	6
6-acetylneomorphine	243–251	EtOH	..	+27·6	20	H_2O	6
— hydrochloride	238–245d.	EtOH	..	+8·8	20	H_2O	6
3:6-diacetylneomorphine	127–127·5	ligroin	..	+17·5	20	95% EtOH	6

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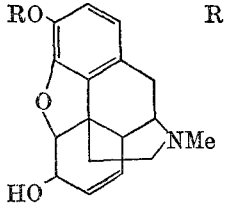
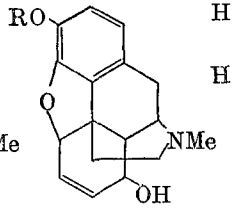
VIII

THE HALOGENOCODIDES AND HALOGENOMORPHIDES

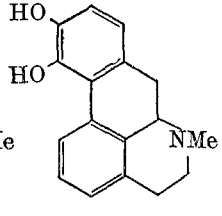
CODEINE [I, R = Me] and morphine [I, R = H] contain an alcoholic hydroxyl group and can form 'esters' of halogen hydracids in which this group is replaced by a halogen atom. Theoretically there are four possible isomers of each halogen derivative as the hydroxyl group is located on an asymmetric carbon atom and Walden inversion is possible during the replacement reaction, and moreover allylic rearrangement is possible, giving rise to 8-substituted derivatives analogous to ψ- and allo-ψ-codeine [II, R = Me] and β- and γ-isomorphine [II, R = H]. Of these possible isomers two only are known in the chloro-series and one in the bromo- and iodo-series.



[I]



[II]



[III]

Bromination of codeine results in 1-bromocodeine and finally in a tribromocompound; chlorination with chlorine water is more complex and gives resinous products [1, 2]. Apomorphine [III] is formed by heating morphine and concentrated hydrochloric acid in a sealed tube above 100° C., and, together with methyl chloride, from codeine under the same conditions [3–6] (see Chap. XXII). When codeine is heated on the water-bath with concentrated hydrochloric acid, however, replacement of the hydroxyl group by chlorine occurs and α-chlorocodide is produced [7–8]; this may be prepared in other ways from codeine and ψ-codeine, and can be isomerized to β-chlorocodide, available directly from the isomers of codeine. The corresponding derivatives of morphine have been prepared. Bromocodide and bromomorphide may be prepared in like manner but cannot be isomerized, and an iodocodide results from the treatment of α-chloro- or bromocodide with potassium iodide.

Replacement of the halogen atom of these compounds by other functional groups results in migration of the double bond and substituent, a phenomenon that confused the early work on codeine and morphine.

α-CHLOROCODIDE AND α-CHLOROMORPHIDE

PREPARATION

α-Chlorocodide may be prepared by heating codeine with concentrated hydrochloric acid below 100° C. [7–8], by the action of phosphorus pentachloride and/or oxychloride [9], or thionyl chloride [10–11] on codeine, and by the action of phosphorus pentachloride on ψ-codeine [12]. In the latter reaction production of 'ψ-chlorocodide' was also reported [12], but repetition using thionyl chloride yielded only α-chlorocodide [10]. Isocodeine and allo-ψ-codeine give exclusively β-chlorocodide with thionyl chloride [10]. If codeine is treated first with 2 to 3 equivalents of pentachloride and the mixture then poured into phosphorus oxychloride a violent reaction occurs at 60–70° C., and a dichlorocodide different from 1-chloro-α-chlorocodide $C_{18}H_{19}O_2NCl_2$ is obtained. (Methyl chloride is evolved if the temperature reaches 100° C. [9].) Wright [13] claimed that the interaction of codeine and hydrochloric acid first gave a derivative containing less chlorine than α-chlorocodide, but this has never been substantiated.

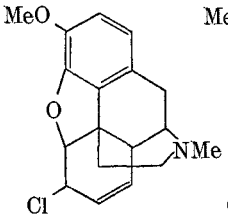
Morphine yields α-chloromorphide when treated with phosphorus trichloride [14] or thionyl chloride [11, 15], but α-isomorphine does not behave similarly [14, 16]. α-Chloromorphide has been directly related to α-chlorocodide by methylation to the latter [17–18]. In the reaction of morphine with thionyl chloride small amounts of β-chloromorphide (5 per cent.) and a trichloromorphide (1·5 per cent.) are formed; the latter can be methylated to a trichlorocodide [19].

STRUCTURE

α-Chlorocodide has been conclusively proved to have the structure [IV] with the chlorine atom at C-6, as it can be reduced without elimination of the halogen to 6-chlorodihydrocodide [V], identical with the product of interaction of dihydrocodeine [VI] and phosphorus pentachloride [20], during which there is no possibility of migration of the substituent to C-8 [19]. This structure is in harmony with all the properties of α-chlorocodide provided allowance is made for allylic rearrangement during replacement of the halogen. There is no evidence to show whether [IV] belongs to the codeine or isocodeine series, as Walden inversion is possible during the production of [IV] and [V] from the corresponding alcohols, or in the hydrolysis of α-chlorocodide to isocodeine (see below).

REDUCTION

The system —O—CH—CH—Cl in α-chlorocodide and α-chloromorphide bears a certain resemblance to the system $-\overset{1}{O}-\overset{2}{CH}-\overset{3}{CH}=\overset{4}{C}$ in desoxycodeine-C [VII] and ψ-codeine [II, R = Me] in that both are



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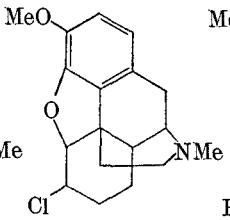

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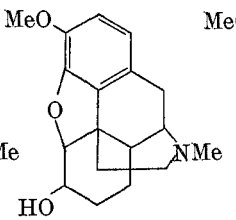

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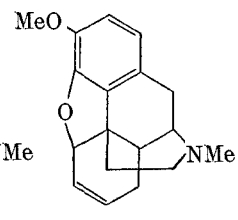


[VII]

capable of undergoing 1:4-addition of hydrogen with opening of the cyclic ether and production of a phenolic base, though the tendency to suffer this reduction is much less marked in the former case than in the latter. The halogen atom is almost always eliminated.

(*a*) Hydrogenation of α-chlorocodide hydrochloride in glacial acetic acid using a platinum oxide catalyst [19] affords 52 per cent. 6-chlorodihydrocodide [V] (cf. the reduction of ψ-codeine without opening of the ether link under similar conditions [21]—see Chap. IV), 40 per cent. tetrahydrodesoxycodeine [VIII] (formed presumably by 1:4 reduction of the $\overset{1}{\text{—O—}}\overset{2}{\text{CH—}}\overset{3}{\text{CH—}}\overset{4}{\text{Cl}}$ system and subsequent reduction of the resulting desoxycodeine-A), and 7·5 per cent. dihydrodesoxycodeine-D [IX] (presumably formed by 1:4 reduction of the system

$$\overset{1}{\text{Cl—}}\overset{2}{\text{CH—}}\overset{3}{\text{CH=}}\overset{4}{\text{CH—}}$$

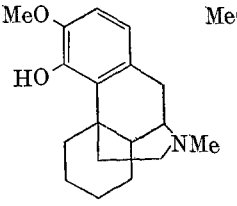
to desoxycodeine-C [VII], which is known to undergo reduction to [IX] under these conditions [22]).

(*b*) Hydrogenation of α-chlorocodide in dilute acetic acid using a colloidal palladium catalyst proceeds slowly with production of 95 per cent. dihydrodesoxycodeine-D [IX]. Under these conditions Freund [20] had earlier reported the production of an alkali-insoluble amorphous base 'α-dihydrodesoxycodeine'.

(*c*) Hydrogenation of α-chlorocodide in ethanol using a palladized barium sulphate catalyst proceeds substantially as in (*b*), but when a large amount of catalyst is used the rate of reduction is increased and only 40 per cent. dihydrodesoxycodeine-D is obtained together with 45 per cent. amorphous base [23].

(*d*) The amorphous base of (*c*) is obtained in 95 per cent. yield using palladized calcium carbonate and 100 per cent. yield using platinum oxide as catalyst. It is alkali-insoluble, cannot be sublimed, and is bimolecular, being believed to be bis-6:6′-dihydrodesoxycodeine-D [X]. Its formation from α-chlorocodide [IV] is analogous to the production of diphenyl in the reduction of bromobenzene by hydrazine and palladized calcium carbonate [24]; the first stage must be removal of halogen, and it is significant that when one mole of hydrogen has been

absorbed all the product is soluble in water as a halide salt [23]. The reduction of bromocodide is similar to the above. The maximum amount of tetrahydrodesoxycodeine [VIII] produced in reductions (*b*), (*c*), and (*d*) is only 5 per cent.—in marked contrast to the hydrogenation of β-chlorocodide (q.v.) when large amounts of [VIII] are formed.



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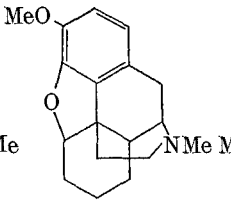
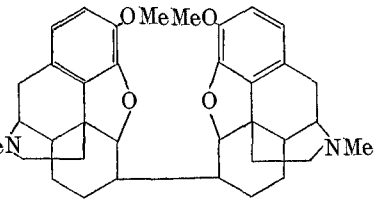


[IX]



[X]

(*e*) Hydrogenation of α-chloromorphide in neutral or weakly acid solution in presence of palladized barium sulphate results in mainly dihydrodesoxymorphine-D [the morphine analogue of IX] and some tetrahydrodesoxymorphine [the analogue of VIII] together with a small quantity of a non-crystalline substance.

(*f*) Reduction of α-chlorocodide with zinc-dust and dilute hydrochloric acid [25] or alcohol [20, 26] gives desoxycodeine-A [XI] by 1:4-reduction of the system $\overset{1}{\text{—O—}}\overset{2}{\text{CH—}}\overset{3}{\text{CH—}}\overset{4}{\text{Cl}}$. The same compound results from the zinc-alcohol reduction of bromo- and β-chlorocodides (see below) and from the reaction between α-chlorocodide and methyl- or ethylmagnesium iodide, a reaction in which the Grignard reagent functions solely in a reducing capacity, and in which iodocodide is doubtless an intermediate [27]. β-Chlorocodide does not react with Grignard reagents [27]. Desoxycodeine-A can be further reduced, catalytically to tetrahydrodesoxycodeine [VIII] [25, 27] and by sodium and alcohol to a constant-composition mixture of dihydrodesoxycodeine-B [XII] (1 part) and dihydrodesoxycodeine-C [XIII] (1 part) [28], originally thought to be a single substance, dihydrodesoxycodeine-A [26–27, 29] (see Chap. IX).

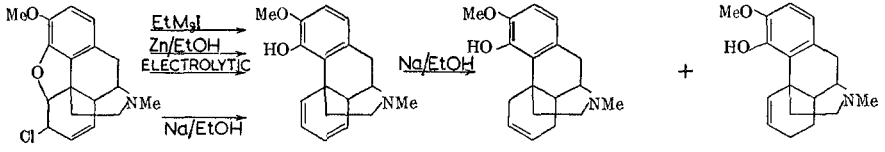
(*g*) The zinc-dust alcohol reduction of α-chloromorphide gives only resins [22].

(*h*) Electrolytic reduction of α-chlorocodide also affords desoxycodeine-A [XI] [22] together with a small amount of a very persistent impurity that originally caused the product to be called desoxycodeine-B [27, 30]. (Freund [20] believed the product to be a dihydrodesoxycodeine.) Electrolytic reduction of β-chlorocodide also gives [XI].

(*i*) Electrolytic reduction of α-chloromorphide yields desoxymorphine-A, the analogue of [XI] [22].

(*j*) The reduction of α-chlorocodide with sodium and alcohol was originally thought to give desoxycodeine-A [XI] [25] but subsequently

shown to give a dihydrodesoxycodeine identical with that formed in the same way by the reduction of desoxycodeine-A [26, 30]. The product is in fact the 1:3 mixture of dihydrodesoxycodeines B [XII] and C [XIII] mentioned above, and the first stage in the reduction is doubtless the production of desoxycodeine-A [XI] which is reduced as fast as it is formed [28].



[IV] [XI] [XII] [XIII]

(*k*) The sodium and alcohol reduction of α-chloromorphide gives only halogen-free gums [22].

(*l*) Reduction of α-chloromorphide with amalgamated zinc and 6 N. hydrochloric acid gives desoxymorphine-A and β-isomorphine, the latter arising from hydrolysis of the chloro-compound [15].

(*m*) Schryver and Lees [14] claimed the production of a desoxymorphine hydrochloride $[\alpha]_D = +140{\cdot}3°$ on reducing α-chloromorphide with tin and hot concentrated hydrochloric acid, but a repetition of this reduction, and the reduction of α-chloromorphide with stannous chloride and hydrochloric acid under pressure afforded only small amounts of a hydrochloride, $[\alpha]_D = -78°$, that does not correspond to any of the known desoxymorphines, and indeed it is unlikely that the morphine structure would survive this treatment as even the $\alpha \rightarrow \beta$-chloromorphide conversion (see below) is accompanied by the production of considerable quantities of apomorphine [15].

(*n*) Electrolytic reduction of 6-chlorodihydrocodide [V] gives dihydrodesoxycodeine-C [XIII], presumably by 1:4 reduction of the system $\overset{1}{-}O-\overset{2}{C}H-\overset{3}{C}H-\overset{4}{C}l$ [27–28, 30]; 6-chlorodihydromorphide (from dihydromorphine), on the other hand, is very resistant to further reduction [22].

(*o*) When 6-chlorodihydrocodide is heated in an autoclave with sodium methoxide and methanol at 140° C. for twenty-four hours desoxycodeine-C is obtained [27, 31–32]. (This was first believed to be a dihydrodesoxycodeine [31–32].) Vongerichten and Müller obtained in this way only a resin [33]. Desoxymorphine-C results in the same way from 6-chlorodihydromorphide [22, 31–32] and can be methylated to desoxycodeine-C [VIII] [22]. 6-Chlorodihydromorphide is prepared by the action of thionyl chloride on dihydromorphine [22] and is doubtless identical with the product of demethylation of 6-chlorodihydrocodide [34].

HYDROLYSIS

The hydrolysis of α-chlorocodide with water at 140–150° C. was first thought to give codeine [7–8, 35], but subsequent investigations have shown that though the other three isomers of codeine can be obtained by the hydrolysis of halogenocodides, in no case is codeine formed. Similarly the hydrolysis of the halogenomorphides affords no morphine.

The first product of hydrolysis of α-chlorocodide to be clearly recognized was ψ-codeine [II, R = Me] [36], and following the isolation of isocodeine [18, 37] and allo-ψ-codeine [18] from the hydrolysis of bromocodide (q.v.) all three isomers were obtained by the hydrolysis of α- and β-chlorocodide with acetic acid, the proportions varying with the two isomeric chloro compounds thus:

α-chlorocodide → 25% isocodeine + 45% ψ-codeine + 15% allo-ψ-codeine [38],

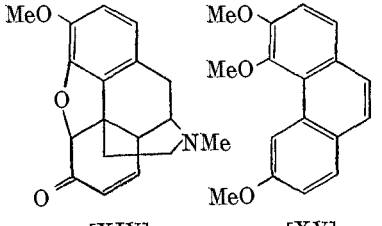
β-chlorocodide → 35% isocodeine + 10% ψ-codeine + 20% allo-ψ-codeine [38].

The production of all three isomers has been confirmed [10]. Iodocodide also yields all three isomers of codeine on hydrolysis [39], but only iso- and allo-ψ-codeine appear to have been isolated from the hydrolysis of bromocodide [14, 16, 18, 37].

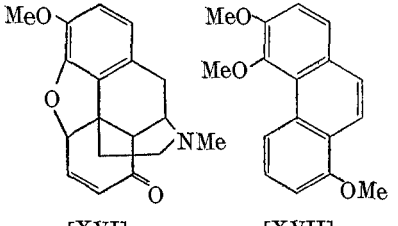
The hydrolysis of α-chloromorphide follows a similar pattern, α- [18, 40], β- [18, 40–41], and γ-isomorphine [18, 40, 42] being formed. Bromomorphide gives all three isomers [18].

Attempts to hydrolyse 6-chlorodihydrocodide have failed [10].

As shown in Chapter IV, codeine and isocodeine are known to have a hydroxyl group at C-6 by oxidation to codeinone [XIV] followed by degradation to 3:4:6-trimethoxyphenanthrene [XV], whereas ψ- and



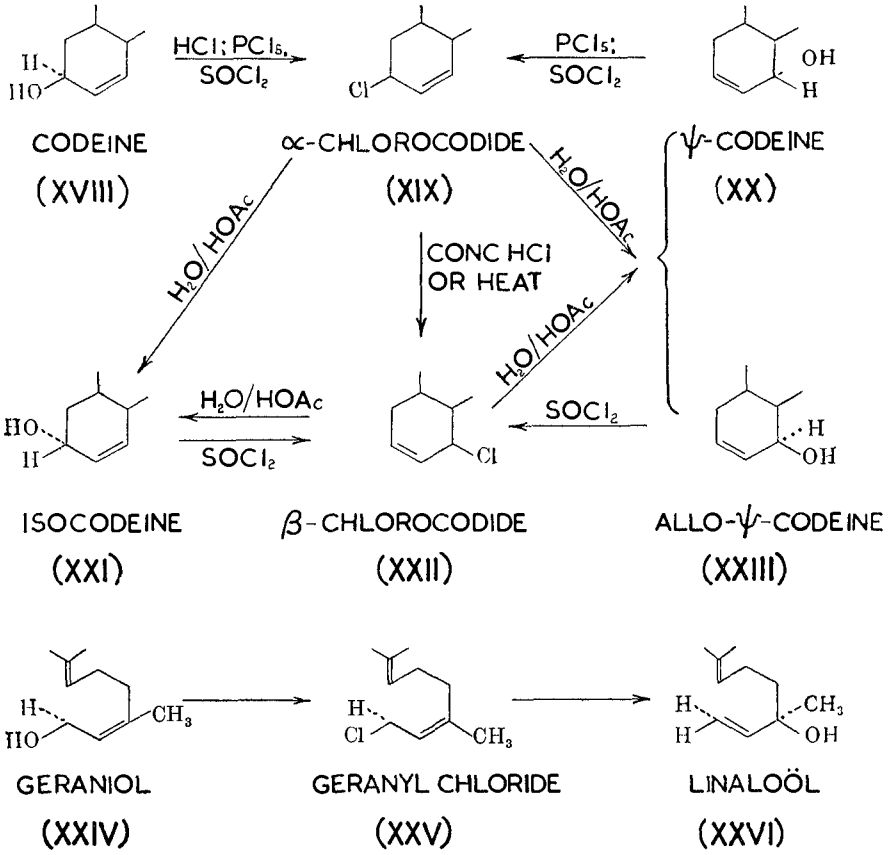
[XIV] [XV]



[XVI] [XVII]

allo-ψ-codeine can be degraded through ψ-codeinone [XVI] to 3:4:8-trimethoxyphenanthrene [XVII], showing that these two isomers have the hydroxyl group at C-8 [43–46]. This wandering of the hydroxyl group during the formation and hydrolysis of the halogenocodides and morphides was not fully understood for some time and could not be satisfactorily explained on the basis of early formulae for the morphine alkaloids. Gulland and Robinson [47] on the basis of a bridge structure for codeine pointed out the analogy between these migrations and the

interconversion of geraniol [XXIV] and linalool [XXVI], an analogy that became even more clear on the adoption of the structure [I, R = Me] for codeine, as is shown in the part formulae [XVIII] to [XXVI] [48].



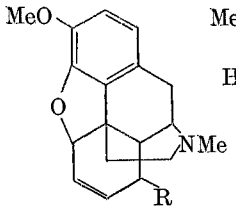
Replacement of Halogen by Groups other than Hydroxyl

Replacement of the halogen atom of α-chlorocodide and α-chloromorphide by groups other than hydroxyl always involves migration of the substituent, which appears at C-8 in the final product. This is demonstrated by the results of hydrogenation of the products, for compounds having a 6:7 double bond conjugated with the cyclic ether group readily suffer scission of the latter during hydrogenation, with the production of phenolic tetrahydro-derivatives.

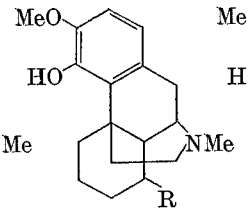
(*a*) ψ-Codeine methyl ether [XXVII, R = OMe] is formed on heating α-chlorocodide with sodium methoxide at 100° C. [49–52]. On catalytic hydrogenation it gives tetrahydro-ψ-codeine methyl ether [XXVIII,

R = OMe] and on reduction with sodium and alcohol yields dihydro-ψ-codeine-C methyl ether [XXXIX, R = OMe] [53]. Such ethers are readily formed by heating α-chlorocodide with alcohols [52, 54] or with the sodium salts of phenols in alcohol [49, 51]. α-Chloromorphide gives γ-isomorphine-8-ethers under similar conditions [55].

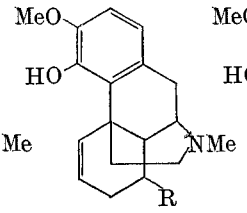
(*b*) δ-Ethylthiocodide [XXVII, R = SEt] results from heating α-chlorocodide with sodium ethoxide and ethyl mercaptan in ethanol in an atmosphere of hydrogen [56]. It is allotted the structure [XXVII, R = SEt], for, though it cannot be reduced catalytically owing to poisoning of the catalyst by liberated mercaptan, it can be reduced with sodium and alcohol to dihydro-δ-ethylthiocodide-A [XXX, R = SEt] and dihydro-δ-ethylthiocodide-B [XXIX, R = SEt] and to the former by electrolytic reduction [57] (see Chap. XVII).



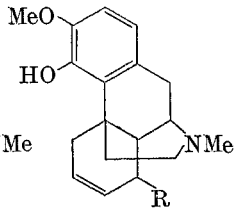
[XXVII]



[XXVIII]



[XXIX]



[XXX]

(*c*) 8-Aminocodide [XXVII, R = NH_2] and 8-piperidocodide [XXVII, R = piperidyl] are obtained when α-chlorocodide is heated with liquid ammonia [58] and piperidine [33, 58] respectively. On hydrogenation in neutral solution they yield phenolic tetrahydro-derivatives ([XXVIII, R = NH_2] and [XXVIII, R = piperidyl]), but hydrogenation of their hydrochlorides in acid solution using a platinum oxide catalyst affords non-phenolic dihydrocompounds [58] (cf. the reduction of ψ-codeine). 8-piperidomorphide [58] and 8-diethylaminomorphide [59–60] likewise give phenolic tetrahydro-derivatives on hydrogenation. 8-Dimethyl- and 8-diethylaminocodides have also been prepared [60].

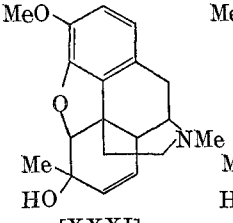
(*d*) α-Chlorocodide and α-chloromorphide are reported to give the formyl esters of codeine and morphine on heating at 150° C. with sodium formate [61]. This seems unlikely in view of the production of the 8-substituted derivatives above, and the absence of codeine amongst the products of hydrolysis of α-chlorocodide, though at 150° C. prior isomerization to the β-chloro isomers may well occur.

Nuclear Substituted Derivatives

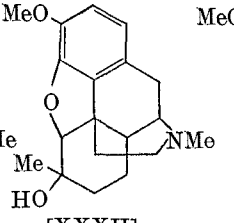
When 1-chloro-, 1-bromo-, and 1-nitrocodeines are treated with phosphorus pentachloride the corresponding 1-chloro-, 1-bromo-, and 1-nitrochlorocodides are formed, and the former of these is not identical with the dichlorocodide that results from successive treatment of

codeine with phosphorus penta- and oxy-chlorides [9]. 1-Bromochlorocodide does not behave like α-chlorocodide on reduction with zinc-dust and alcohol, giving not the expected 1-bromodesoxycodeine-A but 1-bromodesoxycodeine-C. The latter can be degraded to 1-bromomethylmorphenol, showing that the ether link is still intact [62].

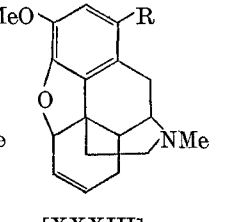
A 6-methylchlorocodide results from the treatment of 6-methylcodeine [XXXI] with hydrochloric acid, phosphorus pentachloride, or acetyl chloride in glacial acetic acid, but, as the hydroxyl group of [XXXI] is not only allylic but also tertiary, the yield is small, and the product is very probably an 8-chlorocompound. Some nuclear chlorination also occurs during this reaction. Treatment of 6-methylcodeine with thionyl chloride gives only an impure halogen-free product having approximately the composition of a dehydrated compound [63]. 6-methyldihydrocodeine [XXXII] with thionyl chloride and phosphorus pentachloride gives 6-methyldesoxycodeine-C [XXXIII, R = H] and 1-chloro-6-methyldesoxycodeine-C [XXIII, R = Cl] respectively [64].



[XXXI]



[XXXII]



[XXXIII]

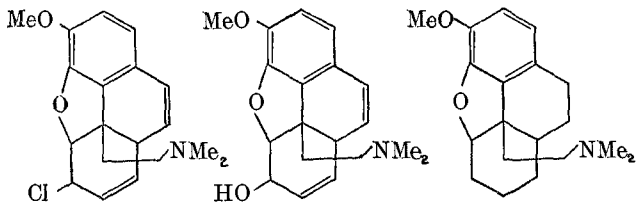
Methine Bases

α-Chlorocodeimethine [XXXIV] can be obtained by the action of phosphorus trichloride on α-codeimethine [XXXV] in chloroform (if no solvent is used only the phosphorous ester of [XXXV] is obtained) [65], but not by the degradation of α-chlorocodide methohydroxide. The latter is a strong base whose solution contains no chloride ions, but on boiling the solution becomes neutral and gives a copious precipitate with silver nitrate [66]. With phosphorus pentachloride [XXXV] gives a dichlorocodeimethine in which the additional chlorine atom is in either position 9 or 10 as acetolysis of the base gives 3-methoxy-4:9 (or 10)-diacetoxyphenanthrene [65] (see Chap. VI).

In the same way that hydrolysis of α-chlorocodide gives a mixture of isomers of codeine but no codeine, so hydrolysis of α-chlorocodeimethine gives a mixture of γ-, δ-, and ε-codeimethines but no α-codeimethine [67]. γ-Codeimethine also gives α-chlorocodeimethine on treatment with phosphorus pentachloride [68].

Catalytic hydrogenation of α-chlorocodeimethine gives a mixture of a crystalline 'desoxytetrahydrocodeimethine' (dihydrodesoxycodeine-D Dihydromethine) [XXXVI] that can be degraded to a nitrogen-free

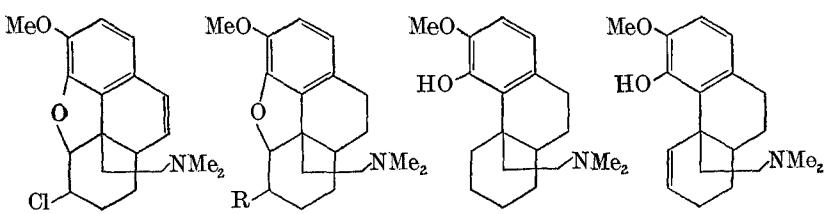
product $C_{17}H_{20}O_2$, and an oily isomer of [XXXVI] that resists degradation [68].



[XXXIV] [XXXV] [XXXVI]

As 6-chlorodihydrocodide cannot be hydrolysed [10] it is not surprising that it can be degraded to α-chlorodihydrocodeimethine-C [XXXVII] [20]. The latter can be reduced to α-chlorotetrahydrocodeimethine [XXXVIII, R = Cl], which is also accessible from α-tetrahydrocodeimethine [XXXVIII, R = OH] [68]. Sodium-alcohol reduction of [XXXVIII, R = Cl] affords a compound originally believed to be 'dihydrodesoxytetrahydrocodeimethine' [XXXIX], but subsequently shown to be unsaturated and to have the structure [XL] (dihydrodesoxycodeine-C dihydromethine) or that of the $\Delta^{6:7}$-isomer (dihydrodesoxycodeine-B dihydromethine) [29]. The structure [XL] is preferable as it can arise from [XXXVIII, R = Cl] by 1:4 reduction of the system

—O—CH—CH—Cl.



[XXXVII] [XXXVIII] [XXXIX] [XL]

The reactions between α-chlorocodide and hydrogen peroxide, cyanogen bromide and ozone are discussed later.

β-CHLOROCODIDE AND β-CHLOROMORPHIDE

PREPARATION

β-Chlorocodide is formed by the isomerization of α-chlorocodide by heating alone above its melting-point [56] or with concentrated hydrochloric acid at 60–70° C. in sealed vessels [69] and also in the last-mentioned manner directly from ψ-codeine or codeine, presumably through the α-isomer [69], though it is formed directly in 10–15 per cent. yield during the interaction of codeine and thionyl chloride [19]. Considerable decomposition occurs when α-chlorocodide is heated alone,

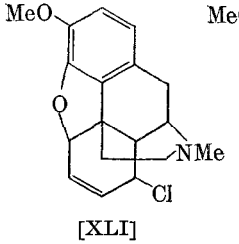
and the yield of β-isomer is greatly increased by boiling the α-form in bromobenzene or tetralin [10].

Speyer and Krauss [70] claimed the production of an allo-ψ-chlorocodide from allo-ψ-codeine and phosphorus pentachloride, but using thionyl chloride only a quantitative yield of the β-isomer was obtained [10]. In the same way isocodeine is converted quantitatively to β-chlorocodide [10].

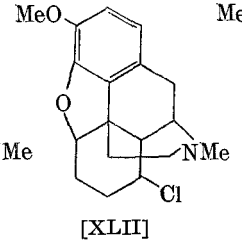
β-Chloromorphide results from the restricted action of hydrochloric acid on morphine or α-chloromorphide [71] and also in 5 per cent. yield during the preparation of the α-isomer by the action of thionyl chloride on morphine [19]. It is probably the product of interaction of α-isomorphine and phosphorus trichloride [14, 16]. It can be methylated to β-chlorocodide by diazomethane [69].

STRUCTURE

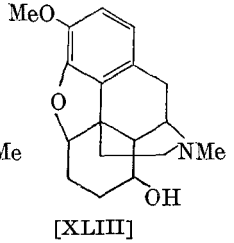
β-Chlorocodide is believed to have the structure [XLI] and to be formed from the α-isomer by an α:γ shift of the halogen, as on catalytic reduction it behaves as if it contained the system —O—CH—C=C, always giving considerable quantities of phenolic products as does ψ-codeine [II, R = Me]. However, [XLI] has not been definitely proved to be the structure as β-chlorodihydrocodide, which can be prepared in low yield by the hydrogenation of β-chlorocodide, is not identical with 8-chlorodihydrocodide [XLII] prepared by the treatment of both dihydro-ψ-codeine-A [XLIII] and its epimer dihydroallo-ψ-codeine-A with phosphorus pentachloride [19]. The configurations epimeric with 6- and 8-chlorodihydrocodides remain possible for β-chlorodihydrocodide. Attempts to chlorinate dihydroisocodeine with phosphorus pentachloride give only phosphorus-containing products, while thionyl chloride chlorinates the dihydrocodeine isomers in the benzene ring only, sodium and alcohol reduction converting the products back to the starting materials [19].



[XLI]



[XLII]



[XLIII]

REDUCTION

(*a*) Hydrogenation of β-chlorocodide hydrochloride in alcoholic hydrogen chloride using a platinum oxide catalyst affords a small quantity of β-chlorodihydrocodide together with tetrahydrodesoxy-

codeine [VIII] [19]. (Speyer and Krauss obtained the latter by the reduction of allo-ψ-chlorocodide [70].)

(*b*) Reduction of β-chlorocodide in dilute acetic acid with a colloidal palladium catalyst gives mainly dihydrodesoxycodeine-D [IX] but also a considerable amount of tetrahydrodesoxycodeine [VIII] [30, 34]. The former is presumably formed by initial 1:4-reduction of the system $\overset{1}{C}{=}\overset{2}{C}{-}\overset{3}{C}{-}\overset{4}{Cl}$ and the latter by 1:6- or 1:4-reduction of the system $-\overset{1}{O}-\overset{2}{C}-\overset{3}{C}{=}\overset{4}{C}-\overset{5}{C}-\overset{6}{Cl}$.

(*c*) Hydrogenation of β-chlorocodide in neutral solution with a palladized barium sulphate catalyst gives substantially the same results as (*b*), the product consisting of 70 per cent. dihydrodesoxycodeine-D and 30 per cent. tetrahydrodesoxycodeine [23], whilst β-chloromorphide under these conditions is converted almost exclusively to dihydrodesoxymorphine-D [15].

(*d*) 100 per cent. tetrahydrodesoxycodeine is formed by hydrogenation of β-chlorocodide in neutral solution with a platinum oxide catalyst [23]. No trace of a dimolecular compound could be detected in reductions of β-chlorocodide. The effect on the hydrogenation in going from the base in neutral solution to the salt in acid solution is less marked with the morphides than with the codides, and weakly acid solutions increase the amount of tetrahydrodesoxymorphine obtained [15].

(*e*) Desoxycodeine-A [XI] results from the zinc-dust and alcohol reduction of β-chlorocodide, which in this way resembles the α-isomer; the reduction must proceed by 1:6-addition of hydrogen to the system $-\overset{1}{O}-\overset{2}{C}-\overset{3}{C}{=}\overset{4}{C}-\overset{5}{C}-\overset{6}{Cl}$. [XI] does not, however, result from the treatment of β-chlorocodide with Grignard reagents, when no reaction occurs [27]; this is no doubt due to the fact that iodocodide is a necessary intermediate in the production of [XI] in this way, and β-chlorocodide cannot be converted to an iodocompound [19, 27].

(*f*) Electrolytic reduction of β-chlorocodide also gives desoxycodeine-A [22, 27].

Hydrolysis

β-Chlorocodide gives the same products as does the α-isomer on hydrolysis, namely, isocodeine [10, 38, 69], ψ-codeine [10, 38], and allo-ψ-codeine [10, 38, 69], but the proportions (55 per cent., 10 per cent., and 20 per cent. respectively) differ from those obtained from α-chlorocodide (25 per cent., 45 per cent., and 15 per cent.) [38].

Replacement of Halogen by Groups Other than Hydroxyl

The replacement of the halogen of the β-chlorocodides and morphides results in derivatives having the new substituent at C-6, and if an

$\alpha:\gamma$-shift of the substituent occurs during the reaction as in the α-chloro series, this is additional support for the theory that β-chlorocodide is to be represented by the structure [XLI].

(i) Attempts to replace the halogen by —SH on heating with potassium hydrosulphide yields the dimolecular bisthiocodide $C_{36}H_{40}O_4N_2S_2$ and bisthiomorphide $C_{34}H_{36}O_4N_2S_2$ in which two desoxycodeine or desoxymorphine units are linked, very probably in the 6:6′ positions, by —S—S— [65].

(ii) This oxidative linking of two units does not occur when β-chlorocodide and β-chloromorphide are heated with mercaptans and sodium hydroxide solution at 100° C., α-alkylthiocodides and morphides being formed [56, 72]. If the aqueous sodium hydroxide is replaced by alcoholic sodium ethoxide β-alkylthiocodides and morphides are formed by a secondary isomerization of the α-compounds that can be independently effected by sodium ethoxide [56, 73]. In these derivatives the —SAlkyl group has been conclusively proved to be situated at C-6 (see Chap. XVII).

(iii) Replacement of the halogen by amines affords 6-aminocodides which give only non-phenolic dihydro-derivatives on hydrogenation [58].

(iv) Formyl esters of morphine and codeine are reported to result from heating β-chlorocodide and morphide with sodium formate at 150° C. [61].

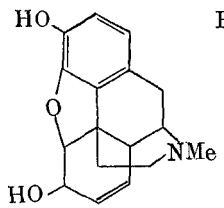
On treatment with concentrated sulphuric acid β-chloromorphide yields a 'sulpho-β-chloromorphide' $C_{17}H_{18}O_5NClS$ [71], probably a sulphonic acid, which gives a halogen-free compound on heating with water[71]. α-Chlorocodide does not give a crystalline derivative in this way [71].

β-Chloromorphide and the Morphine → Apomorphine Conversion

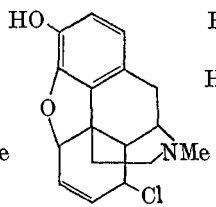
In warm concentrated hydrochloric acid morphine [XLIV] adds one mole of hydrogen chloride at the 4:5 oxygen bridge and suffers replacement of the alcoholic hydroxyl group by chlorine, coupled with an $\alpha:\gamma$-shift of the latter as in the production of β-chloromorphide, the product being dichlorodihydrodesoxymorphine [XLVI] hydrochloride. This readily suffers loss of hydrogen chloride and closure of the oxygen bridge to give β-chloromorphide [XLV] even in boiling water. The ease of this bridge-closure is remarkable in view of the unreactivity of the 4-hydroxyl group to diazomethane, which converts [XLVI] only to a monomethyl ether that can be converted to β-chlorocodide by sodium bicarbonate. β-Chloromorphide is an intermediate in the production of [XLVI] from morphine, as is shown by the fact that if the reaction between morphine and hydrochloric acid is arrested at the point at which

crystals first appear, morphine and β-chloromorphide can be isolated in roughly equal amounts together with [XLVI], and moreover β-chloromorphide can be converted to [XLVI] by heating with hydrochloric acid [19, 74].

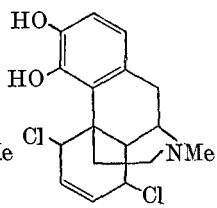
β-Chloromorphide was early recognized as an intermediate in the conversion of morphine to apomorphine [69, 72, 75], and both β-chloromorphide and [XLVI] give yields of apomorphine comparable to those obtained from morphine under the same conditions [19, 74]. The mechanism of the morphine → apomorphine conversion is regarded by Small as being as follows [19] (see, however, Chap. XXII):



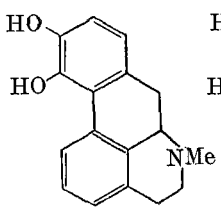
[XLIV]



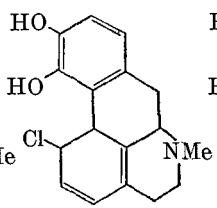
[XLV]



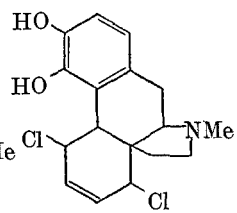
[XLVI]



[XLIX]



[XLVIII]



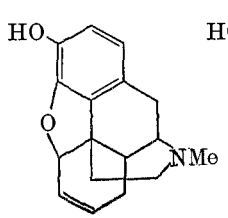
[XLVII]

(*a*) Replacement of the alcoholic hydroxyl of morphine by chlorine followed by, or simultaneously with, an α:γ-shift of the halogen to give β-chloromorphide [XLV].

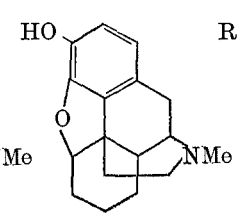
(*b*) Addition of hydrogen chloride to the cyclic ether group, which is now activated by the 6:7-double bond, giving [XLVI].

(*c*) Rearrangement of [XLVI] with the loss of hydrogen chloride to apomorphine [XLIX] via [XLVII] or [XLVIII].

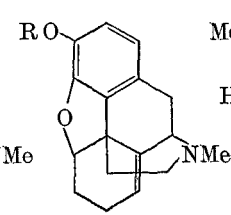
Prolonged action of hydrochloric acid on morphine at 50–60° C.,



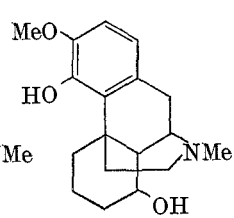
[L]



[LI]



[LII]



[LIII]

followed by hydrogenation of the resultant dichlorodihydrodesoxymorphine [XLVI] with a noble metal catalyst, affords desoxymorphine-C [L] and dihydrodesoxymorphine-D [LI] [74, 76–79].

8-Chlorodihydrocodide [XLII]

This base is formed together with a small quantity of 1:8-dichlorodihydrocodide by the action of phosphorus pentachloride on dihydro-ψ-codeine-A [XLIII] and its epimer dihydroallo-ψ-codeine-A. It is an exceptionally stable substance, being unaffected by electrolytic or sodium and alcohol reduction; heating with sodium methoxide under pressure simply causes demethylation to 8-chlorodihydromorphide [19], but prolonged boiling with sodium in *cyclo*hexanol causes loss of hydrogenchloride and production of desoxycodeine-D [LII, R = Me] and a small amount of the demethylated substance, desoxymorphine-D [LII, R = H] [19, 80].

ψ-Chlorocodide, obtained together with α-chlorocodide by the treatment of ψ-codeine with phosphorus pentachloride [12] is most probably identical with the α-isomer [10].

Allo-ψ-chlorocodide, reported to result from the interaction of phosphorus pentachloride and allo-ψ-codeine [70], was subsequently shown to be β-chlorocodide [10].

Tetrahydro-ψ-chlorocodide was prepared by the action of phosphorus pentachloride on tetrahydro-ψ-codeine [LIII] and reported to be reduced by sodium and alcohol to a tetrahydrodesoxycodeine [70], the properties of which are so inadequately described as to preclude the establishment of its identity.

BROMOCODIDE AND BROMOMORPHIDE

Preparation

Bromocodide is produced when codeine is gently boiled with hydrobromic acid [81–84]; when codeine [18, 37] and ψ-codeine [12] are treated with phosphorus pentachloride and when codeine is treated with thionyl bromide, excess of which causes production of 1-bromobromocodide [85]. In the same way morphine [14] and α-isomorphine [16] can be converted to bromomorphide, which yields bromocodide on methylation [17]. Attempts to isomerize these bases have failed.

Structure

Bromocodide and bromomorphide are believed to have structures analogous to those of the β-chloro-compounds, which they resemble in many of their reactions. Replacement of the halogen atom by other groups gives rise in all cases to 6-substituted compounds. However, the

reduction of these bases more closely resembles the reduction of the α-chloro-compounds than the reduction of the β-chloro ones. Moreover, bromo- and α-chlorocodides can be converted to iodocodide, whereas the β-chloro-compound cannot, though this is unreliable evidence on which to base a structural theory, as bromo-compounds are generally more reactive than their chloro-analogues. Bromocodide has not been reduced to a bromodihydrocodide.

Reduction

In all reductions of bromocodide the bromine atom is eliminated.

(*a*) Hydrogenation of bromocodide over palladized barium sulphate in neutral solution gives 94 per cent. dihydrodesoxycodeine-D [IX] [23].

(*b*) Hydrogenation using a palladized calcium carbonate catalyst in neutral solution gives 94 per cent. amorphous base, which is obtained in 100 per cent. yield using platinum oxide as catalyst. It is bis-6:6′-dihydrodesoxycodeine-D [X], identical with the product obtained from α-chlorocodide [23].

(*c*) Reduction of bromomorphide in neutral solution over palladized barium sulphate gives a small amount of dihydrodesoxymorphine-D and 70 per cent. of an undistillable oil, probably bis-6:6′-dihydrodesoxymorphine-D [15].

(*d*) Electrolytic reduction of bromomorphide gives desoxymorphine-A [15].

(*e*) Bromomorphide is converted to β-isomorphine (by hydrolysis) and desoxymorphine-A by reduction with amalgamated zinc and 6 N. hydrochloric acid [15].

Hydrolysis

Hydrolysis of bromocodide affords a mixture of isocodeine [16, 37] and allo-ψ-codeine [17, 37, 69], which readily form a molecular compound, m.p. 145–145·5° C., $[\alpha]_D^{14} = -205°$ [17, 37, 69]. Neither codeine nor ψ-codeine have been isolated from this hydrolysis. Bromomorphine furnishes a mixture of α- [14, 18], β- [14, 18], and γ-isomorphine [18].

Replacement of Halogen by Groups Other than Hydroxyl

These replacement reactions are parallel to those in the β-chloro-series and yield 6-substituted products.

(i) β-Isomorphine-6-ethyl ether [heteroethyl-β-isomorphine] is obtained by heating bromomorphide with ethyl alcohol [55].

(ii) Bis-thiocodide and bis-thiomorphide are formed when bromocodide and bromomorphide are heated with potassium hydrosulphide [65].

(iii) α-Alkylthiocodides and morphides result from heating bromocodide and morphide with mercaptans in aqueous sodium hydroxide, and the β-isomers are formed in alcoholic sodium ethoxide [56, 72–73].

(iv) 6-Piperidocodide and morphide are obtained by the action of piperidine on bromocodide and morphide; these give only non-phenolic dihydro-compounds on reduction [58]. 6-Aminocodide is formed from bromocodide and alcoholic ammonia at 100° C. under pressure; it can be converted to 6-carbamidoaminocodide [86].

(v) Bromocodide is reported to give the formyl ester of codeine on heating with sodium formate at 150° C. [61].

Wright claimed to have isolated a desoxycodeine and a desoxymorphine from the products obtained by heating bromocodide with hydrobromic acid [81, 87–89].

8-Bromodihydrocodide

This base is produced in very poor yield by the interaction of dihydro-ψ-codeine-A [XLIII] and phosphorus tribromide. In this way dihydrocodeine and dihydroisocodeine give only phosphorus-containing products (though the former on one occasion gave a compound having the composition of a dihydrobromo*morphide*), whilst dihydroallo-ψ-codeine-A apparently suffers bromination, loss of hydrogen bromide, and demethylation, as the product is desoxymorphine-D [LII, R = H] [19, 80].

IODOCODIDE AND IODOMORPHIDE

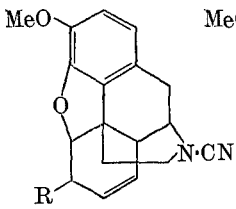
Iodocodide is formed by the treatment of bromo- and α-chlorocodide, but not β-chlorocodide, with potassium iodide [27, 39], and is an intermediate in the reduction of α-chlorocodide to desoxycodeine-A by methyl- and ethyl-magnesium iodide, a reduction that the iodocompound itself undergoes [27]. On catalytic hydrogenation iodocodide behaves like bromo- and α-chlorocodide, giving dihydrodesoxycodeine-D over palladized barium sulphate and bis-6:6′-dihydrodesoxycodeine-D over palladized calcium carbonate [23]. On hydrolysis it gives a mixture of isocodeine, ψ-codeine, and allo-ψ-codeine [39]. Iodomorphide results from the action of hydriodic acid on bromo- or α-chloromorphide [19].

Miscellaneous Reactions of the Halogenocodides

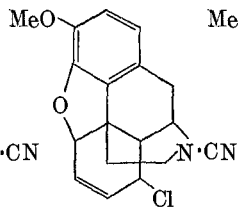
(*a*) 6-Chlorodihydrocodide yields an N-oxide on heating with hydrogen peroxide in acetic acid [20], and this can be sulphonated to 6-chlorodihydrocodide-N-oxide sulphonic acid and nitrated [90]. Both the N-oxide and its sulphonic acid are reduced to the base by sulphurous acid [20, 90].

(*b*) α- and β-Chlorocodide suffer the expected replacement of the N·Me group by N·CN on treatment with cyanogen bromide, giving

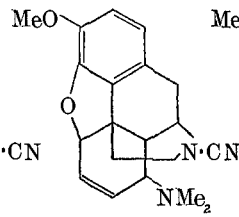
α- [LIV, R = Cl] and β-chlorocyanonorcodide [LV] respectively [91–92], the former of which is also accessible by the action of thionyl chloride on cyanonorcodeine [LIV, R = OH] and can be isomerized to the latter [91]. Cyanonormorphine can be converted to α-chlorocyanonormorphide by thionyl chloride. 8-Diethylaminocyanonormorphide [91] and 8-dimethylaminocyanonorcodide [LVI] [60] are formed from the corresponding α-chlorocompounds by heating with diethylamine and dimethylamine respectively. [LVI] is converted to 8-dimethylamino-N-(β-hydroxyethyl)-norcodide [LVII] on heating with ethylene oxide [60].



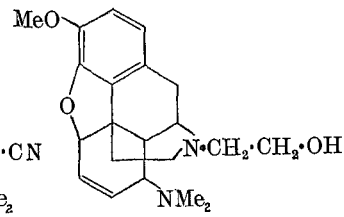
[LIV]



[LV]

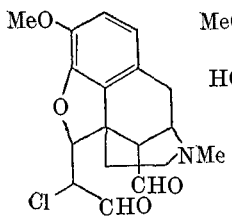


[LVI]

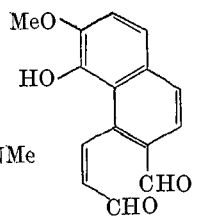


[LVII]

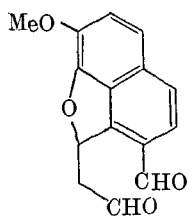
(*c*) **Ozonolysis.** Wieland and Small [93] subjected α-chlorocodide to ozonolysis and obtained a base $C_{18}H_{20}O_4NCl$, chlorocodizone, which they claimed was an aldehyde, giving it the structure [LVIII]. Hot methanolic potash was reported to convert the base in fifteen minutes to anhydrocodizone and on longer action to two nitrogen-free substances $C_{15}H_{12}O_2$, one non-phenolic (given the structure [LX]) and the other phenolic (given the structure [LIX]). Zinc and acetic acid reduction of chlorocodizone was stated to give 'desoxycodizone' $C_{18}H_{21}O_4N$ [93].



[LVIII]



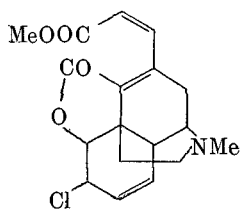
[LIX]



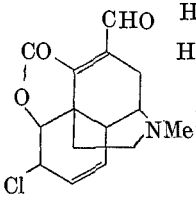
[LX]

Repetition of this ozonolysis by Speyer and Roell [94] confirmed the formula $C_{18}H_{20}O_4NCl$ for the primary product, which, however, is not an aldehyde. It can, however, be further ozonized to an aldehyde, α-chlorocodinal, $C_{13}H_{18}O_3NCl$, and the reaction is clearly analogous to the ozonolysis of dihydrocodeine, dihydroethylmorphine, and dihydrohydroxycodeinone, in which the aromatic nucleus is opened between carbon atoms 3 and 4 to give an ester-lactone capable of yielding an aldehyde on further ozonolysis. Chlorocodizone, therefore, has the structure [LXI] and α-chlorocodinal [LXII]. The former undergoes

saponification with great ease to α-chloromorphinic acid [LXIII] and can be hydrogenated with absorption of three moles of hydrogen to give what Speyer and Roell [94] believed to be 3-methyl-6-desoxy-7:8-dihydromorphinate [LXIV], but what, in the light of a recent reinterpretation of the reduction of α-ozodihydrocodeine (see Chap. IV), must now be regarded as methyl 6-desoxytetrahydromorphilactonate [LXV].



[LXI]



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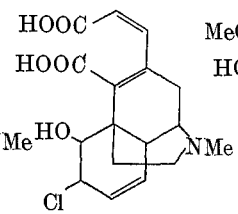
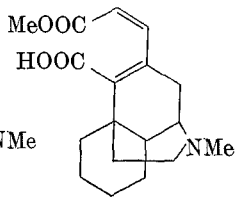


[LXIII]



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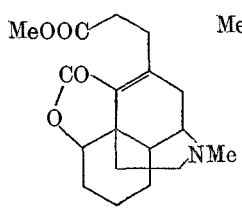
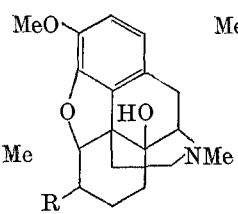
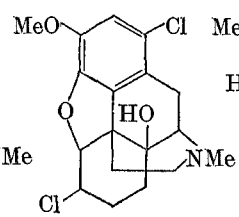


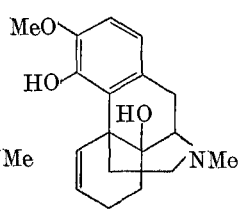
[LXV]



[LXVI]



[LXVII]



[LXVIII]

β-Chlorocodide on ozonolysis gives an oily base characterized as a picrate [94] and 6-chlorodihydrocodide gives ozochlorodihydrocodide (7:8 dihydrochlorocodizone), which on further ozonolysis gives chlorodihydrocodinal or the hydrolysed lactone chlorodihydrodikonal, according to the conditions [95].

Dihydrohydroxycodeine-B [LXVI, R = OH] with phosphorus pentachloride gives dihydrohydroxychlorocodide [LXVI, R = Cl] which gives [LXVII] on treatment with thionylchloride. [LXVI, R = OH] is chlorinated only in the nucleus by thionylchloride, and the product gives [LXVII] with phosphorus pentachloride. Sodium and alcohol reduction of [LXVI, R = Cl] gives 14-hydroxydihydrodesoxycodeine-C [LXVIII]. Dihydrohydroxycodeine-C, an isomer of [LXVI, R = OH] gives only phosphorus-containing compounds with phosphorus pentachloride [96] (cf. the behaviour of the dihydrocodeine isomers with the latter reagent).

Codeine and sulphuryl chloride give pentachlorooxycodide, $C_{18}H_{20}O_3NCl_5$, of unknown constitution [19].

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
α-chlorocodide	151–153	..	prisms	−383	26	$CHCl_3$	10, 18–19
— hydrochloride	..	..	syrup	..	..	..	10
— acid sulphate·$2H_2O$	192–193	H_2O	..	−101·1	20	H_2O	27
— acid tartrate	198–200	H_2O	needles	−219·3	27·5	H_2O	27
— methiodide	168	..	..	−215	15	..	12, 65
β-chlorocodide	152–153	EtOH or Et_2O	plates	−10	15	EtOH	10
— hydrochloride	168–171	EtOH	..	−3·9	30	MeOH	10
— hydriodide	..	H_2O	needles	0	26	H_2O	19
— acid tartrate	190–192	H_2O	..	+8·3	20	H_2O	27
— methiodide	indefinite	MeOH	..	+4·6	15	20% MeOH	12
α:β-chlorocodide molecular compd.	115–117	EtOH	..	−150·4	25	EtOH	19
1-chloro-α-chlorocodide	..	..	..	..	..	..	..
Dichlorocodide	196–197	EtOH	prisms	..	..	..	9
— hydrochloride	D.160–170	..	..	..	..	..	9
1-bromo-α-chlorocodide	131	ligroin	prisms	..	..	..	9
α-chloromorphide	193	MeOH	..	−375·2	..	MeOH	14, 59
— hydrochloride	..	EtOH	..	−315·3	20	H_2O	14
— hydrobromide	..	EtOH	..	−268·6	19	H_2O	14
— methiodide	207	MeOH	prisms	..	..	..	65
Acetyl-α-chloromorphide	174–178	EtOH	..	..	..	..	14
— hydrochloride	..	..	needles	..	..	..	14
β-chloromorphide	188	Et_2O	prisms	−5	15	MeOH	69
— nitrate	..	..	cryst.	..	..	..	71
— methiodide	210d.	H_2O	..	..	..	..	71
Acetyl-β-chloromorphido	163	EtOH	needles	..	..	..	71
— hydrochloride	..	..	cryst.	..	..	..	71
— methiodide	177	..	..	..	..	..	71
Trichloromorphide	c. 195d.	EtOAc	..	−285	21	MeOH	19
— hydrochloride	..	H_2O	..	−245·6	20	H_2O	19
Trichlorocodide	143–143·5	EtOH	..	−302	25	EtOAc	19
— hydrochloride	..	H_2O	..	−218	25	H_2O	19
6-chlorodihydrocodide	146* 172·5–174	EtOH	..	−177·8	27	$CHCl_3$	97–98 19, 20, 34
— hydrochloride	203–204 then 225	..	..	−129·5	26	H_2O	19
— *d*-tartrate	191–192	..	..	..	..	..	19
— methiodide	253* 244	..	.. needles	..	..	..	97–98 20
— N-oxide	214	H_2O	..	..	..	..	20
6-chlorodihydrocodide methine: *see* α-chlorodihydrocodeimethine-C (Chap. IV).							
β-chlorodihydrocodide	c. 145	EtOH	..	+37·5	25	EtOH	19
8-chlorodihydocodide	123–124	75% acetone	..	−42·7	25	EtOH	19
— tartrate	230–232	..	..	..	..	..	19
1:8-dichlorodihydrocodide	190–191·5	EtOH	..	..	..	..	19
Dihydrocodeine + $SOCl_2$ →	187–190	..	..	..	..	..	19
Dihydroisocodeine + $SOCl_2$ →	103–105	..	..	..	..	..	19
Dihydro-ψ-codeine-A + $SOCl_2$ →	108–112	..	..	..	..	..	19
6-chlorodihydromorphide	155 and 233 228–229	..	..	−145·0	30	EtOH	34 22
— hydrochloride	323–326	H_2O	..	−131·0	28	H_2O	22
Bromocodide	162	EtOH	plates	+56·5	20	EtOH	16, 85
1-bromo-bromocodide	171–173	EtOH	..	+39	23	dioxane	85
Bromomorphide	169–170 > 200	.. MeOH	.. ..	+65·9 +73·9	25 28	MeOH MeOH	14, 16
— hydrochloride·H_2O	..	H_2O	..	+41·1	27	H_2O	15
— hydrobromide·H_2O	196	EtOH	..	+39·5	25	..	14
— methiodide	200	..	needles	..	..	..	14
— phenylcarbamate	204	..	needles	..	..	..	14
8-bromodihydrocodide	230–232	..	..	..	..	..	14
6-bromodihydromorphide?	260–262	..	..	..	..	..	19
Iodocodide	159–160	MeOH	needles or prisms	+136·5	22·5	$CHCl_3$	19 27
— hydrochloride·xH_2O	100–101	MeOH	..	+127	23	H_2O	27
— hydriodide	180–182	..	..	..	..	..	27, 39

* m.p. of racemate with 6-chlorodihydrocodide derived from stereoisomeric series.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Iodocodide methiodide	187–188	H_2O	needles	..	..	..	27
Iodomorphide	..	..	vitreous	+123·2	27	MeOH	19
— hydriodide	..	H_2O+ atm. CO_2	..	+114·5	25	H_2O	19
— acid tartrate	..	50% EtOH	..	+120·3	25	H_2O	19
— benzoate	159–160	EtOH	..	+115·5	26	EtOH	19
— salicylate	161	EtOH	..	+113·4	26	H_2O	19
— methiodide	..	50% EtOH	..	+90	26	50% EtOH	19
α-chlorocyanonorcodide	187–188	..	..	−390	20	$CHCl_3$	91–92
β-chlorocyanonorcodide	197–198	..	..	−97·5	20	$CHCl_3$	91–92
α-chlorocyanonormorphide	D. 300	..	..	..	..	..	91
Chlorocodizone	104	ligroin	..	−231	22	EtOH	93–94
— hydrochloride	D. 213	..	needles	..	..	..	93
— hydrobromide	D. 201	..	..	..	..	..	93
— hydriodide	D. 174	..	..	..	..	..	93
— picrate	171	..	..	..	..	..	93
Anhydrocodizone	110	..	yellow needles	..	..	..	93
Chlorocodizone+KOAc→	189	..	..	..	..	..	93
Desoxycodizone	161	..	..	..	..	..	93
— hydrochloride	223–224d.	MeOH	..	..	..	..	93
α-chloromorphinic acid	D. 192	MeOH	plates	..	..	..	94
Methyl 6-desoxytetrahydromorphilactonate picrate	200–205	..	plates	..	..	..	94
α-chlorocodinal	..	..	..	..	..	..	94
— phenylhydrazone	..	..	amorph.	..	..	..	94
Ozo-β-chlorocodide	..	..	oil	..	..	..	94
— picrate	D. 217	HOAc	needles	..	..	..	94
Ozo-6-chlorodihydrocodide [7:8-dihydrochlorocodizone]	..	..	..	..	..	..	95
Chlorodihydrocodinal	206–207d.	96% EtOH	plates	..	..	..	95
— perchlorate	D. 270	..	prisms	..	..	..	95
Chlorodihydrodikonal perchlorate	D. 266	..	..	..	..	..	95
6-chlorodihydrocodide-N-oxide sulphonic acid	D. 290–295	..	..	..	..	..	20
6-chlorodihydrocodide sulphonic acid	D. c. 300	..	prisms	..	..	..	20
HNO_3+6-chlorodihydrocodide→	223–224	EtOH	yellow crystals	..	..	..	20
'sulpho-β-chloromorphide'·H_2O	..	H_2O	crystalline	..	..	..	71
6-methyl-(β?)-chlorocodide	162·5–163·5	ligroin	..	..	..	..	63
6-aminocodide, acetyl deriv.	117d.	..	..	..	..	..	86
6-carbamidoaminocodide	238–240	..	..	..	..	..	86
6-piperidocodide	75–80	subl.	..	−233·9	25	MeOH	58
— diperchlorate	172–175	H_2O	..	−113·4	23	H_2O	58
6-piperidomorphide	216–217	EtOAc	..	−234·8	23	MeOH	58
— monomethiodide	236–241	H_2O	needles	−145·8	23	50% EtOH	58
Dihydro-6-piperidomorphide	215–217	EtOAc	..	−155·9	24	MeOH	58
8-aminocodide	128·5–129	Et_2O	..	−79·2	21	EtOH	58
—dihydrochloride	300–305	95% EtOH	..	−40·7	24	H_2O	58
Diacetyl-8-aminocodide	218–220d.	EtOAc	..	+83·1	24	EtOH	58
Dihydro-8-aminocodide	..	..	amorph.	−28·7	21	EtOH	58
— dihydrochloride	274–277	97% EtOH	..	−14·7	24	H_2O	58
Tetrahydro-8-aminocodide	138·5–140	subl.	..	−9·7	24	EtOH	58
— dihydrochloride	..	EtOH	..	+6·6	24	H_2O	58
8-dimethylaminocodide	118	..	..	..	..	..	60
— platinichloride	250	..	..	..	..	..	60
8-diethylaminocodide	101–103	subl.	..	+42·6	23	MeOH	60, 58
— dihydriodide	179–182	H_2O	..	+22·9	26	EtOH	58
— diperchlorate	180–183	H_2O	..	+3·3	19	H_2O	58
— platinichloride	D. 240	..	..	..	..	..	60
Tetrahydro-8-diethylaminocodide	154–157	subl.	..	+81·5	25	MeOH	58
— monoperchlorate	234–238	H_2O	..	+18·3	26	H_2O	58
8-diethylaminomorphide	187–188	..	..	..	..	..	91
— platinichloride	D. 250	..	..	..	..	..	91
8-diethylaminomorphide	201–204	subl.	..	−140·1	21	MeOH	16, 58

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
8-diethylaminomorphide dihydriodide·1½H_2O	87–93	H_2O	..	+2·6	25	H_2O	58
— diperchlorate	114–116	H_2O	..	+4·4	19	H_2O	58
8-piperidocodide	116–117	subl.	..	+25·8	22	MeOH	33, 58
— monohydriodide	234–237	H_2O	..	+13·4	24	H_2O	58
— diperchlorate	181–183	H_2O	..	+13·2	23	50% EtOH	58
— diacidsulphate	161–163·5	EtOH	..	+19·8	26	H_2O	58
— monomethiodide	..	..	..	+22·0	25	H_2O	58
Dihydro-8-piperidocodide	167–169	EtOH	..	−1·2	23	MeOH	58
Tetrahydro-8-piperidocodide	c. 125	subl.	..	+36·7	25	MeOH	58
8-piperidomorphide	222–224	EtOH	..	+28·7	24	MeOH	58
— dihydriodide	208–214	H_2O	..	+14·9	23	H_2O	58
— monomethiodide	243–245	H_2O	..	+23·7	23	50% EtOH	58
Tetrahydro-8-piperidomorphide	270–280	..	..	+45·1	26	10% HOAc	58
Acetyltetrahydro-8-piperidomorphide	172–178	..	..	..	..	..	58
Dihydrohydroxychlorocodide	213·5–214	EtOAc	..	−151	22	10% HOAc	96
1-chlorodihydrohydroxychlorocodide	163·5	EtOH	prisms	−141	22	10% HOAc	96
Pentachloroöxycodide	D.	..	..	−289·8	25	acetone	19
Dichlorodihydrodesoxymorphine hydrochloride	230–235	..	..	+276	27	50% EtOH	19

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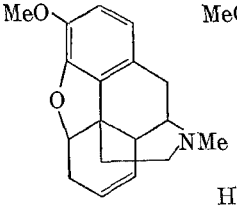
IX

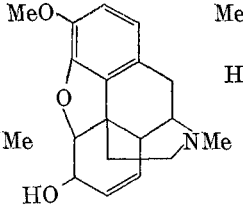
THE DESOXYCODEINES AND THEIR DERIVATIVES

THE DESOXYCODEINES

THE name desoxycodeine should logically be applied only to the substance of structure [I], in which the alcoholic oxygen of codeine [II] has been eliminated; it is, however, also applied to two isomers of [I] differing in the position of the double bond, and to a phenolic base [III] having an additional double bond in ring C.



[I]



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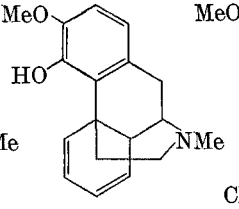

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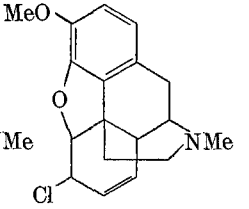
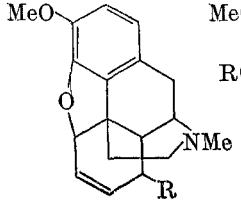


[IV]

DESOXYCODEINE-A

Desoxycodeine-A [III] was first prepared by Knorr and Waentig [1] (and called simply desoxycodeine) by reducing α-chlorocodide [IV] with zinc-dust and alcohol, a process that must involve 1:4-addition of hydrogen to the system $-\overset{1}{O}-\overset{2}{CH}-\overset{3}{CH}-\overset{4}{Cl}$ of [IV]. It may be prepared in the same way from β-chlorocodide [V, R = Cl] [1], bromocodide [V, R = Br] [2], and iodocodide [V, R = I] [3]; by the interaction of α-chlorocodide and methyl- or ethylmagnesium iodide, a reaction in which the Grignard reagent functions solely in a reducing capacity and in which iodocodide is very probably an intermediate [3]; and also by the electrolytic reduction of α-chlorocodide [3–4].



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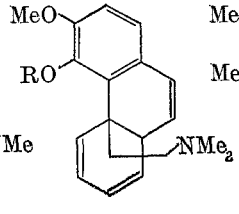
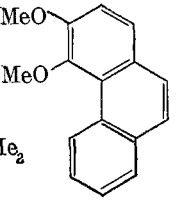


[VI]



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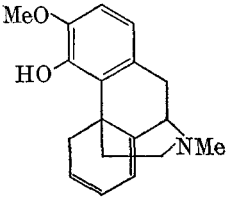


[VIII]

Desoxycodeine-A is phenolic, being soluble in alkali, giving a colour with ferric chloride and forming a methyl ether [1]. The phenol may be degraded to a methine base [VI, R = H], which oxidizes rapidly in air, and the methyl ether to [VI, R = Me], which decomposes spontaneously to an amine and dimethylmorphol [VII] [1].

Reduction of desoxycodeine-A with sodium and alcohol gives a mixture of dihydrodesoxycodeines-B and -C [1] and catalytic hydrogenation affords tetrahydrodesoxycodeine [4] (see below).

Bromination of the aromatic nucleus occurs when desoxycodeine-A is treated with bromine, and the hydrogen bromide thus formed adds (1:4?) to the diene system, giving dibromodihydrodesoxycodeine, also obtained by addition of hydrogen bromide to desoxycodeine-A followed by bromination. Acetolysis of the dibromide yields 1-bromo-3-methoxy-4-acetoxyphenanthrene (structure proved by conversion to the 3:4-dimethoxycompound and synthesis of the latter), also prepared by the degradation of 1-bromocodeine [5].

An attempt to prepare 1-bromodesoxycodeine-A by the zinc-dust and acetic acid reduction of 1-bromo-α-chlorocodide gave instead, 1-bromodesoxycodeine-C (q.v.) [5].

DESOXYCODEINE-B

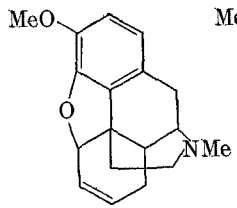
Desoxycodeine-B, first thought to be a definite entity, was subsequently shown to be anhydrous desoxycodeine-A containing a small amount of a very persistent impurity. It was obtained by the electrolytic reduction of α- and β-chlorocodide [3–4]. Freund believed it to be a dihydrodesoxycodeine and claimed it was formed in the electrolytic reduction of desoxycodeine-A and of 6-chlorodihydrocodide [4]. In fact the two latter reactions yield isomeric dihydrodesoxycodeines [3].

Small and Cohen [3] showed that 'desoxycodeine-B' is indeed a desoxycodeine and that on reduction it yields the same substances as does desoxycodeine-A and accordingly suggested the structure [VIII] for it. However, Small and Morris [6], finding that electrolytic reduction of α-chloromorphide gives desoxymorphine-A, which can be methylated to desoxycodeine-A, re-examined desoxycodeine-B and discovered that it is identical with desoxycodeine-A.

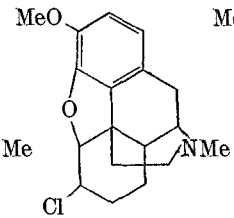
DESOXYCODEINE-C

Desoxycodeine-C [IX] was the first of the non-phenolic desoxycodeines to be isolated. It is obtained by heating 6-chlorodihydrocodide [X] with sodium methoxide in methyl alcohol at 140° C. [3]; previously no reaction had been observed at 120° C. [7]. Desoxycodeine-C was presumably obtained by Knoll and Co. in this way, but was believed to be a dihydrodesoxycodeine [8–9]. It is allotted the structure [IX] on account of the ease with which phenolic substances are produced during

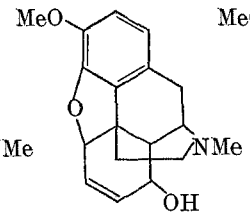
reduction (cf. the reduction of ψ-codeine, allo-ψ-codeine [XI], Chap. IV, and ϵ- and ζ-codeimethine [XII], Chap. VI).



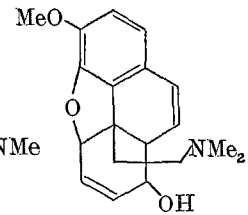
[IX]



[X]

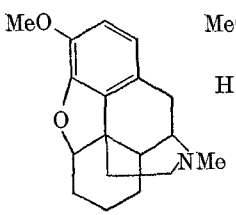


[XI]

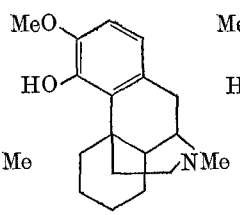


[XII]

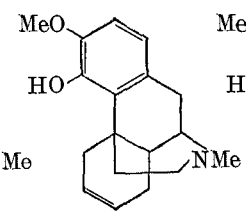
The non-phenolic dihydrodesoxycodeine-D [XIII] is produced, together with tetrahydrodesoxycodeine [XIV], by the hydrogenation of desoxycodeine-C hydrochloride in glacial acetic acid over platinum oxide [6], but only tetrahydrodesoxycodeine is formed by hydrogenation of the base. Electrolytic reduction proceeds with opening of the cyclic ether and production of dihydrodesoxycodeine-B [XV], obtained together with dihydrodesoxycodeine-C [XVI] by reduction with sodium and alcohol [3, 10].



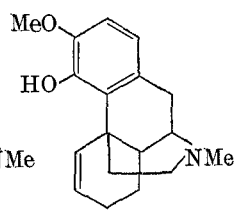
[XIII]



[XIV]

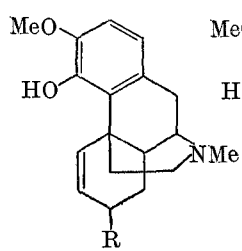


[XV]

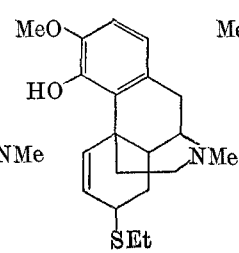


[XVI]

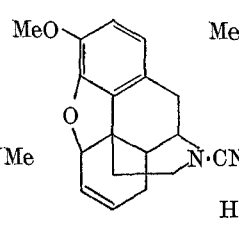
The cyclic ether link is activated by the presence of the 6:7-double bond, and desoxycodeine-C will react with Grignard reagents giving phenolic bases probably of the type [XVII] (see Chap. XIX) [11], and with ethyl mercaptan to give ethylthiodihydrodesoxycodeine-C [XVIII] [12].



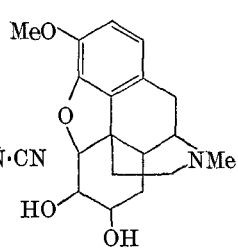
[XVII]



[XVIII]



[XIX]



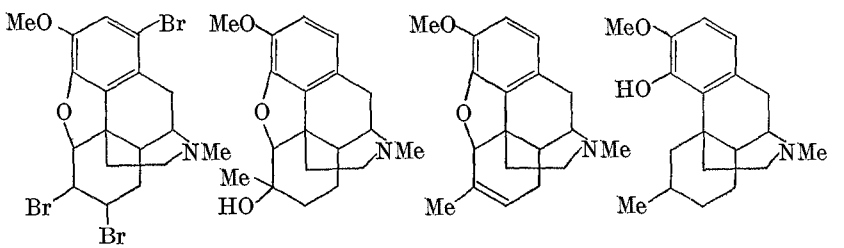
[XX]

Cyanogen bromide reacts with desoxycodeine-C to give cyanonordesoxycodeine-C [XIX] [13]. Oxidation of the base with 1 per cent. potassium permanganate solution affords 7-hydroxydihydrocodeine [XX] [14].

The optical antipode of desoxycodeine-C can be prepared in the sinomenine series [15] (see Chap. XXVII).

1-bromodesoxycodeine-C is accessible by zinc-dust and acetic acid reduction of 1-bromo-α-chlorocodide; it can be degraded to a methine base and finally to 1-bromomethylmorphenol, identical with the product of exhaustive methylation of 1-bromocodeine, showing that the cyclic ether link remains unbroken. Catalytic hydrogenation converts it to 1-bromotetrahydrodesoxycodeine, identical with the product of bromination of tetrahydrodesoxycodeine [5].

Bromination of desoxycodeine-C affords 1:6:7-tribromodihydrodesoxycodeine-D [XXI]; this absorbs three moles of hydrogen on hydrogenation, giving a bromotetrahydrodesoxycodeine not identical with that obtained from tetrahydrodesoxycodeine, and this on reduction with sodium and alcohol yields a substance isomeric with tetrahydrodesoxycodeine [5].



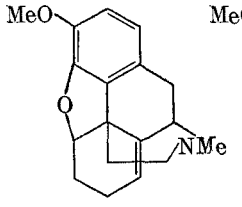
[XXI] [XXII] [XXIII] [XXIV]

6-Methyldihydrocodeine [XXII] on heating with thionyl chloride is dehydrated to 6-methyldesoxycodeine-C [XXIII]; phosphorus pentachloride effects chlorination in position 1 in addition to dehydration. 6-methyldesoxycodeine-C is non-phenolic and gives no formaldehyde on ozonolysis; the ozonide on treatment with iodine and alkali yields iodoform, indicating formation of a methyl ketone. Catalytic reduction of [XXIII] gives 6-methyltetrahydrodesoxycodeine [XXIV] [16].

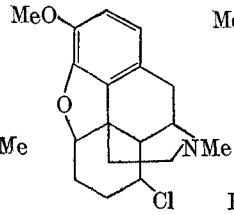
Desoxycodeine-D [Desoxyneopine]

Desoxycodeine-D [XXV] was first prepared from 8-chlorodihydrocodide [XXVI] by prolonged boiling with sodium in cyclohexanol [13] and subsequently from neopine [XXVII] by reduction of its *p*-toluenesulphonyl ester with lithium aluminium hydride [17]. Degradation of desoxycodeine-D affords desoxy-β-codeimethine [XXVIII] [13, 17], which can also be obtained by the isomerization of desoxy-α-codeimethine

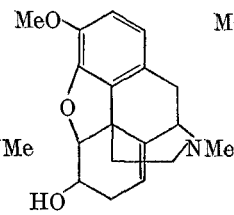
[XXIX] (from desoxycodeine-E) [17]. Desoxycodeine-D also reacts with cyanogen bromide as an allylamine, yielding an amorphous bromo-compound that slowly loses bromine, indicating that ring fission occurs during the reaction [13]. Hydrogenation of desoxycodeine-D affords dihydrodesoxycodeine-D [XIII], and bromination gives the 1-bromo-compound [13].



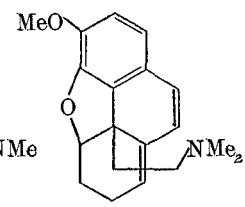
[XXV]



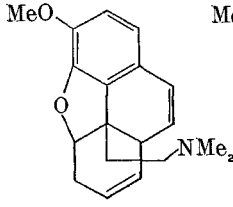
[XXVI]



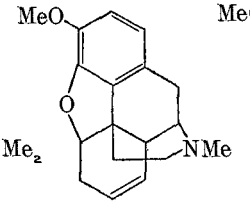
[XXVII]



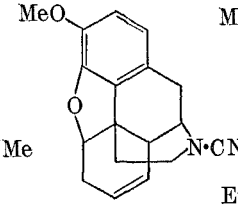
[XXVIII]



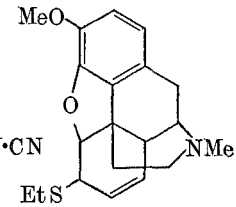
[XXIX]



[XXX]



[XXXI]



[XXXII]

DESOXYCODEINE-E

Desoxycodeine-E [XXX] can be prepared by the lithium aluminium hydride reduction of codeine [II] *p*-toluenesulphonyl ester [17–18]. Its structure is shown to be [XXX] by hydrogenation of the base to dihydrodesoxycodeine-D [XIII], degradation of the methiodide to desoxy-α-codeimethine [XXIX], and isomerization of the latter to desoxy-β-codeimethine [XXVIII], production of cyanonordesoxycodeine-E [XXXI] by the action of cyanogen bromide on the base, and by the facts that desoxycodeine-E is neither a phenol nor an enol ether [17]. Desoxycodeine-E can be demethylated to desoxymorphine-E [62].

Attempts to prepare the base by desulphurization of α-ethylthiocodide [XXXII] with Raney nickel failed owing to opening of the oxide ring, partial hydrogenation, or both [17].

A 'desoxycodeine' was described by Wright [19, 20], but nothing is known of its structure.

THE DIHYDRODESOXYCODEINES

Much inaccurate work by Freund, Melber, and Schlesinger [4] led to considerable confusion in the chemistry of the dihydrodesoxycodeines, which was only resolved ten years later by Small and Cohen [21]. For a

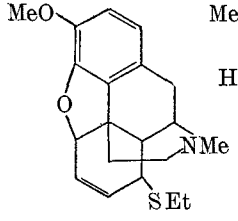
full criticism of Freund's work the reader is referred to the original paper by Small and Cohen [21].

DIHYDRODESOXYCODEINE-A

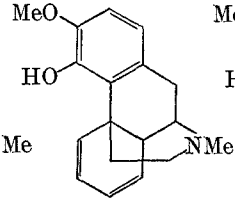
Dihydrodesoxycodeine-A was originally thought to be a definite compound, but is now known to be a mixture of two bases. It is obtained by the sodium and alcohol reduction of desoxycodeine-A [III], α-chlorocodide [IV] [1, 3, 10, 22], and desoxycodeine-C [IX] [3, 10], and can be further reduced catalytically to tetrahydrodesoxycodeine [XIV] [3]. It was first stated to yield on degradation a methine base that absorbed two moles of hydrogen on reduction, giving tetrahydrodesoxycodeine dihydromethine (see below) [21], but later attempts to isolate the methine base from the products of degradation were unsuccessful [23].

Subsequently dihydrodesoxycodeine-A was proved to be a mixture of dihydrodesoxycodeine-B [XV] (1 part) and dihydrodesoxycodeine-C [XVI] (3 parts), isolated together as a result of the extraordinary tendency of the salts of these two isomers to crystallize together.

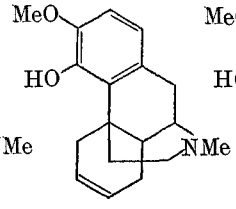
This constant-proportion mixture is also obtained in small amount by the sodium and alcohol reduction of the epimeric pair ψ-codeine [24] and allo-ψ-codeine [XI] [25], and of δ-ethylthiocodide [XXXIII] [12]. Elimination of the group at C-8 presumably proceeds by 1:6-addition of hydrogen to the system $-\overset{1}{O}-\overset{2}{CH}-\overset{3}{CH}=\overset{4}{CH}-\overset{5}{CH}-\overset{6}{R}$ giving desoxycodeine-A [III] and the latter is then further reduced; 3:6-reduction would give desoxycodeine-E and 5:6-reduction would involve an activating effect of the double bond not found in codeine [24].



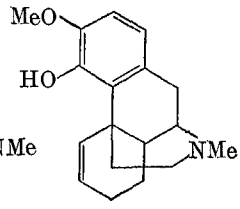
[XXXIII]



[III]



[XV]



[XVI]

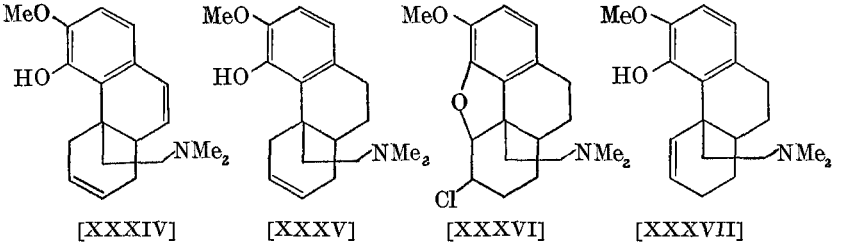
Desoxycodeine-A is doubtless also an intermediate in the reduction of α-chlorocodide by sodium and alcohol, being reduced as fast as it is formed to dihydrodesoxycodeines B [XV] and C [XVI]. The latter two compounds must be produced from desoxycodeine-C [IX] by competing 1:2- and 1:4-reduction of the system $-\overset{1}{O}-\overset{2}{C}-\overset{3}{C}=\overset{4}{C}$.

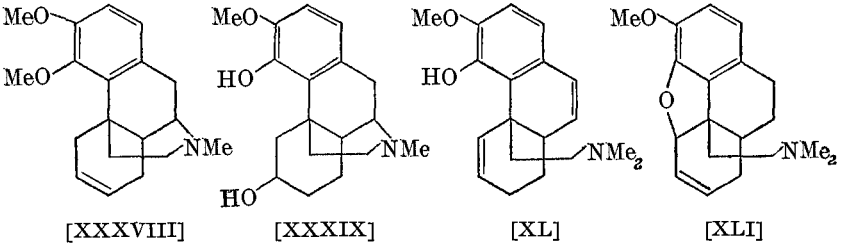
The two components comprising dihydrodesoxycodeine-A can be separated through the bases and by degradation and separation of the methine bases [10].

DIHYDRODESOXYCODEINE-B

In addition to the production, mixed with dihydrodesoxycodeine-C as described above, this dihydrodesoxycodeine-B [XV] can be obtained by the electrolytic reduction of desoxycodeine-C [IX], the double bond simply exerting an activating effect on the cyclic ether group in the latter [3, 10, 21]. It suffers no melting-point depression when mixed with 'dihydrodesoxycodeine-A', a phenomenon frequently encountered in this series [21–22]. On catalytic reduction it yields tetrahydrodesoxycodeine [21], and on degradation it gives dihydrodesoxycodeine-B methine [XXXIV] [10]. A compound that may be the dihydromethine [XXXV] results from sodium and alcohol reduction of α-chlorotetrahydrocodeimethine [XXXVI] [22, 26], though this product may have the isomeric structure [XXXVII].

Two stereoisomers of dihydrodesoxycodeine-B methyl ether [XXXVIII] have been prepared by the dehydration of the methyl ethers of dihydrothebainol [XXXIX] and its C-14 epimer β-dihydrothebainol, and a racemic mixture of structure [XXXVIII] prepared by an unambiguous synthesis was shown by comparison of infra-red spectra to be identical with the compound derived from the β-series [27] (see Chap. XXVIII).





DIHYDRODESOXYCODEINE-C

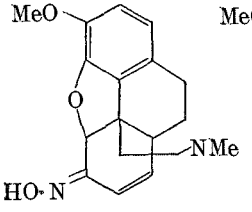
Dihydrodesoxycodeine-C [XVI] results from the electrolytic reduction of 6-chlorodihydrocodide [X] [3–4, 21], and, mixed with dihydrodesoxycodeine-B, as described under 'dihydrodesoxycodeine-A'. A substance having the properties of dihydrodesoxycodeine-C is obtained by the electrolytic reduction of δ-ethylthiocodide [XXXIII], but on degradation

this yields a methine base that depresses the melting-point of dihydrodesoxycodeine-C methine [12].

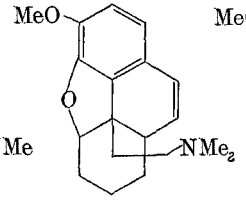
Dihydrodesoxycodeine-C can be hydrogenated to tetrahydrodesoxycodeine [XIV] [21], and degraded to a methine base [XL] [10]. A substance having the composition of dihydrodesoxycodeine-C dihydromethine [XXXVII] and the properties of a phenol is obtained by the sodium–liquid ammonia–alcohol reduction of codeine methiodide [28]. This could arise by reductive scission of the nitrogen-containing ring and 1:4 reduction of the allylic alcohol giving desoxycodeine-C dihydromethine [XLI], which would be expected to undergo further reduction under such conditions to [XXXVII] or a mixture of [XXXVII] and [XXXV]. Codeine, however, is recovered unchanged from attempted reduction with sodium, liquid ammonia, and alcohol [28].

DIHYDRODESOXYCODEINE-D

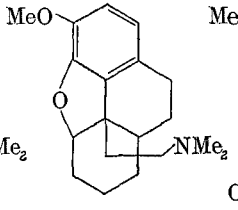
Dihydrodesoxycodeine-D [XIII], the only non-phenolic dihydrodesoxycodeine, can be prepared by the catalytic hydrogenation of α-chlorocodide [IV] [29], β-chlorocodide [V, R = Cl] [7, 29], bromocodide [V, R = Br] [29], and desoxycodeine-C [IX] hydrochloride [6]. It has also been reported to be formed by catalytic reduction of codeinone oxime [XLII] hydrochloride [30]. Dihydrodesoxycodeine-D methine [XLIII] results from Hofmann degradation of the methiodide [7], and a substance that is presumably the dihydromethine [XLIV] is obtained by catalytic reduction of α-chlorocodeimethine [XLV] [26].



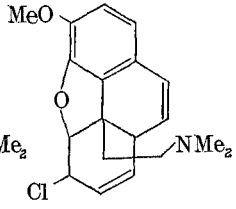
[XLII]



[XLIII]



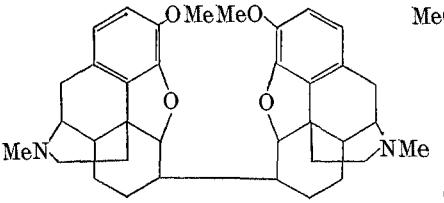
[XLIV]



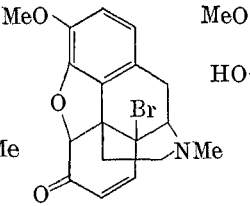
[XLV]

An 'α-dihydrodesoxycodeine', amorphous, alkali-insoluble, and poorly characterized, was reported by Freund [4] to result from the reduction of α-chlorocodide using a colloidal palladium catalyst. A reinvestigation of this reduction, however, showed that under the conditions prescribed by Freund the product consists of 95 per cent. dihydrodesoxycodeine-D; with palladized barium sulphate the results are substantially the same, but an amorphous product is obtained in 40 per cent. yield if the amount of catalyst used is large, and this can be increased to 96–100 per cent. using palladized calcium carbonate and 100 per cent. using platinum oxide as catalyst [29]. The product appears to be bis-6:6'-dihydrodesoxycodeine-D [XLVI] and is probably formed

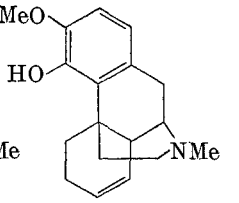
from α-chlorocodide in a manner analogous to the formation of diphenyl by the reduction of bromobenzene [31]. This substance is also obtained by the reduction of bromocodide under the same conditions [29]. It is quite unaffected by electrolytic reduction [29].



[XLVI]



[XLVII]



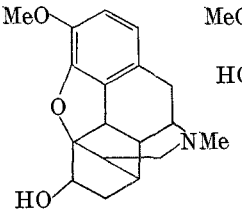
[XLVIII]

DIHYDRODESOXYCODEINE-E

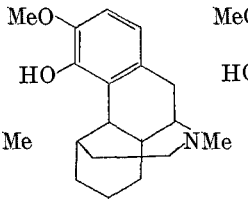
Dihydrodesoxycodeine-E is produced by the electrolytic reduction of 14-bromocodeinone [XLVII] [21, 32]; beyond the facts that it is phenolic, can be reduced catalytically to tetrahydrodesoxycodeine, and can be degraded to a methine base [32], nothing is known of its properties. It may have the structure [XLVIII].

TETRAHYDRODESOXYCODEINE

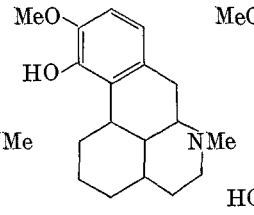
Only one tetrahydrodesoxycodeine has been prepared from thebaine, though its antipode has been obtained from sinomenine. However, for many years it was thought, as a result of the inaccurate work of Freund [4], that two isomers, α- and β-, existed, and it was required that any satisfactory formula for codeine be able to explain the isomerism. Freund accounted for the isomerism on the basis of the bridge structure for codeine [XLIX], developed in connexion with phenyldihydrothebaine, by postulating fission of the bridge in two ways to give [L] and [LI] [4], and Gulland and Robinson suggested a similar explanation based on [LII] [33], but later postulated stereoisomerism at C-14 when [LII] was modified to [II] [34].



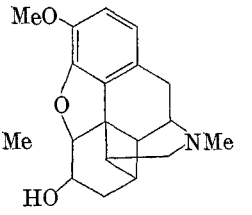
[XLIX]



[L]



[LI]



[LII]

Freund claimed that the dihydrodesoxycodeine (-A), m.p. 134–135° C., prepared by Knorr and Waentig [1] was identical with 'α-tetrahydrodesoxycodeine' [4], but it was subsequently shown by Small and Cohen [21] to be indeed a dihydro-compound. Cahn, in an attempt

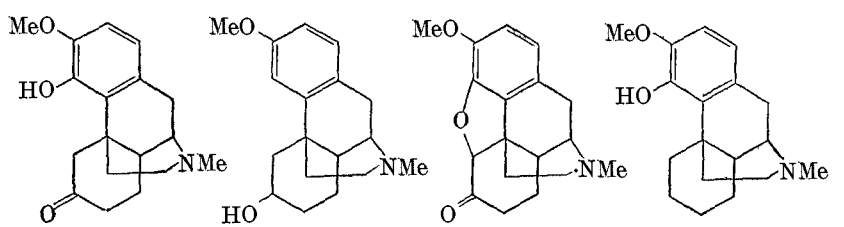
to show that the isomerism was not illusory, prepared the α- and β-compounds *but omitted to prove that they were isomeric* [22].

A base m.p. 130–132° C. obtained by the hydrogenation of dihydrodesoxycodeine-C, when pure has m.p. 144–145° C. and is in fact (β-) tetrahydrodesoxycodeine [28]. Speyer and Krauss [35] also claimed to have prepared α-tetrahydrodesoxycodeine by the reduction of allo-ψ-chlorocodide, later shown to be β-chlorocodide [36], but reinvestigation of the reduction revealed the production of only dihydrodesoxycodeine-D and (β-) tetrahydrodesoxycodeine [21]. The desoxytetrahydro-ψ-codeine obtained by the catalytic reduction of tetrahydro-ψ-chlorocodide and stated to be identical with α-tetrahydrodesoxycodeine [35] is too inadequately described to admit identification.

In no case has the existence of α-tetrahydrodesoxycodeine been substantiated and only one form (and its antipode) is at present known. The C-14 epimer could presumably be prepared from β-dihydrothebainone.

Tetrahydrodesoxycodeine [XIV] is the end-product of reduction of desoxycodeine-A [4], desoxycodeine-C [3], and dihydrodesoxycodeines-B [21], -C [21], and -E [32]. It is also formed in varying amounts during the reduction of the halogenocodides [6–7, 21, 29] (see Chap. VIII) and during the catalytic hydrogenation of allo-ψ-codeine [25]; it is identical with Mannich's dehydroxytetrahydrocodeine [7].

Electrolytic reduction of dihydrothebainone [LIII] was stated by Speyer and Siebert [37] to give dihydrothebacodine [LIV], and Clemmensen reduction of both dihydrothebainone and dihydrocodeinone [LV] [38–40] also yields this base, which is almost certainly identical with tetrahydrodesoxycodeine, as all preparations having the properties of dihydrothebacodine that have been subjected to direct comparison have been shown to be identical with tetrahydrodesoxycodeine [23, 39–40]. The C-14 epimer of the latter should therefore be available by the Clemmensen reduction of β-dihydrothebainone, the C-14 epimer of [LIII].



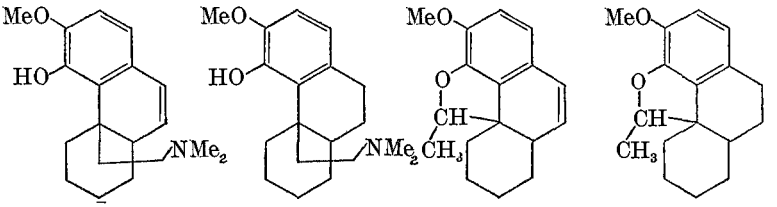
[LIII] [LIV] [LV] [XIV]

The optical antipode of tetrahydrodesoxycodeine has been prepared in the sinomenine series and called desmethoxydesoxydihydrosinomonine [41], desoxytetrahydrosinomenine-[38, 42–43], and dihydrothebainan [43].

Tetrahydrodesoxycodeine [XIV] is exceptionally stable and can be demethylated with hydriodic acid to tetrahydrodesoxymorphine, the two hydroxyl groups of which differ in activity as it gives only [XIV] on treatment with diazomethane. The inertness of the hydroxyl group at position 4 is demonstrated by the facts that tetrahydrodesoxycodeine is insoluble in alkali and cannot be methylated with diazomethane or phenyltrimethylammonium hydroxide. The base can, however, be methylated to the methyl ether methiodide [4] and this can be converted to the methochloride, vacuum-distillation of which affords tetrahydrodesoxycodeine methyl ether [23].

Racemic tetrahydrodesoxycodeine has been synthesized by Grewe, Mondon, and Nolte [44] and the synthetic material shown to be identical with the racemate obtained by mixing the (−) and (+) isomers from the thebaine-codeine and sinomenine series (see Chap. XXVIII).

Tetrahydrodesoxycodeine methine [LVI] results from degradation of tetrahydrodesoxycodeine, and can be hydrogenated to the dihydromethine [LVII] [23], which is identical with the 'dihydrodesoxytetrahydromethylmorphimethine' of Cahn [22] obtained by reducing the product of sodium and alcohol reduction of [XXXVI]. The methine [LVI] and dihydromethine [LVII] and their antipodes have been degraded to (+) and (−) forms of 9:10-dehydrothebenane [LVIII] and thebenane [LIX] [45–46]. An isomeric dehydrothebenane was prepared by Cahn [22] by the degradation of [XXXV] or [XXXVII] (see Chap. XV). Tetrahydrodesoxycodeine and its antipode can be oxidized to (+) and (−) bis-1:1'-tetrahydrodesoxycodeine by silver nitrate [46].



[LVI] [LVII] [LVIII] [LIX]

THE DESOXYMORPHINES AND THEIR DERIVATIVES

The desoxymorphines bear the same relationship to morphine as the desoxycodeines do to codeine and, though the series is less extensive, each desoxymorphine can be methylated to the corresponding desoxycodeine.

DESOXYMORPHINE-A

Desoxymorphine-A can be obtained by the electrolytic reduction of α-chloromorphide [6] or bromomorphide [47] and, together with β-isomorphine, by the reduction of these bases with amalgamated zinc

and 6 N. hydrochloric acid [47]. Methylation of desoxymorphine-A with diazomethane yields desoxycodeine-A [III] [6]. Hydrogenation of the base affords tetrahydrodesoxymorphine [6].

DESOXYMORPHINE-C

This compound results from heating 6-chlorodihydromorphide with sodium methoxide and methyl alcohol at 140° C. [6, 8–9] and, together with dihydrodesoxymorphine-D, from the catalytic reduction of dichlorodihydrodesoxymorphine [LX], obtained by the prolonged action of concentrated hydrochloric acid on morphine at 50° C. [48–51, 52]. It gives desoxycodeine-C [IX] on methylation [6]. Catalytic reduction of the base in glacial acetic acid over platinum oxide affords dihydrodesoxymorphine-D and tetrahydrodesoxymorphine [47], but only the latter is formed on hydrogenation of an aqueous solution of the hydrochloride [6].

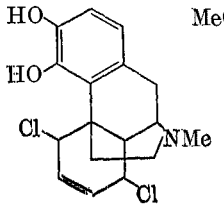
DESOXYMORPHINE-D

Desoxymorphine-D can be prepared by the demethylation of desoxycodeine-D [XXV] with pyridine hydrochloride at 215° C. [17], by the action of phosphorus tribromide on dihydroallo-ψ-codeine [LXI] [13, 53], and as a by-product in the preparation of desoxycodeine-D from 8-chlorodihydrocodide [13]. On methylation it gives desoxycodeine-D [13, 17].

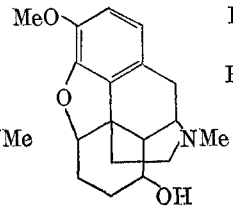
DESOXYMORPHINE-E

This results from the demethylation of desoxycodeine-E [XXX] [62].

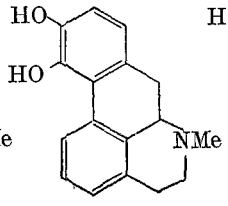
A desoxymorphine was stated by Schryver and Lees [54] to result from the reduction of α-chloromorphide with tin and hot concentrated hydrochloric acid, but a repetition of this reaction afforded only small amounts of material of different specific rotation that does not correspond to any of the known desoxymorphines, and indeed it is doubtful whether the morphine structure would survive such treatment, as even in the $\alpha \rightarrow \beta$-chloromorphide conversion considerable amounts of apomorphine [LXII] are formed. Wright also reported the production of a desoxymorphine on heating bromocodide with hydrobromic acid [55–58], but nothing further is known about this.



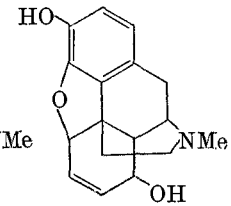
[LX]



[LXI]



[LXII]



[LXIII]

DIHYDRODESOXYMORPHINE-D

Dihydrodesoxymorphine-D can be prepared by the hydrogenation of the halogenomorphides in neutral or weakly acid solution [47, 59], of desoxymorphine-C in glacial acetic acid [47], and, with desoxymorphine-C, by reduction of the dichloro-compound [LX] [48–52]. The yield from bromomorphide is low, the main product being an undistillable oil, probably bis-6:6′-dihydrodesoxymorphine-D [47]. Dihydrodesoxymorphine-D can be methylated to dihydrodesoxycodeine-D and the reverse change can also be accomplished [47]. Mild oxidation of dihydrodesoxymorphine-D in alkaline solution affords tetrahydrodidesoxypseudomorphine [60].

TETRAHYDRODESOXYMORPHINE

This is formed by the demethylation of tetrahydrodesoxycodeine [6] and by the hydrogenation of desoxymorphine-C [47], α-chloromorphide [47], and β-isomorphine [LXIII] [61].

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Desoxycodeine-A·½H_2O	121–122	50% MeOH	leaflets	+118·1	22	96% EtOH	3
Desoxycodeine-A (*anhyd.*)	157	..	..	+119·0	24	EtOH	6
— hydrochloride	{255–257	..	..	+93·6	..	..	6
	{*c.* 270	..	..	+87·0	15	H_2O	21
— hydriodide	268–269	..	..	+71·4	..	..	6
— benzoate	*c.* 188	..	..	+106·0	15	EtOH	1
— salicylate	220·5–221	..	..	+104·4	..	..	6
— methiodide	219–221	..	..	+95·7	..	..	6
Acetyldesoxycodeine-A	..	..	oil	..	..	..	1
— hydriodide	230	..	..	..	..	..	1
— methiodide	270	..	..	..	..	..	1
Desoxycodeine-A methyl ether methiodide	251–252	..	..	+108·0	15	EtOH	1
Desoxycodeine-A + Br_2→	189–189·5	..	..	+10·2	25	benzene	5
Desoxycodeine-A + HBr→	149–151	..	..	−3·8	25	EtOH	5
Desoxycodeine-A methine	..	..	..	..	..	..	1
Desoxycodeine-A methyl ether methine	..	..	oil	..	..	..	1
Desoxycodeine-B: identical with desoxycodeine-A.							
Desoxycodeine-C	105–106	EtOAc	..	−199·4	20	95% EtOH	3
— hydrochloride·H_2O	114	EtOH	..	−132·7	20·5	H_2O	3
— hydriodide·H_2O	160–165	H_2O	prisms	−131·6	19	95% EtOH	3
— salicylate	195–196	EtOH	..	−112·2	24	EtOH	11
— methiodide	236–240	MeOH	..	..	..	..	3
Racemate with antipode from sinomenine series	85	..	..	..	..	..	15
— methiodide	218	..	..	..	..	..	15
1-bromodesoxycodeine-C	131–133·5	MeOH	..	−288·5	26	EtOH	5
Cyanonordesoxycodeine-C	159·5–161	EtOH	..	..	..	..	13
6-methyldesoxycodeine-C	172–174	EtOH	..	−242·0	20	EtOH	16
— hydrochloride	262–263	Et_2O + EtOH	..	−192·0	20	EtOH	16
— methiodide	280–281	..	..	−149·0	20	EtOH	16
1-chloro-6-methyldesoxycodeine-C	171–172	EtOH	..	−226·0	20	EtOH	16
Desoxycodeine-D	61·5–62	subl.	..	−21·1	25	EtOH	17
— hydrochloride	{234–235	butanone	..	−12·1	20	H_2O	13
	{238–239	..	..	+5·9	25	H_2O	17
— acid oxalate	225–226	MeOH	..	−10·9	25	H_2O	17
— acid tartrate	206–206	H_2O	..	0	25	H_2O	13

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Desoxycodeine-D methiodide	233–234	MeOH	..	+16·1	25	MeOH	17
Desoxycodeine-D methine (desoxy-β-codeimethine)	75–76	H_2O+EtOH	plates	+314·0	25	dioxane	13, 17
— perchlorate	230–231	EtOH	..	+182·5	25	acetone	17
— picrate	173–175d.	EtOH	..	+91·5	25	acetone	17
— methiodide	314d.	MeOH	..	+157·0	25	MeOH	17
1-bromodesoxycodeine-D	125–126	60% EtOH	plates	..	..	..	13
Desoxycodeine-E	82–83	H_2O+EtOH	..	−68·0	25	MeOH	17
	84	H_2O+EtOH	..	−58·9	20	EtOH	18
— hydrochloride	239–240	butanone	..	−40·3	25	EtOH	17
— perchlorate	250d.	H_2O+EtOH	..	−41·3	25	acetone	17
— acid tartrate	123–125	H_2O	..	−41·1	25	H_2O	17
— picrate	196–197	..	..	..	..	..	18
— methiodide	257–258d.	MeOH	..	−25·9	25	MeOH	17
Cyanonordesoxycodeine-E	149–150	H_2O+EtOH	..	−133·8	25	EtOH	17
Desoxycodeine-E methine (desoxy-α-codeimethine)	..	..	oil	+130·0	25	dioxane	17
— perchlorate	180–181	EtOH	..	+86·3	25	acetone	17
— picrate	163–164	EtOH	..	+54·7	25	acetone	17
'Dihydrodesoxycodeine-A'	c. 157	EtOAc	..	−18·7	28	..	10
	(is a mixture of dihydrodesoxycodeines-B and -C)						
— hydrochloride·EtOH	158–160	EtOH	..	−41·4	22	H_2O	21
— hydriodide	242–243	..	prisms	..	..	..	22
— benzoate	180	..	..	..	..	..	1
— methiodide	250–251d.	..	..	−7·5	20	EtOH	21
Dihydrodesoxycodeine-B	170–173	..	..	..	..	..	10
	128–131	H_2O+EtOH	..	−106·9	20	90% EtOH	21
— hydrochloride	154–156d.	EtOH	..	−76·4	21	H_2O	21
— hydriodide	255–256	H_2O	..	−79·3	19	96% EtOH	21
— methiodide	c. 175	H_2O	needles	..	..	..	21
Dihydrodesoxycodeine-B methyl ether	..	..	oil	..	..	..	27
— fumarate	233–235	..	..	..	..	..	27
β-dihydrodesoxycodeine-B methyl ether	..	..	oil	..	..	..	27
— picrate	210–212	..	..	..	..	..	27
Dihydrodesoxycodeine-B methine	144–145·5	acetone	..	−9·5	20	$CHCl_3$	10
				−7·4	20	$CHCl_3$	
— hydrochloride	..	..	cryst.	..	..	..	10
Dihydrodesoxycodeine-C	109–111	H_2O+EtOH	..	+5·6	24	EtOH	10, 21
— hydrochloride	241–243	EtOH	..	+11·2	27	H_2O	10, 21
— hydriodide	242–243	H_2O	prisms	+8·2	24	H_2O	10, 21
— methiodide	245–246	..	needles	+15·3	29	H_2O	10, 21
Ethylthiodihydrodesoxycodeine-C ?	..	..	oil	−59·8	24	EtOH	12
Dihydrodesoxycodeine-C methine	175–176	..	..	−13·8	25	$CHCl_3$	10
Dihydrodesoxycodeine-C dihydromethine ?	156–157	petrol	plates	..	..	..	28
Dihydrodesoxycodeine-C (or -B)-dihydromethine (desoxytetrahydro-α-codeimethine)	163–164	φBr	..	..	..	..	22
— perchlorate	159	..	..	..	..	..	22
— methiodide	248	..	..	..	..	..	22
— methyl ether hydriodide	170–171	..	..	..	..	..	22
— methyl ether perchlorate	206–208	..	..	..	..	..	22
— methyl ether methiodide	210–212	..	..	..	..	..	22
Dihydrodesoxycodeine-D	106–107	Et_2O	prisms	−82·5	20	96% EtOH	21
— hydriodide	250–251d.	H_2O	needles	..	..	..	21
— acid tartrate	154–154·5	..	..	−29·9	18	H_2O	6
	123–125	H_2O	..	−30·6	30	H_2O	21
— picrate	207	..	..	..	..	..	7
— methiodide	250	MeOH	prisms	..	..	..	7, 21
1-bromodihydrodesoxycodeine-D	158–157	MeOH	..	−37·0	20	MeOH	5

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
1:6:7-tribromodihydrodesoxy-codeine-D	184·5–185·5	..	..	−156·7	26	EtOH	5
Dihydrodesoxycodeine-D methine	86	Et_2O	rhombs	..	..	..	7
— hydrochloride·H_2O	222	..	..	..	..	..	7
— picrate	154	..	..	..	..	..	7
— methiodide	238	..	..	..	..	..	7
Dihydrodesoxycodeine-D dihydro-methine (desoxytetrahydro-α-codei-methine)	156	EtOH	..	..	..	..	26
— methiodide	235	..	..	..	..	..	26
— isomeric base	..	..	oil	..	..	..	26
— isomer hydriodide	208–210	..	..	..	..	..	26
— isomer methiodide	D.272–273	..	..	..	..	..	26
Bis-6:6′-dihydrodesoxycodeine-D	..	..	amorph.	−113·0	26	EtOH	29
— monomethiodide	246–250d.	..	needles	−8·6	23	EtOH	29
— dimethiodide	230–250d.	..	amorph.	−71·5	28	φ·CH_2OH	29
Dihydrodesoxycodeine-E	139–140	..	..	+58·1	13	dil. HOAc	21, 32
— salicylate	198	..	..	..	..	..	32
— methiodide	199	..	..	..	..	..	32
Dihydrodesoxycodeine-E methyl ether methiodide	245	..	..	..	..	..	32
Dihydrodesoxycodeine-E methine	..	..	..	..	..	..	32
— hydriodide	220	..	..	..	..	..	32
— methiodide	103	..	..	..	..	..	32
Tetrahydrodesoxycodeine (*a*)	135*	..	..	..	..	..	41
	123–124	petrol	..	−72·3	18	benzene	23
(*b*)	157–158	..	..	−70·3	21	benzene	23
				−33·6	24	95% EtOH	23
				−32·0	20	95% EtOH	23
				−66·7	19	benzene	23
Tetrahydrodesoxycodeine·½H_2O	..	..	..				
— hydrochloride·EtOH	260–262	EtOH+Et_2O	prisms	−23·5	20	H_2O	4, 23
— hydriodide·H_2O	245–246d.	H_2O	needles	−24·3	19	95% EtOH	4, 22–23
— methiodide	235†	..	..	..	..	..	41
	260–263	H_2O	..	−33·3	26	H_2O	4, 23
Bis-1:1′-tetrahydrodesoxycodeine	230–238	(see also Chap. XXVI)			..	..	46
Tetrahydrodesoxycodeine methyl ether	..	..	oil	..	..	..	23
— hydriodide	164–166†	..	..	+20·5†	14	H_2O	40
	217–218	H_2O	needles	−21·8	21	EtOH	23
— methochloride	255–256	acetone	..	−9·5	22	H_2O	23
— methiodide	257–258†	Et_2O+	..	..	..	..	40
	256–257	EtOH	..	−3·5	21	EtOH	4, 23
1-bromotetrahydrodesoxycodeine	135	EtOH	..	..	..	..	4
	156–157·5	MeOH	..	−28·2	26	EtOH	5
1-bromotetrahydrodesoxy-codeine·H_2O	119–128	acetone	..	..	..	..	5
Tetrahydrodesoxycodeine methine	152–154	H_2O+EtOH	flakes	+66·2	24	MeOH	23
Tetrahydrodesoxycodeine methyl ether methine	..	..	oil	..	..	..	4
— hydriodide	175–185	..	..	..	..	..	4
— methiodide	185–188	..	..	..	..	..	4
Tetrahydrodesoxycodeine dihydro-methine	156–157	..	..	..	..	..	10, 22
	148–150	H_2O+EtOH	needles	−14·5	26	96% EtOH	23
— hydrochloride	251–252	H_2O	needles	−82·1	26	96% EtOH	23
— hydriodide	219–220	H_2O	plates	..	..	..	22
— perchlorate	150–153	H_2O	rods	..	..	..	22
Tetrahydrodesoxycodeine methyl ether dihydromethine	..	..	oil	..	..	..	22
— hydriodide	174–176	H_2O	..	..	..	..	22
— perchlorate	104–105	H_2O	..	..	..	..	22
— methiodide	..	..	oil	..	..	..	22

* Racemate with desmethoxydesoxydihydroisocodeine. † Racemate. ‡ Antipode.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Bromotetrahydrodesoxycodeine from tribromodihydrodesoxycodeine-D	116–117·5	..	..	−3·3	25	EtOH	5
Isomer of tetrahydrodesoxycodeine from above bromocompound	88–89	subl.	needles	..	..	..	5
6-methyltetrahydrodesoxycodeine	157·5–158·5	acetone	..	−4·5	20	EtOH	16
— hydrochloride	254–255	Et_2O+EtOH	..	+8·0	20	EtOH	16
— acid oxalate	171–172	Et_2O+EtOH	..	+4·8	20	EtOH	16
— methiodide	265–266	Et_2O+MeOH	..	+6·4	20	EtOH	16
Other alkyldi- and tetrahydrodesoxycodeines: *see* Chap. XIX.							
Desoxymorphine-A	257–258	..	..	..	..	..	47
— sulphate	145–151	..	..	+61·6	32	H_2O	6
— benzoate	240–245	..	..	+81·9	31	95% EtOH	6
— salicylate	248–250	EtOH	..	+93·6	25	MeOH	6
Desoxymorphine-C	189–190	EtOAc	..	−155·7	31	95% EtOH	6
— hydrochloride·1½H_2O	uncertain	..	..	−147·0	30	H_2O	6
— hydriodide	292–294	H_2O	..	−109·6	32	H_2O	6
— methiodide	260–264	85% EtOH	..	−98·2	32	MeOH	6
Desoxymorphine-D	260–261	EtOH	..	−15·3	25	MeOH	17
	254–255	EtOH	..	..	..	..	13
— perchlorate	261–262	EtOH	..	−23·5	25	H_2O	17
Desoxymorphine-E	143–144	benzene	..	−67·2	25	EtOH	62
Dihydrodesoxymorphine-D	188–189	EtOAc	..	−76·8	28	MeOH	47
Dihydrodesoxymorphine-D·½H_2O	162–164	..	..	−78·6	28	EtOAc	47
— hydrochloride	..	95% EtOH	..	−68·6	27	H_2O	47
— hydriodide	..	H_2O	..	−48·4	25	H_2O	47
— sulphate	..	H_2O	..	−51·9	29	H_2O	47
— acid oxalate	..	50% EtOH	..	−57·9	28	H_2O	47
— salicylate	..	95% EtOH	..	−42·8	28	EtOH	47
— methiodide	..	EtOH	..	−46·6	27	H_2O	47
Bis-6:6′-dihydrodesoxymorphine-D ?	..	..	oil	..	..	..	47
Dichlorodihydrodesoxymorphine: *see* Chap. VIII							
Tetrahydrodesoxymorphine	237–239	..	..	..	..	..	6
	172–184	EtOAc	..	..	..	..	47
— hydriodide	268–271	H_2O	..	−32·7	24	H_2O	6
— methiodide	269–271	95% EtOH	..	−31·4	31	MeOH	6

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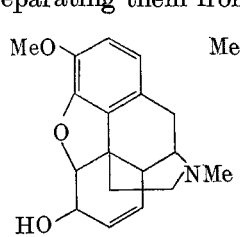
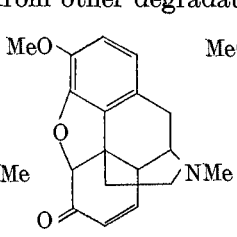
X

CODEINONE, ψ-CODEINONE, AND THEIR DERIVATIVES

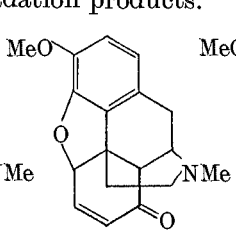
THE secondary alcoholic group in codeine [I] can be oxidized by potassium permanganate in acetone [1], and by chromic acid in sulphuric [1] or acetic [2–3] acid to carbonyl, giving the ketone codeinone [II], also obtained by the oxidation of codeine methyl ether [4]. The same ketone is produced by the oxidation of isocodeine [5], showing that the latter differs from codeine only in the spatial arrangement of the alcoholic group. ψ-Codeinone [III] results from the oxidation of ψ-codeine [5–7] and allo-ψ-codeine [5–6], which are thus also an epimeric pair of alcohols [IV]. The yields of ketone are poor, due to side reactions, the instability of the products in acid solution, and the difficulty of separating them from other degradation products.



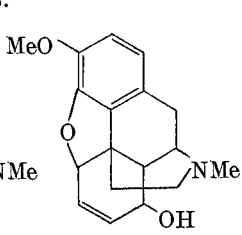
[I]



[II]



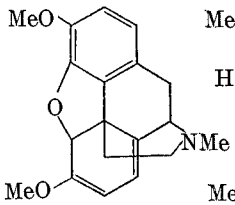
[III]

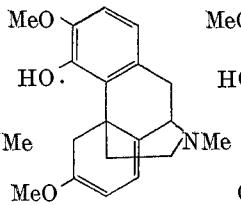


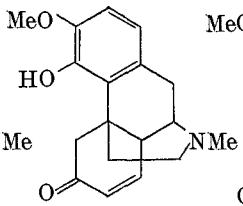
[IV]

CODEINONE

Codeinone [II] is a non-phenolic ketonic base giving an oxime [1, 5, 8] and semicarbazone [6]. In addition to the methods of preparation given above, it has also been isolated in very poor yield [*c.* 7 per cent.] as its oxime from the products of hydrolysis of thebaine [V] in acid solution [8–9], and the latter base can be regarded as an enol ether of codeinone. Thebaine is unstable in acid solution, in which it undergoes with great ease various types of rearrangement involving migration of the side-chain from position 13 (see Chap. XI), so that codeinone would not be expected to be the main product of hydrolysis. Moreover, the main product of hydrolysis of β-dihydrothebaine [VI] (formed by the lithium aluminium hydride reduction of thebaine [10–11]) is β-thebainone [VII] [10], in which the configuration at the asymmetric carbon atom C-14 is opposite to that generally found in morphine derivatives [12], and the C-14 epimer of codeinone may well be produced in greater quantities in the hydrolysis of thebaine than is codeinone, although it has not yet been prepared.


[V]


[VI]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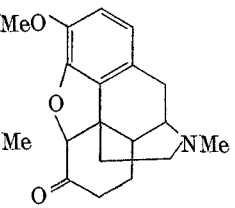
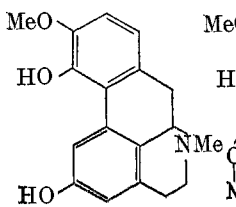
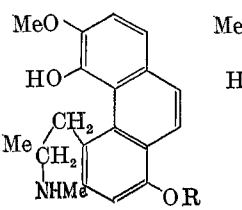

[VIII]

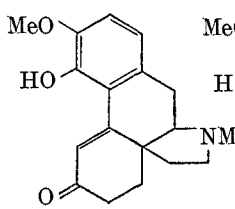
Codeinone contains a double bond and is readily reduced to dihydrocodeinone [VIII] [3, 13] (see below); it shows the properties of an $\alpha:\beta$-unsaturated ketone, e.g. attempts to prepare its oxime in concentrated acid solution, or from a solution of thebaine in concentrated acid, result in an oxime containing an additional molecule of hydroxylamine by addition of the latter to the double bond [9].

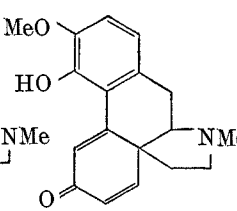
Rearrangement in Acid

Like thebaine [V], which is in the same state of oxidation, codeinone [II] undergoes rearrangement in acid solution, though it is more stable than the former, being recovered in 80 per cent. yield after standing for fifteen minutes in concentrated hydrochloric acid at 15–20° C. [9]. It is converted to β-methylaminoethanol and 3-methoxy-4:6-diacetoxyphenanthrene (identified by conversion to 3:4:6-trimethoxyphenanthrene [14] identical with an authentic specimen [15]) on heating with acetic anhydride [14]; to morphothebaine [IX] by concentrated hydrochloric acid at 100° C. [14]; to thebenine [X, R = H] by hot dilute aqueous hydrochloric acid or methebenine [X, R = Me], by hot dilute methanolic hydrochloric acid [14]; and to metathebainone [XI] on reduction with stannous chloride and hot concentrated hydrochloric acid [16]. With the exception of the product of acetic anhydride degradation these rearrangement products are the same as those obtained from thebaine under the same conditions [17–20] and the reactions are in both cases believed to involve the primary intermediate [XII] which has not yet been isolated [21]. The mechanisms of the transformations are discussed in Chapters XXIII and XXV.


[IX]


[X]


[XI]

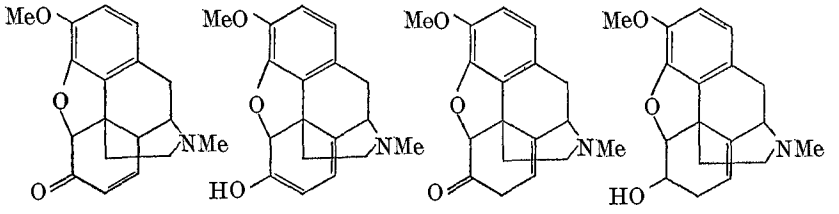

[XII]

On long standing in concentrated hydrochloric acid codeinone adds one molecule of water to give a phenolic base $C_{18}H_{21}O_4N$, about which nothing is known beyond the facts that it appears to yield an oxime and can be catalytically hydrogenated to a dihydro-derivative [3].

The production of a 3:4:6-trihydroxyphenanthrene derivative by the acetolysis of codeinone clearly indicates the position of the three oxygen atoms in this ketone [5]. A similar degradation takes place when codeinone methiodide is heated with alcohol at 160° C., 3-methoxy-4:6-dihydroxyphenanthrene and β-dimethylaminoethyl ethyl ether being the products [22].

Structure

Codeinone was at one time thought to contain a reactive methylene group, the original Knorr formula [XIV] being based on the fact that ψ-codeinone condenses with benzaldehyde and gives an *iso*nitroso-derivative (see below) [23]; codeinone does not give similar compounds [24] but does condense with diazonium salts to give azo-derivatives [23], possibly containing the system Ar—N=N—CH—CO, as more intensely coloured substances (Ar—N=N—C=C—O⁻Na⁺ ?) result from treating these with alkali [24]. It has been suggested that in acid or alkaline solution codeinone [II] is in equilibrium with [XIV] through the intermediate enol form [XIII] [25–26]; in this connexion it is of interest to note that attempts to prepare [XIV] by the oxidation of neopine [XV] have so far been unsuccessful [27].



[II] [XIII] [XIV] [XV]

Reduction

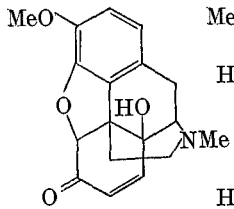
(*a*) Catalytic hydrogenation of codeinone using palladium [13] or Raney nickel [3] as catalyst affords dihydrocodeinone [VIII], identical with the product prepared in other ways (see below).

(*b*) Electrolytic reduction in sulphuric acid with a lead cathode, reduction with sodium hydrosulphite or hydrazine [28], and reduction of the oxime [1], have all been reported to give codeine, but the sodium hydrosulphite and hydrazine reductions have been reinvestigated by Findlay and Small [3], who obtained only complex transformation products and suggest that Hill's starting material [28] (much more

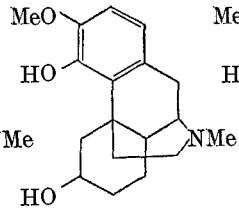
soluble in alcohol than is codeinone) was in reality codeine itself. No details of the reduction of the oxime have been published and it is of interest to note that reduction of the oximes of the $\alpha:\beta$-unsaturated ketones 14-hydroxycodeinone [XVI], benzylidene acetone, and dibenzylidene acetone results in formation of the saturated ketones [29], so that reduction of codeinone oxime would be expected to give dihydrocodeinone [VIII], isomeric with codeine.

(*c*) Codeine has been isolated from the products of reduction of codeinone with stannous chloride and concentrated hydrochloric acid [9].

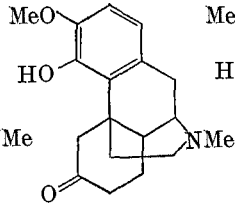
(*d*) Catalytic reduction with a platinum oxide catalyst results in reduction of the double bond, carbonyl group and cyclic ether, the product being the high-melting dihydrothebainol-B [XVII], obtained also by the catalytic hydrogenation of dihydrothebainone [XVIII] [30].



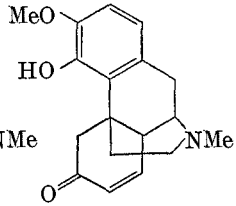
[XVI]



[XVII]



[XVIII]



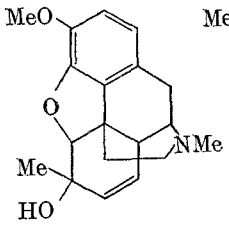
[XIX]

(*e*) As already stated, stannous chloride and hot concentrated hydrochloric acid convert codeinone to metathebainone [XI] with migration of the carbon end of the ethanamine side-chain from C-13 to C-14 [16], but variation of the conditions of the reduction allow of the isolation of the true thebainone-A [XIX] in which migration has not occurred, the nature of the product being revealed by its reduction to dihydrothebainone [XVIII] [9], which can be converted to dihydrocodeinone [VIII] (see below). If the reduction is carried out at 70° C. the product consists of 3 per cent. metathebainone, 25 per cent. thebainone-A, and 49 per cent. codeine [9].

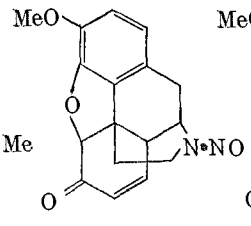
Miscellaneous Reactions

(i) The carbonyl group of codeinone is remarkably unreactive towards Grignard reagents, with which no reaction occurs at temperatures below 170° C., at which temperature decomposition begins [31]. In marked contrast to this, however, treatment with methyl lithium gives an almost quantitative yield of one isomer of 6-methylcodeine [XX] [32].

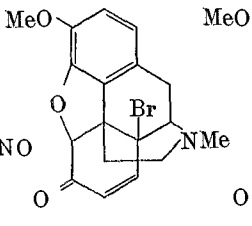
(ii) N-nitrosonorcodeinone [XXI] is produced when codeinone is treated with nitrous acid, the N·Me group being replaced by N·NO [33–34]; the reaction is analogous to the conversion of codeine to N-nitrosonorcodeine [34].



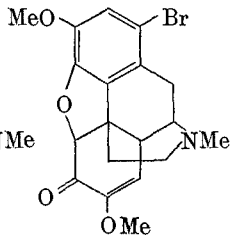
[XX]



[XXI]



[XXII]



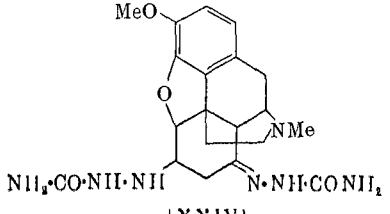
[XXIII]

(iii) Bromination of codeinone in glacial acetic acid affords 1-bromocodeinone [28], an isomer of which, 14-bromocodeinone [XXII], results from the bromination of thebaine [v] in glacial acetic acid [35–36]. [XXII] yields codeinone on reduction with iron and sulphuric acid [35]; it is discussed together with 14-hydroxycodeinone [XVI] (formed by the action of 30 per cent. hydrogen peroxide on thebaine in hot glacial acetic acid [37–38]) in Chapter XVIII.

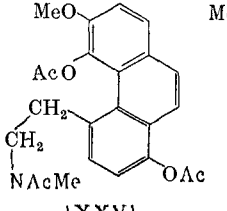
(iv) The antipode of 1-bromo-7-methoxycodeinone [XXIII], which unlike codeinone can be degraded to methine bases, can be prepared in the sinomenine series. It is discussed in detail as 1-bromosinomeneine in Chapter XXVI.

ψ-CODEINONE

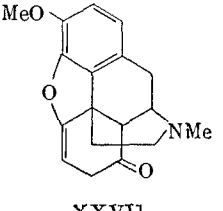
ψ-codeinone [III] results from the oxidation of ψ-codeine [5–7] and allo-ψ-codeine [5–6]. It is ketonic, giving an oxime [6] and semicarbazone [6–7], and the ketone is α:β-unsaturated, as is shown by the formation of a semicarbazino-semicarbazone [XXIV] by the addition of semicarbazide to the 6:7-double bond on standing for several hours with excess of the reagent [7]. It is substantially more stable than codeinone, but is degraded by heating with acetic anhydride to 3-methoxy-4:8-diacetoxyphenanthrene (identified by conversion to 3:4:8-trimethoxyphenanthrene [5], identical with an authentic specimen [39]) and β-methylaminoethanol, though the main product of this reaction is triacetylthebenine [XXV] [6]. With concentrated hydrochloric acid ψ-codeinone is converted to phenolic substances, though it is stable in dilute acid [6]. The methiodide too is more stable than that of codeinone, and is converted to a phenolic base $C_{19}H_{21}O_3N$ (decomp. 235° C.)



[XXIV]



[XXV]



XXVI]

by alkalis, but on heating with alcohol at 160° C. it is degraded to 3-methoxy-4:8-dihydroxyphenanthrene [6, 23].

STRUCTURE

ψ-Codeine was originally thought to contain a reactive methylene group as it condenses with benzaldehyde in the presence of sodium ethoxide [7, 23], forms an *iso*nitroso-derivative, and condenses with diazonium salts [23]. Presumably these reactions arise from an isomeric form [XXVI], production of which via the enol form would be favoured in alkaline solution [25]. Lutz and Small have shown that codeine will condense with benzaldehyde under the same conditions, and doubt whether any reliance can be placed on this reaction as indicating the presence of a reactive methylene group in this series [7].

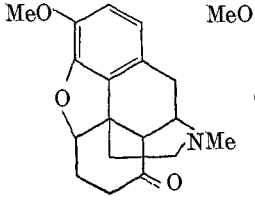
REDUCTION

As ψ-codeinone contains a 6:7-double bond and is in effect an allylic ether it can, like ψ-codeine, give both phenolic and non-phenolic products on reduction.

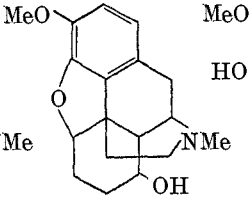
(*a*) As with ψ-codeine reduction of the hydrochloride in glacial acetic acid over platinum oxide favours mainly non-phenolic reduction, the product being dihydro-ψ-codeinone [XXVII], which is identified by its reduction to dihydro-ψ-codeine-A [XXVIII] by sodium and alcohol, no dihydroallo-ψ-codeine being formed [7].

(*b*) Hydrogenation in neutral or weakly acid solution with a palladium catalyst affords tetrahydro-ψ-codeinone [XXIX] [7, 28] which is further reduced by sodium and alcohol to tetrahydro-ψ-codeine [XXX], the latter being obtained directly from ψ-codeinone by sodium and alcohol reduction. In no case do derivatives of allo-ψ-codeine result from these reductions [7].

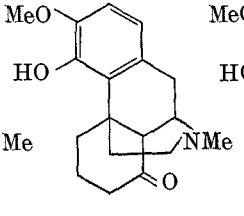
Speyer and Rosenfeld on reduction of 14-bromocodeinone [XXII] with sodium hydrosulphite obtained an amorphous halogen-free base that was converted by hot alkali to a crystalline, ketonic, tertiary base $C_{18}H_{21}O_3N$ that they suggested was dihydro-ψ-codeinone [40], but its properties do not agree with those of the latter [7] and its nature remains obscure.



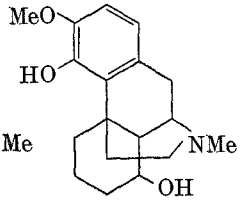
[XXVII]



[XXVIII]



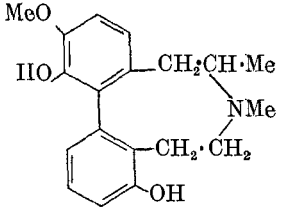
[XXIX]



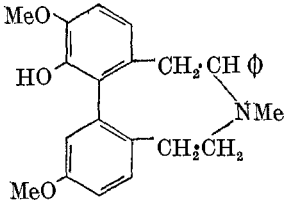
[XXX]

Reaction with Grignard Reagents

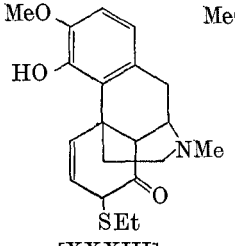
Unlike codeinone ψ-codeinone readily reacts with methylmagnesium iodide, giving methyldihydro-ψ-codeinone, which is indifferent to hydrogenation and shows none of the properties of a ketone [7]. It has the structure [XXXI], analogous to that of phenyldihydrothebaine [XXXII] [41–42]. The mechanism of the production of these two bases is discussed in Chapter XX.



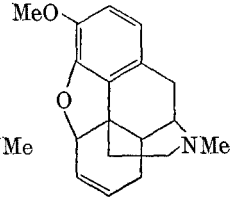
[XXXI]



[XXXII]



[XXXIII]



[XXXIV]

Ethyl mercaptan will add to the double bond of α:β-unsaturated ketones such as thebainone [XIX] [43], and it will also add to ψ-codeinone, but here the allylic ether is involved and the product is phenolic, probably having the constitution [XXXIII] [43–44]. Desoxycodeine-C [XXXIV] will also add mercaptan to give a phenol [43].

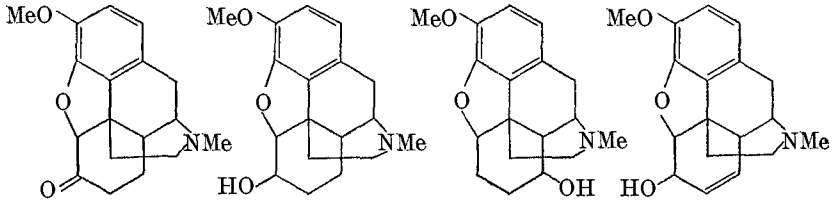
DIHYDROCODEINONE, DIHYDRO-ψ-CODEINONE, AND THEIR DERIVATIVES

Preparation

Dihydrocodeinone [VIII], obtained by the catalytic reduction of codeinone [3, 13], is best prepared in other ways.

(*a*) Contrary to a statement by Merck and Co. [45] it cannot be prepared by the oxidation of dihydrocodeine [XXXV] with chromic acid or potassium permanganate [13, 46]. It can, however, be obtained from dihydrocodeine in 83 per cent. yield by Oppenauer oxidation with potassium tertiary butoxide and benzophenone in boiling benzene, and the morphine analogue results in the same way from dihydromorphine

in 71 per cent. yield. In contrast to this only 3 per cent. of [VIII] can be obtained by Oppenauer oxidation of dihydroisocodeine, and a similar difference between the two epimers exists in the ψ-series, dihydroallo-ψ-codeine-A [XXXVI] giving 40 per cent. dihydro-ψ-codeinone, whilst dihydro-ψ-codeine-A is recovered unchanged. This susceptibility to the Oppenauer oxidation is parallel to the physiological activity of the alkaloids in which codeine can be paired with allo-ψ-codeine and ψ-codeine with isocodeine [47].

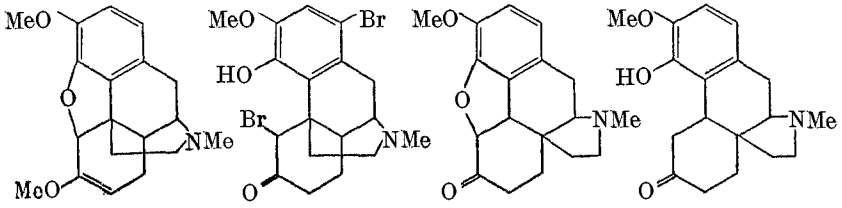


(*b*) Dihydrocodeinone and dihydromorphinone can be prepared by the catalytic rearrangement of codeine [I] and morphine respectively on heating solutions of the base in alcohol, with [48–52] or without [53] acid, with [48–50] or without [51–53] hydrogen, in the presence of noble metal catalysts. The yields reported by Knoll and Co. for this method are up to 95 per cent. [52], but Rapoport claims that the maximum is about 50 per cent. [47]. As a by-product in this rearrangement phenolic bases were noted and these may be made the principal products by modifying the conditions. In this way thebainone-A [XIX] can be prepared from codeine, and its analogue, 0-desmethylthebainone-A, from morphine in 60 per cent. yield [54] (see Chap. XV).

Other methods by which dihydrocodeinone can be obtained are of little preparative importance; they are:

(*c*) Hydrolysis of dihydrothebaine [XXXVII], which is the enol ether of dihydrocodeinone [55], a reaction that occurs when thebaine is hydrogenated in 2–2·5 N. hydrochloric acid, when the products are dihydrocodeinone and dihydrothebainone [XVIII] [56–58].

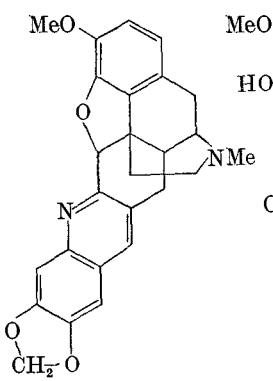
(*d*) Catalytic reduction of 14-bromocodeinone [XXII] [59].



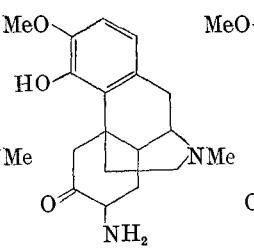
(*e*) From dihydrothebainone [XVIII] by bromination and treatment of the resulting dibromo-compound [XXXVIII] with alkali, causing closure of the 4:5 ether bridge with loss of hydrogen bromide, followed by reductive elimination of the remaining bromine [60–61]. In this way the antipode of dihydrothebainone, from the sinomenine series, can be converted to the antipode of dihydrocodeinone [62]; 14-hydroxycodeinone can be prepared from 14-hydroxydihydrothebainone (see Chap. XVIII); dihydrometacodeinone [XXXIX] from dihydrometathebainone [XL] [60–63], and nuclear alkylated dihydrocodeinones from the nuclear alkylated dihydrothebainones that result from the interaction of Grignard reagents and dihydrothebaine or dihydrocodeinone enol acetate [64–65].

Dihydrocodeinone behaves as a typical methylene ketone giving ketonic derivatives [55], and giving a quinoline derivative, dianhydro-6-aminopiperonaldihydrocodeinone [XLI], on condensation with 6-aminopiperonal. [XLI], like the corresponding derivative of 14-hydroxydihydrocodeinone, but unlike that of metathebainone and other simpler methylenedioxyquinolines, exhibits no fluorescence in concentrated sulphuric acid or other solvents [66].

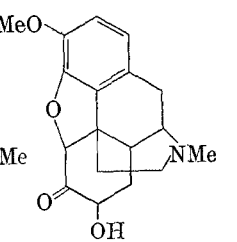
*Iso*nitrosodihydrocodeinone can be catalytically reduced to 7-aminodihydrothebainone [XLII], the benzyl ether of which on diazotization is converted to 7-hydroxydihydrocodeinone [XLIII], thus providing another means of effecting closure of the 4:5-ether bridge in the morphine group [67].



[XLI]



[XLII]

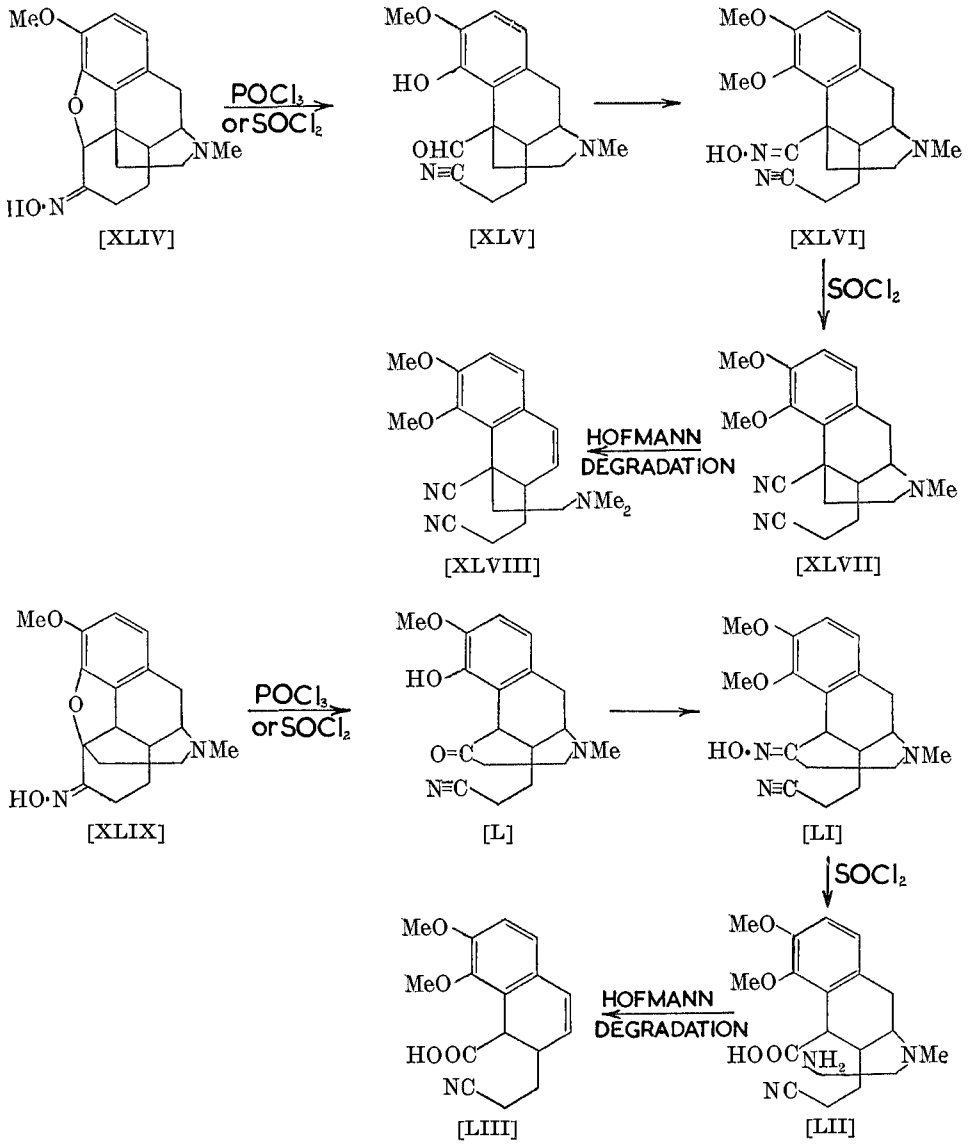


[XLIII]

Beckmann Transformation

The Beckmann transformation of dihydrocodeinone oxime was investigated by Schöpf [68] in an attempt to determine the point of attachment of the carbon end of the ethanamine side-chain. If the point of attachment is C-13 [XLIV] the product of transformation should be an aldehyde [XLV], whereas if it is C-5 [XLIX] the product should be a

ketone [L]. The requisite proof of the nature of the rearrangement product was not directly forthcoming, so recourse was made to the further Beckmann transformation of its methyl ether oxime. This, assuming a C-13 attachment of the side-chain [XLVI], should yield a



cyclic base [XLVII] that should retain the nitrogen on Hofmann degradation, giving [XLVIII]. However, attachment of the side-chain at C-5 would result in production of [LII], degradation of which would involve

loss of the entire side-chain and production of a non-basic substance [LIII].

In fact this sequence of reactions gave a base [XLVIII] as final product, showing that C-13 is the point of attachment of the side-chain in dihydrocodeinone, and therefore in the morphine alkaloids generally [68].

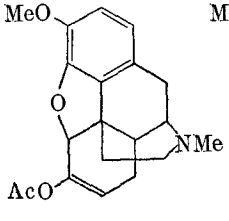
Derivatives of the Enol Form

Dihydrocodeinone [65, 69–70], 1-bromodihydrocodeinone [69], 14-hydroxydihydrocodeinone [38], and the alkyldihydrocodeinones [65] can be converted into esters of the enol form by heating the ketones with acid anhydrides and sodium salts. The enol esters and their salts are stable even in hot solution, but they are hydrolysed to the original ketones by boiling with acids [69]. Dihydrocodeinone enol acetate [LIV] is marketed as the drug acedicon.

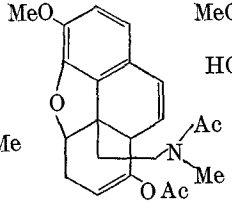
Attempts to prepare a similar enol acetate of dihydro-ψ-codeinone [XXVII] failed owing to the lability of the nitrogen-containing ring, which is opened with the introduction of an acetyl group on the nitrogen and the production of a 9:10 double bond (compare apomorphine and morphothebaine), the product being des-N-acetyldihydro-ψ-codeinone enol acetate [LV] [7]. (The name dihydro-ψ-codeinone acetine enol acetate is here suggested for [LV] by analogy with the methine bases.) Rupture of the ring was first noticed by Tiffeneau [71].

The enol ether of dihydrocodeinone, dihydrothebaine, can be prepared by the action of methyl sulphate and potassium tertiary butoxide on the ketone [72].

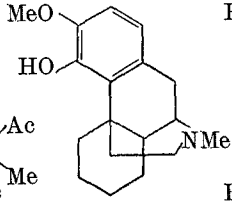
Dihydrothebaine and the above-mentioned enol esters react with Grignard reagents to give phenolic bases that are discussed in Chapter XIX.



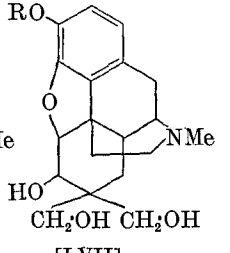
[LIV]



[LV]



[LVI]



[LVII]

Reduction

(*a*) Dihydrocodeinone [63], its antipode [73–74], and the substituted dihydrocodeinones and dihydromorphinones [38, 65] can be catalytically reduced over platinum oxide in pyridine to the corresponding dihydrocodeines and dihydromorphines, with no trace of the epimeric isocodeine types.

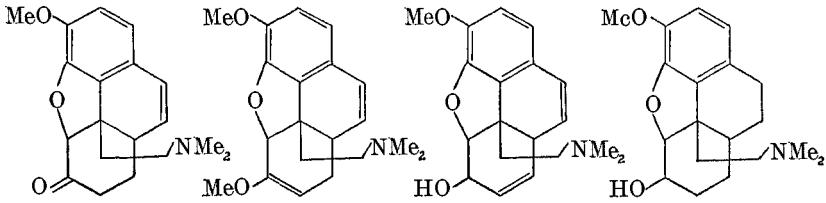
(*b*) Sodium amalgam reduction proceeds with opening of the cyclic ether and reduction of the carbonyl group, giving dihydrothebainol-A, identical with that prepared in the same way from dihydrothebainone [33] and epimeric with that obtained by the catalytic reduction of codeinone [3].

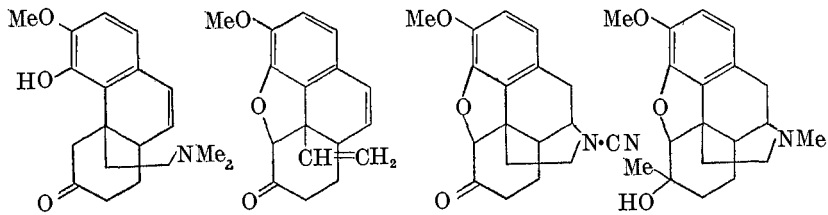
(*c*) Clemmensen reduction converts dihydrocodeinone to tetrahydrodesoxycodeine [LVI], which is almost certainly the product of Clemmensen reduction of dihydrothebainone [33, 75–76] (see Chap. XV).

(*d*) Reduction occurs when dihydrocodeinone and dihydromorphinone are heated with formaldehyde and calcium oxide in methanol, aldol condensation also taking place, the products being 7:7-bis-(hydroxymethyl)dihydrocodeine [LVII, R = Me] and 7:7-bis-(hydroxymethyl)dihydromorphine [LVII, R = H] respectively [77].

HOFMANN DEGRADATION

Hofmann degradation of dihydrocodeinone methiodide affords dihydrocodeinone methine [LVIII] [55] which can also be prepared by the hydrolysis of dihydrothebaine methine [LIX] [78], and by the catalytic rearrangement of α-codeimethine [LX] by boiling with Raney nickel in alcohol [79]. It can be reduced to the dihydromethine, available by the hydrolysis of dihydrothebaine dihydromethine and by the chromic acid oxidation of α-tetrahydrocodeimethine [LXI] [78]. The cyclic ether link of the methine [LVIII] and dihydromethine can be opened by aluminium amalgam reduction in wet ether, giving dihydrothebainone methine [LXII] and dihydromethine respectively [78].





Further degradation of dihydrocodeinone methine methiodide results

in production of trimethylamine but 6-keto-13-vinylhexahydromorphenol methyl ether [LXIII] could not be isolated [55]. The latter can, however, be prepared from dihydrothebaine [80] (see Chap. XIII).

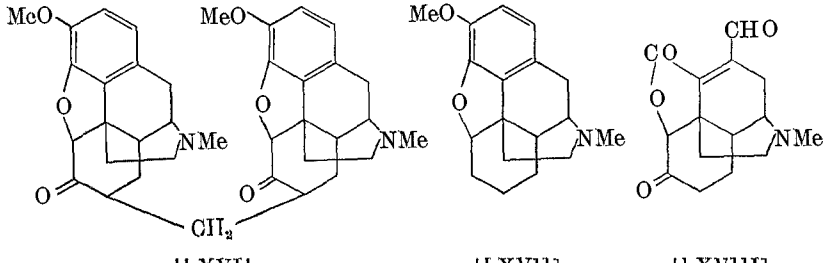
Treatment of dihydrocodeinone with cyanogen bromide leads to cyanonordihydrocodeinone [LXIV], the nitrogen ring being unaffected.

Reaction with Lithium Alkyls

Dihydrocodeinone is only slightly attacked by Grignard reagents, giving traces of a phenolic product [7], but with lithium methyl an excellent yield of 6-methyldihydrocodeine (only one isomer) [LXV] is obtained. In the same way 6-ethyl-, *n*-amyl-, and phenyldihydrocodeines and 6-methyldihydromorphine (from dihydromorphinone) can be prepared; 1-chloro- and 1-bromodihydrocodeinone react without elimination of the halogen [81]. The latter compounds are formed by the halogenation of dihydrocodeinone in acid solution [82].

Mannich Reaction

As dihydrocodeinone contains the system —CO—CH_2— it was expected to undergo the Mannich reaction, and indeed after heating with dimethylamine hydrochloride and formaldehyde no dihydrocodeinone could be recovered, and only 40 per cent. of the product was crystalline. Under the same conditions 1-bromodihydrocodeinone (in which the reactive position of the aromatic nucleus is blocked, thus preventing any nuclear condensation) gave a 90 per cent. yield of crystalline material, also obtained when diethylamine hydrochloride was used in the reaction. The product cannot be sublimed, evidently being dimolecular, and has been allotted the structure [LXVI, R = Br], i.e. 7:7′-methylenebis-(1-bromodihydrocodeinone). It is converted to 7:7′-methylenebis-(dihydrocodeinone) [LXVI, R = H] by catalytic reduction, and this is identical with the crystalline material obtained from dihydrocodeinone. A 5:5′ or 5:7′-linkage is of course also possible, but the 7:7′ union was considered to be most likely as it is the least hindered. No reaction occurs if triethylamine is substituted for the secondary amine, so that formation of a complex between the latter and



[LXVI] [LXVII] [LXVIII]

formaldehyde must be a necessary stage in the reaction. Demethylation of [LXVI, R = H] gave only resins [83].

Proof that the ·CH—CO—CH_2 system is involved in this reaction and not the aromatic nucleus is provided by the recovery of dihydrodesoxycodeine-D [LXVII] unchanged from the Mannich reaction [82].

OZONOLYSIS

Ozonolysis of dihydrocodeinone involves opening of the aromatic nucleus and loss of methyl glyoxylate, the product being 6-ketodihydrocodinal [LXVIII] [84].

DIHYDROISOMORPHINONE

This compound, the morphine analogue of dihydro-ψ-codeinone is obtained in unsatisfactory yield by the demethylation of the latter [7].

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Codeinone	185–186	EtOAc	prisms	−205	15	99% EtOH	1, 3
— hydrochloride·$2H_2O$	179–180	H_2O	..	..	..	..	1, 3
— sulphate	176–177	H_2O	..	..	..	..	3
— picrate	208·5	EtOH	..	..	..	..	1, 3
— picrolonate	228	..	..	..	..	..	1
— methiodide·$2H_2O$	180	H_2O	needles	..	..	..	1, 3
— oxime·EtOH	212	..	..	−499	15	EtOH	1
— oxime hydrochloride	260	..	.	..	..	..	1, 5, 8
— 2:4-dinitrophenylhydrazone	261	..	orange tablets	..	..	..	3
— N-oxide hydriodide·H_2O	110	H_2O	needles	..	..	..	28
Codeinone acid transformation prod.	200	EtOAc	plates	−135	20	EtOH	3
— oxime?	274	..	..	..	..	..	3
— oxime hydrochloride?	262	..	..	.	.	..	3
— dihydro-derivative	207	EtOAc	prisms	−115	20	EtOH	3
1-bromocodeinone	192	..	..	..	..	..	28
N-nitrosonorcodeinone	241–242	EtOH	rods	..	..	..	33
ψ-codeinone	174–175	EtOH	..	−25	15	EtOH	6, 23
— hydrochloride	201–203	EtOH	..	−24	25	H_2O	7
— methiodide	220	..	..	−12	15	H_2O	6
— oxime	..	..	amorph.	..	..	..	6
— semicarbazone	180	..	needles	..	..	..	6
— semicarbazino-semicarbazone	225–227d.	70% EtOH	..	..	..	..	7
Benzal-ψ-codeinone	..	..	oil	..	..	..	23
— methiodide	250	..	..	..	..	..	23
Isonitroso-ψ-codeinone	D. 200	..	..	..	..	..	23
Dihydroethylthio-ψ-codeinone	..	..	amorph.	..	..	..	43–44
Dihydrocodeinone	197–198	EtOH	..	−208·2	26	$CHCl_3$	55, 62, 47
— hydrochloride·$2H_2O$	82	H_2O	..	..	..	..	55
— hydrochloride (anhyd.)	125d.	..	..	..	..	..	13
— hydriodide	219–220	..	..	..	..	..	55
— methiodide	250–251	..	..	..	..	..	55
— bitartrate·$2\frac{1}{2}H_2O$	146–148	..	..	..	..	..	50
— oxime	264	..	..	..	..	..	62
— oxime hydrochloride	63	..	..	..	..	..	13
— phenylhydrazone·EtOH	106–107	EtOH	..	..	..	..	55
— N-oxide	..	..	..	..	..	..	55
Racemate with antipode*	163	..	..	0	26	$CHCl_3$	62
— methiodide	268	..	prisms	..	..	..	62
Cyanonordihydrocodeinone	224–225	..	..	..	..	..	55
Dihydrocodeinone enol acetate	154–155	EtOH	..	..	..	..	65, 69
— hydrochloride	132–135	H_2O	needles	..	..	..	69
Dihydrocodeinone enol *n*-butyrate	..	..	rosin	..	..	..	69
— hydrochloride	225	..	..	..	..	..	69
— methiodide	220	EtOH	plates	..	..	..	69

*From thebaine series.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Dihydrocodeinone enol benzoate	..	..	resin	..	..	..	69
— methiodide	D.240–242	HOAc	..	..	..	..	69
1-chlorodihydrocodeinone	177–178	MeOH	..	..	..	..	60
1-bromodihydrocodeinone	205–207	EtOH	needles	..	..	..	60
— hydrobromide	217–218	..	..	..	..	..	60
1-bromodihydrocodeinone enol acetate	160–162	EtOH	prisms	..	..	..	69
— hydrobromide	128–132	H_2O	..	..	..	..	69
7-isonitrosodihydrocodeinone	D.230–240	..	..	..	..	..	67
7-hydroxydihydrocodeinone	195–197d.	..	..	..	..	..	67
— oxime	178–180	..	..	..	..	..	67
Dihydrocodeinone methine	121–122	EtOH	..	..	..	..	55, 78
perchlorate	268d.	50% EtOH	needles	..	..	..	79
— methiodide	280	..	..	..	..	..	55
— oxime	191–192·5	EtOH	..	..	..	..	55
Dihydrocodeinone dihydromethine	110	Et_2O	..	..	..	..	78
— methiodide	295–298	..	..	..	..	..	78
— oxime	183–185	..	..	..	..	..	78
— oxime hydrochloride	271–272	..	..	..	..	..	78
Dianhydro-6-aminopiperonaldihydrocodeinone	270–271	..	..	..	..	..	66
— methiodide	D. 260	..	..	..	..	..	66
Dihydrocodeinone isoxime (XLV)	196–198	..	..	..	..	..	68
— picrate	207–208	..	prisms	..	..	..	68
Acetyl dihydrocodeinone isoxime picrate	D. 225	..	..	..	..	..	68
Dihydrocodeinone isoxime oxime	218–219	EtOH	..	..	..	..	68
Dihydrocodeinone isoxime methyl ether	..	..	..	..	..	..	68
— hydriodide	249–250	..	..	..	..	..	68
— picrate	221d.	acetone	prisms	..	..	..	68
Di-nitrile [XLVII] methiodide	205–207	MeOH	needles	..	..	..	68
Di-nitrile methine [XLVIII]	..	..	oil	..	..	..	68
— perchlorate	203–204	H_2O	needles	..	..	..	68
Di-nitrile dihydromethine	..	..	oil	..	..	..	68
— perchlorate	197–198	H_2O	needles	..	..	..	68
Dihydromorphinone	266–267	EtOH	..	−194	25	dioxane	47
— oxime	234–235	..	..	..	..	..	47, 85
7:7′-methylenebis-dihydrocodeinone	174–175 247–248	acetone acetone	.. ..	−318	20	dioxane	83
— dihydrochloride·$5H_2O$	278–280	..	..	−252	20	EtOH	83
— dimethiodide·$2H_2O$	270–272	..	..	−177	20	75% EtOH	83
— monosemicarbazone	218–220	..	..	−338	20	EtOH	83
7:7′-methylenebis-1-bromodihydrocodeinone	274–275	acetone	..	−287	20	dioxane	83
— dihydrochloride·$3H_2O$	271–273	..	..	−243	20	EtOH	83
6-ketodihydrocodinal semicarbazone	D. 280	..	spears	..	..	..	84
Dihydro-ψ-codeinone	113	EtOAc + ligroin	plates or prisms	+37	25	EtOH	7, 47
— hydrochloride	172–173	acetone + EtOH	..	+13	26	H_2O	7
— hydriodide	250–255d.	H_2O	..	+8·1	25	H_2O	7
— tartrate	199–200	H_2O	..	+20	25	H_2O	7
— oxime	244–245	EtOH	..	..	..	..	7
Dos-N-acetyldihydro-ψ-codeinone enol acetate	191·5–192·5	EtOH	needles	..	..	..	7
Tetrahydro-ψ-codeinone·$\frac{1}{2}H_2O$	137–138·5	EtOH	..	..	..	..	7
— anhydrous	170–171	subl.	..	+8·0	30	EtOH	7
— hydrochloride·$2H_2O$	165–166	EtOH	..	−6·2	25	H_2O	7
— hydriodide·H_2O	154–155	H_2O	..	−5·9	25	H_2O	7
— oxime	218–219	EtOH	..	..	..	..	7
Acetyltetrahydro-ψ-codeinone	..	..	oil	..	..	..	7
Methyldihydro-ψ-codeinone	213–214·5	isopropyl alcohol subl.	..	..	..	..	7
Dihydroisomorphinone	198	subl.	..	+46	26	EtOH	7
7:7:bis-hydroxymethyldihydrocodeine	110–113	H_2O	needles	..	..	..	77
Trimethyl 7:7-bis-hydroxymethyldihydrocodeine hydriodide	128	H_2O	needles	..	..	..	77

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
7:7-bis-hydroxymethyldihydromorphine	282–283d.	..	..	..	..	..	77
Dihydrometacodeinone	196–201	MeOH	needles	..	..	..	63
— oxime	176–180	MeOH	..	..	..	..	63
1-bromodihydrometacodeinone	241–246	EtOH+$CHCl_3$	..	..	..	..	63

14-hydroxycodeinone, 14-bromocodeinone } *see* Chap. XVIII.
6-methyldihydrocodeine, etc.: *see* Chap. IV.
6-methyldihydromorphine: *see* Chap. I.
Alkyldihydrocodeinones and morphinones: *see* Chap. XIX.

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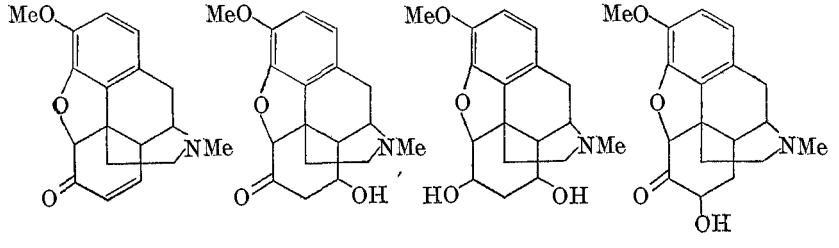
ADDENDUM TO CHAPTER X

Codeinone [A] has now been shown to result in 30–40 per cent. yield from the Oppenauer oxidation of codeine; ψ-codeinone cannot be prepared in the same way from ψ-codeine.

The phenolic substance previously stated to be formed when codeinone is allowed to stand in hydrochloric acid, to have the composition $C_{18}H_{21}O_4N$ [3], and to be phenolic has now been identified as 8-hydroxydihydrocodeinone [B], which is formed from codeinone by the addition of a molecule of water to the double bond. Reduction of [B] catalytically or with lithium aluminium hydride affords 8-hydroxydihydrocodeine [C], which is not oxidized by periodates, thus eliminating formula [D] for the parent ketone.



The erroneous statement that these two new bases were phenolic was based upon a diazo-coupling reaction during which other changes must occur (Findlay and Small, *J.A.C.S.*, 1951, **73**, 4001). Acetolysis of [B] yields 3-methoxy-4:6-diacetoxyphenanthrene.

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Ref.*
8-hydroxydihydrocodeinone	201	EtOAc	sheaves	−136	20	?	Findlay and Small, *J.A.C.S.*, 1951, **73**, 4001.
— hydrochloride	186–189	H_2O	prisms	..	..	..	
— oxime	274	EtOH	prisms	..	..	..	
— oxime hydrochloride	261·5	EtOH	prisms	..	..	..	
— 2:4-dinitrophenylhydrazone hydrochloride	220–230	EtOH	prisms	..	..	..	
8-hydroxydihydrocodeine	207	EtOAc	..	−115	20	?	
— hydrochloride	238·5–240	EtOH	..	..	..	..	
— methiodide	250	MeOH + EtOAc	needles	..	..	..	
— diacetyl ester	149·5–150·5	EtOAc	tablets	..	..	..	

XI

THEBAINE

THEBAINE was discovered by Pelletier and Thiboumery during an investigation of the alkaloids of opium, and, being thought to be an isomer of morphine, was called paramorphine [1–3]; the name thebaine was subsequently suggested by Couerbe [4].

OCCURRENCE

Thebaine appears in *Papaver somniferum* after narcotine, codeine, morphine, papaverine, and narceine [5]; the amount in opium is always small, varying between 0·2 and 0·8 per cent. [6–7], though a substantially higher figure (up to 2·68 per cent.) has been recorded for Manchurian opium [8]. Unlike morphine and codeine it is also found in *Papaver orientale*, which contains thebaine as the only alkaloid during periods of great vegetative activity, but only an isomer of totally different constitution (isothebaine, Chap. XXIV) is found during periods of withering and rest of the plant [9–11].

ISOLATION

(*a*) The aqueous extract of opium is treated with sodium acetate and the precipitated narcotine and papaverine collected, the filtrate concentrated to small bulk with sodium acetate when narceine is precipitated and removed, thebaine being finally isolated from the filtrate as its sparingly soluble salicylate. In this way 90 per cent. of the alkaloid can be extracted [12–13].

(*b*) The concentrated aqueous extract of opium, diluted with an equal volume of water, is treated with ammonia and left for twenty-four hours, when all the narcotine and morphine are precipitated. The remaining alkaloids are extracted by benzene, from which thebaine and codeine are removed by dilute acetic acid and the former precipitated by the addition of sodium carbonate to the acetate solution [14].

(*c*) The liquid remaining after the extraction of morphine by other processes is treated with slaked lime and the calcium precipitates leached with benzene, from which thebaine, narcotine, and papaverine can be recovered [15].

Other methods of isolation and purification are given by Busse and Busse [16] and by Willsteadt [17]. Barbier [18] has given a critical and detailed account of the methods available for the extraction of alkaloids from opium.

PHYSICAL PROPERTIES

Thebaine crystallizes from absolute or dilute alcohol in rectangular plates associated in tufts, an illustration of which is given by Dean and Brady [19]; on sublimation at 135° C. it is obtained as needles and at 160° C. also in cubes and prisms [20]. It can be recrystallized from alcohol, is readily soluble in benzene [21], chloroform [3], and pyridine [22], but very sparingly soluble in petroleum [23]. The base can be sublimed at atmospheric pressure [20] and *in vacuo* [24–27]. Vacuum-sublimed thebaine has m.p. 192·5° C. The molten alkaloid forms a glass on cooling [28]. Crystal density measurements have been made by Schröder [29]. The specific rotation of the base has been recorded as −218·64°/15° C., −216·36°/22·5° C., −215·5°/25° C., and of the hydrochloride as −163·25°/15° C. [30].

DETECTION

The following colour tests have been recorded for thebaine:

Reagent	*Colour*	*References*
conc. H_2SO_4	red → yellow	31–32
conc. H_2SO_4 + conc. HNO_3	red	33
conc. H_2SO_4 + H·CHO	red	34
conc. H_2SO_4 + sodium molybdate	red	34
conc. H_2SO_4 + ammonium vanadate	red	34
conc. H_2SO_4 + $KReO_4$	brown	35
conc. H_2SO_4 + ϕ_2NH	dark red-brown → green	32
conc. HNO_3	colourless $\xrightarrow{10\text{ min.}}$ yellow $\xrightarrow{60\text{ min.}}$ dk. yellow	32
conc. HCl	orange-red (characteristic)	
conc. HCl. Reduce + excess zinc, 2–3 drops of solution in 2–3 ml. conc. H_2SO_4	intense purple	36
HOAc + PbO_2, filter	orange-red	37
HOAc + PbO_2, filter, add conc. H_2SO_4	golden yellow	37
Basic magnesium hypochlorite + HOAc layered on to conc. H_2SO_4	red ring at interface	38
$ZnCl_2$ + dil. HCl. Evaporate with base on porcelain	yellow	39–41
HCl + α-nitroso-β-naphthol	light green $\xrightarrow{\text{evaporate}}$ violet	32
$CuSO_4$ + 25% HCl	green	32
$HgCl_2$ + 25% HCl	yellow → grey	32
$BiCl_3$ + HCl	yellow	32
Evap. + $SnCl_2$, then moisten + 40% KOH	black	32
Evap. + $SbCl_3$, then moisten + 40% KOH	yellow	32
$Hg_2(NO_3)_2$	black in 30 min.	32
2% aqueous furfurol	red	34
Benzoquinone in hot benzene	deep orange; fades with appearance of lemon-yellow prisms	42–44
Methiodide + benzoquinone in hot $CHCl_3$	orange ppt. in 5 min.	36
$SbCl_3$	weak blue $\xrightarrow{\text{heat}}$ colourless	45–46
Iodine monochloride	ppt. evolves iodine on heating	47

Colour tests are also given by Fulton [48]. Precipitation tests [49–53] and microprecipitation tests [54] have also been devised.

Estimation

The estimation of thebaine in the analysis of opium is described by Klyachkina [55] and Anneler [56]. The alkaloid has been estimated in opium residues by condensation with benzoquinone, isolation of the very sparingly soluble adduct, and iodimetric titration of this in chloroform solution. This method is reported to be accurate to 0·5 per cent., provided resins, dyeing substances, and phenolic alkaloids are first removed [57]. Thebaine can also be estimated as its silicotungstate [53] or salicylate [54].

Composition

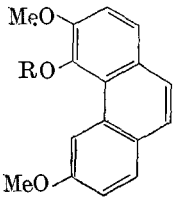
The empirical formula of thebaine was variously given as $C_{17}H_{18}O_3N$ [3], $C_{15}H_{27}O_4N_2$ [4], $C_{25}H_{14}O_3N$ [58] before the correct percentage composition, corresponding to $C_{19}H_{21}O_3N$, was determined by Anderson [59–61] and by Hesse [31]. Thebaine is a tertiary base, readily forming quaternary salts [62–64], reacts alkaline to litmus, and gives stable salts from solutions of which the base is not precipitated by neutral sodium acetate [65].

Degradation

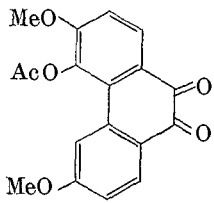
Alkaline degradation of thebaine methiodide was stated by Howard and Roser [66] to give trimethylamine and a substance of composition $C_{14}H_{12}O_3$, but Freund [63] showed that loss of the nitrogen-containing side-chain occurs, the basic product being in fact tetramethylethylenediamine. Loss of the side-chain with production of phenanthrene derivatives also takes place when the base or the methiodide is heated with acetic anhydride [67–68] and benzoyl chloride [69], when the products are acetylthebaol [I, R = Ac] and benzoylthebaol [I, R = ϕ·CO] respectively. (Beckett and Wright [70] obtained only a resin on heating thebaine with acetic anhydride.) Thebaol [I, R = H] results from the hydrolysis of these compounds and also from thebaine and ethanol or sodium ethoxide at 150–160° C. [71]; it is no doubt the product of Hofmann degradation.

Acetylthebaol [I, R = Ac] can be oxidized to a quinone [II] without loss of groups, showing that the 9:10 positions are free from substituents [67–68], and methylthebaol [I, R = Me] [72] was shown to be identical with 3:4:6-trimethoxyphenanthrene by synthesis of the latter [73]. In this way the positions of the oxygen functions in thebaine were established and the base identified as a derivative of a partially hydrogenated phenanthrene.

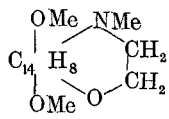
On the basis of the degradation of thebaine to derivatives of thebaol and β-dimethylaminoethanol (Chap. XXVII) the oxazine formulae



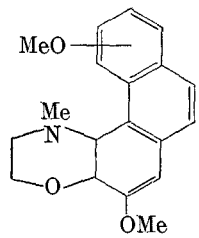
[I]



[II]



[III]

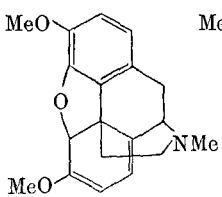


[IV]

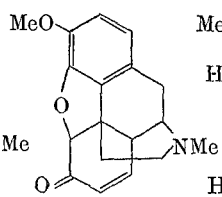
[III] and [IV] were advanced for the alkaloid [63, 67–68], β-dimethylaminoethanol being assumed to arise by hydrolytic scission of the oxazine ring; but this theory was abandoned when metathebainone (see below), in which all three oxygen atoms were accounted for in methoxyl, phenolic hydroxyl, and carbonyl groups, was found to give β-dimethylaminoethanol on degradation to a phenanthrene derivative [74].

Hydrolysis

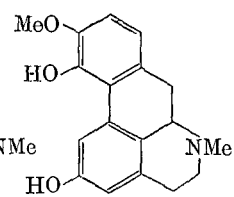
Thebaine [V] is an enol ether and though fairly stable in cold dilute acid is hydrolysed to codeinone [VI] on standing with N. sulphuric acid for several weeks in the cold or six to seven minutes at 100° C. [75], and codeinone can also be isolated from the orange-red solution of thebaine in concentrated hydrochloric acid [76]. In this way the relationship of the alkaloid to codeine and morphine was established. The yield of codeinone is very poor (< 7 per cent.), doubtless as a result of the ease with which thebaine undergoes rearrangement in acid solution.



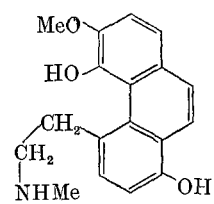
[V]



[VI]



[VII]



[VIII]

Acid Transformations

(*a*) If the orange-red solution of thebaine in concentrated hydrochloric acid, from which no thebaine can be recovered, is heated in sealed vessels at 80–90° C. the colour slowly fades and morphothebaine [VII] (Chap. XXIII) is formed [62, 66, 77].

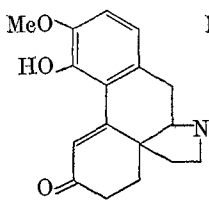
(*b*) Thebaine is completely converted to thebenine [VIII] (Chap. XXV) on boiling for 1½–2 minutes with dilute hydrochloric acid [31, 77].

(*c*) Reduction of thebaine with stannous chloride and hot concentrated hydrochloric acid affords metathebainone [IX] (Chap. XVI)

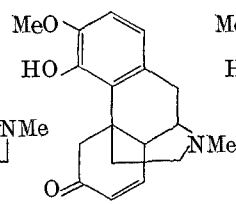
[76, 78–79], though thebainone-A [X] can be obtained by modifying the conditions [76].

These substances can all be obtained from codeinone [VI] under the same conditions [76, 79–81], and [VII], [VIII], and [IX] are believed to be formed via the intermediate [XI] [82–83].

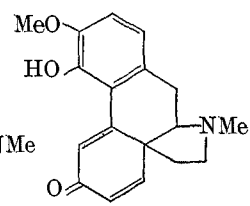
Thebaine reacts with cyanogen bromide as an allylamine suffering scission of the nitrogen-containing ring, the product being cyanonorthebenine [XII] [84–85].



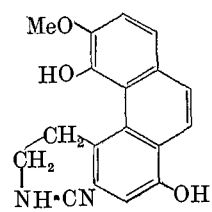
[IX]



[X]



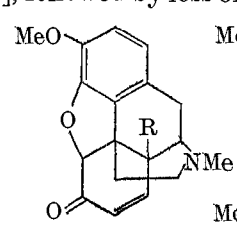
[XI]



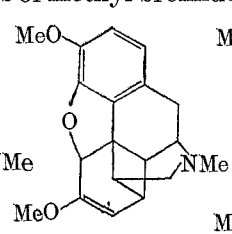
[XII]

Reaction with Halogens and Hydrogen Peroxide

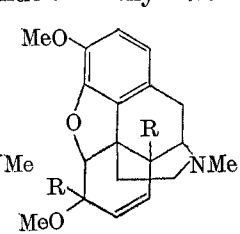
Bromination of thebaine in dilute hydrobromic acid affords bromothebaine and bromothebaine tetrabromide [62]. Bromination in glacial acetic acid, however, takes a different course resulting in production of 14-bromocodeinone [XIII, R = Br] [86]. 14-Chlorocodeinone [XIII, R = Cl] is obtained in 80 per cent. yield by the action of iodobenzene dichloride ϕICl_2 on thebaine [87]. 14-Bromocodeinone is converted on attempted preparation of its oxime to the oxime of 14-hydroxycodeinone [XIII, R = OH] [86, 88], and the latter ketone is formed directly from thebaine by the action of 30 per cent. hydrogen peroxide on the base in boiling glacial acetic acid [88–92], or of potassium dichromate on the base in dilute acetic or sulphuric acid [88–90, 93–94]. The fact that 14-hydroxycodeinone does not contain the system —CO—CH_2— whilst 14-hydroxydihydrocodeinone does, caused Gulland and Robinson to modify the bridge-structure [XIV] earlier proposed for thebaine [95] to the now-accepted [V] [96], from which 14-bromo- and 14-hydroxycodeinone are formed by the addition of bromine or hydrogen peroxide to the ends of the conjugated diene, to give [XV, R = Br] or [XV, R = OH], followed by loss of methyl bromide or methyl alcohol [96–97].



[XIII]

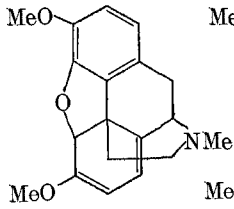


[XIV]

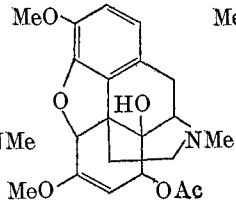


[XV]

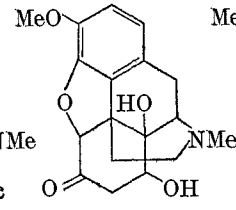
The oxidation of thebaine with manganic acetate first gives [XVI], which on hydrolysis with 20 per cent. hydrochloric acid affords after three minutes at 100° C. the dihydroxyketone [XVII], and 14-hydroxycodeinone [XVIII] after twenty minutes [98]. The 14-substituted codeinones are discussed in Chapter XVIII.



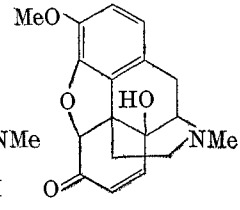
[V]



[XVI]



[XVII]



[XVIII]

On warming with 30 per cent. hydrogen peroxide in the absence of acid, thebaine is converted to a normal amine oxide, which is reduced to the base by sulphurous acid [99–100] and oxidized to an amorphous brown solid by potassium chromate [101].

Diels–Alder Additions

Thebaine behaves as an active conjugated diene in undergoing addition of maleic anhydride [42–43], benzoquinone [42–43], 1:4-naphthoquinone [42], and acrolein [102]. The adduct with benzoquinone undergoes deep-seated rearrangement on heating for three hours with concentrated hydrochloric acid to give flavothebaone [43–44] (see Chap. XXI).

Reduction

The reduction of thebaine and the chemistry of its reduction products are dealt with in Chapters XII, XIII, XIV, XV, and XVI.

Reaction with Grignard Reagents

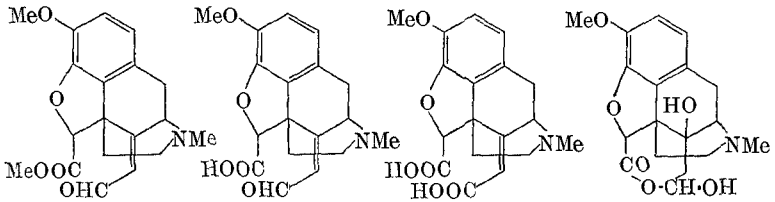
Thebaine readily reacts with Grignard reagents to give phenolic bases having unexpected properties. The reaction involves a new type of molecular rearrangement [82–83, 109] and is discussed in Chapter XX.

Ozonolysis

When ozone is passed through an aqueous solution of thebaine hydrochloride and the resulting base precipitated a 60 per cent. yield of α-thebaizone [XIX] is obtained [110–12]. This substance contains two methoxyl groups and one carbonyl group, and is the methyl ester of an aldehydo-acid, though Faltis [113] claimed that it does not give the Angeli–Rimini reaction. It gives a semicarbazone [110] and *p*-nitrophenylhydrazone [112] and reduces cold ammoniacal silver nitrate

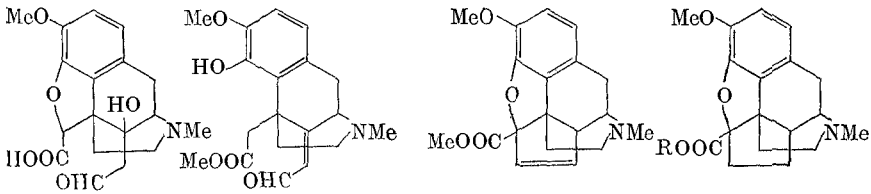
[112]. With hydroxylamine it appears to give a hydroxamic acid. It can be brominated to 1-bromo-α-thebaizone [112].

α-Thebaizone may be hydrolysed by alkali to thebaizonic acid [XX] [110–12], which is not converted back to α-thebaizone by diazomethane and gives an amorphous product that is neither aldehydic nor acidic on reduction with aluminium amalgam [112]. Thebaizone dicarboxylic acid [XXI] is formed when α-thebaizone is stood in acetic acid and 30 per cent. hydrogen peroxide for forty-eight hours at 15–20° C. [112, 114].



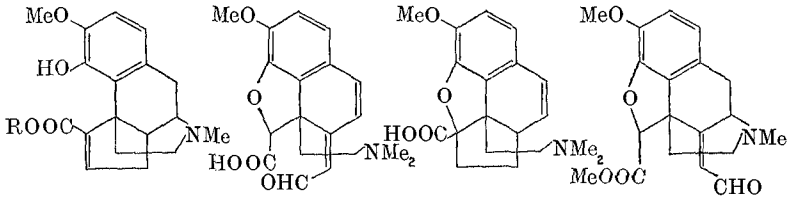
[XIX] [XX] [XXI] [XXII]

Hydrolysis and addition of water to the double bond occurs when α-thebaizone is heated with concentrated hydrochloric acid at 95–98° C. for one hour, the product being hydroxydihydrothebaizonic acid in the aldehyde hydrate lactone form [XXII], which is converted to the free acid [XXIII] by methanolic sodium methoxide; hydrolysis with thallous hydroxide affords a compound $C_{18}H_{23}O_7N$ containing an additional molecule of water [112].



[XXIII] [XXIV] [XXV] [XXVI]

Reduction of α-thebaizone with hydrogen and platinum oxide in methanol affords phenolic dihydrothebaizone [XXIV], whereas reduction with aluminium amalgam in wet ether yields desoxythebaizone, also obtained by reduction with zinc and hydrochloric acid. Desoxythebaizone shows no aldehydic properties and has been allotted the structure [XXV]; it gives dihydrodesoxythebaizone on hydrogenation and dihydrodesoxythebaizonic acid on hydrolysis and hydrogenation [112]. These two substances may be allotted the formulae [XXVI, R = Me] and [XXVI, R = H] respectively, though as desoxythebaizone is an allylic ether they may be phenols and have the structures [XXVII, R = Me] and [XXVII, R = H].



[XXVII] [XXVIII] [XXIX] [XXX]

Hofmann degradation of α-thebaizone and its derivatives by thallous hydroxide proceeds as follows [112]:

(*a*) α-thebaizone methiodide yields α-thebaizonic acid methine [XXVIII];

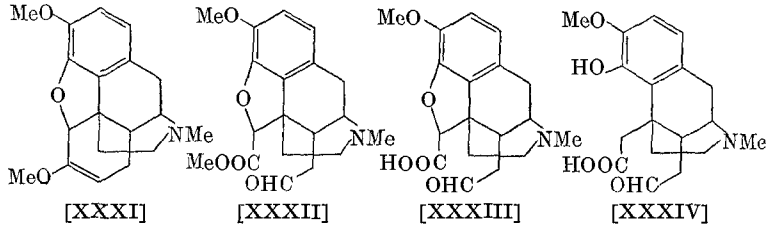
(*b*) hydroxydihydrothebaizonic acid methiodide loses methyl iodide;

(*c*) dihydrodesoxythebaizone methiodide gives dihydrodesoxythebaizonic acid methine [XXIX];

(*d*) dihydrodesoxythebaizonic acid on heating with methyl iodide gives a dimolecular substance $C_{37}H_{45}O_8N_2I \cdot H_2O$, which on decomposition with thallous hydroxide and treatment with methyl iodide gives the simple methiodide, $C_{18}H_{21}O_4N \cdot MeI$.

On heating for a short time at 200° C. α-thebaizone is transformed to β-thebaizone, which is probably the geometrical isomer [XXX]. This can be converted to hydroxydihydro-β-thebaizonic acid, an isomer of [XXIII], but gives desoxythebaizone on reduction with aluminium amalgam in wet ether [112]. On oxidation it yields β-thebaizone carboxylic acid [112].

Ozonolysis of dihydrothebaine [XXXI] (Chap. XIII) affords isodihydrothebaizone [XXXII], which yields isodihydrothebaizonic acid [XXXIII] on hydrolysis, and the latter can be hydrogenated to tetrahydrothebaizonic acid [XXXIV] [112].



[XXXI] [XXXII] [XXXIII] [XXXIV]

Miscellaneous Reactions

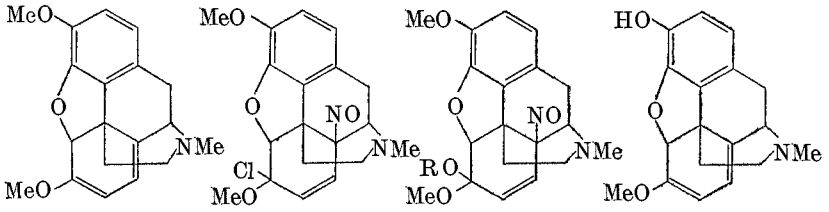
(*a*) Thebaine undergoes a reaction with nitrosyl chloride, organic nitrites, and nitrosyl sulphuric acid when its salts are treated with these reagents in methyl or ethyl alcohol, the products being the same (if the same alcohol is used) whatever the nitrosating agent. With thebaine and nitrosyl chloride two isomeric substances are obtained, one alkali-soluble and one alkali insoluble. The reaction in ethyl alcohol is

reported to give compounds allotted formulae $C_{22}H_{28}O_5N_2$ according to the equation

$$C_{19}H_{21}O_3N+NOCl+2C_2H_5OH = H_2O+CH_3Cl+C_{22}H_{28}O_5N_2,$$

whilst the reaction in methyl alcohol yields $C_{20}H_{24}O_5N_2$ [115]. This reaction has not been further investigated, but it seems probable that it takes a course similar to the reaction between bromine or hydrogen peroxide and thebaine in glacial acetic acid with the nitrosyl chloride adding to the diene system to give [XXXV], replacement of the chlorine of which by OEt (in ethanol) or OMe (in methanol) would give [XXXVI, R = Et] and [XXXVI, R = Me]. On this hypothesis the product in ethanol would be $C_{21}H_{26}O_5N_2$ and not $C_{22}H_{28}O_5N_2$ as reported, but analytical data could not reliably distinguish between the two. This reaction is being investigated.

(*b*) Thebaine has been reported to react with hydrogen sulphide, no definite product being isolated [116], but the author has been unable to confirm this [101].



[V] [XXXV] [XXXVI] [XXXVII]

(*c*) With phosphorus pentachloride it yields substances containing no chlorine [62].

(*d*) Pyrene is obtained in small quantity by heating thebaine with hydriodic acid and phosphorus or distilling it with zinc-dust [117, 68].

Thermochemical studies of thebaine have been made by Leroy [118–19]. The absorption spectrum of the alkaloid has been determined by Hartley [120] and the ultra-violet absorption spectrum (Fig. 4) by Girardet [121], Steiner [122], and Kitasato [123].

ORIPAVINE

In 1935 an alkaloid named oripavine having the composition $C_{18}H_{21}O_3N$ was isolated from *Papaver orientale* [124] and subsequently from *Papaver bracteatum* [125]. It was shown to contain one —OMe, one —NMe, and one phenolic —OH group [124], and was eventually converted to thebaine [V] by methylation with diazomethane [126] and is in fact 3-0-desmethylthebaine [XXXVII]; it bears the same relationship to morphine as thebaine does to codeine. On boiling with

5 per cent. hydrochloric acid it is converted to amorphous material from which no crystalline derivatives can be prepared [126].

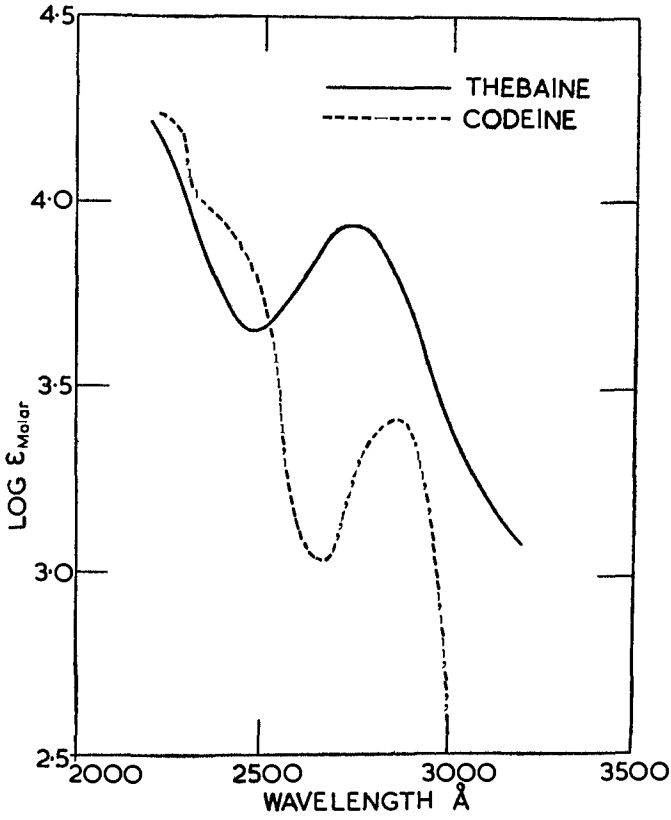


FIG. 4.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Thebaine	193	EtOH	plates	−218 6	15	EtOH	30
— hydrochloride·H_2O	..	H_2O	plates	−574	..	H_2O	127
				−163 6	15	H_2O	30
— sulphate	..	..	cryst.	.	..	..	60–61
— chromate	..	..	prisms	..	..	..	31, 49
— dichromate	..	..	needles	..	..	..	49
— fluorocolumbate	..	..	..	−132	..	..	128
— oxalate·$6H_2O$	..	..	prisms	..	..	..	31
— binoxalate·H_2O	..	..	prisms	..	..	..	..
— diphenylviolurate	123	..	..	..	..	..	129
— meconate·$6H_2O$	..	EtOH	prisms	..	..	..	..
— salicylate	..	..	..	..	..	..	65
— picrate	217	β-ethoxy ethanol	needles	..	..	..	101, 130
— platinichloride	..	..	amorph.	..	..	..	60–61
— methiodide	224	cyclo-hoxanono	prisms	..	..	..	36
— methobromide	..	..	..	..	..	..	64
— methomethylsulphate	..	..	..	..	..	..	64
— ethiodide	..	EtOH	needles	..	..	..	62

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Thebaine N-oxide	c. 80	..	..	..	..	..	100
—N-oxide hydrochloride	238–239	EtOH or H_2O	needles	..	..	..	100
Bromothebaine	..	..	amorph.	..	..	..	62
Bromothebaine tetrabromide	..	..	amorph.	..	..	..	62
α-thebaizone	125–126	MeOH	yellow crystals	..	..	..	110–12
— hydrochloride	..	..	cryst.	..	..	..	112
— hydriodide	185–187	acetone	..	..	..	..	112
— methiodide	D.250–251	H_2O + MeOH	..	..	..	..	112
— semicarbazone	202	EtOAc	..	..	..	..	110
β-thebaizone	151	MeOH	yellow crystals	..	..	..	112
1-bromo-α-thebaizone	147	MeOH	..	..	..	..	112
Thebaizonic acid	D. 235	EtOAc	..	..	..	..	112
Thebaizonic acid methine	..	..	..	..	..	..	112
— hydrochloride	260–270d.	..	..	..	..	..	112
— hydriodide	250–255	..	..	..	..	..	112
Hydroxydihydrothebaizonic acid	230–240d.	..	..	..	..	..	112
— hydrochloride	D.205–210	MeOH	..	..	..	..	112
— methiodide	D. 163	..	..	..	..	..	112
Hydroxydihydro-β-thebaizonic acid	D. c. 200	H_2O + MeOH	..	..	..	..	112
— hydrochloride	D. 260	..	..	..	..	.	112
β-thebaizone carboxylic acid	D. *c.* 220	MeOH	cubes	..	..	..	112
Thebaizone dicarboxylic acid	208–209		yellow	..	..	..	114
	189–190*d*	H_2O	rods				112
Desoxythebaizone	147	MeOH	yellow prisms	..	..	..	112
Dihydrodesoxythebaizone	..	..	oil	..	..	..	112
— methiodide	175–177	MeOH	..	..	..	..	112
— methiodide	148–152	H_2O	..	..	..	..	112
Dihydrodesoxythebaizonic acid	163–165*d*	..	..	..	..	..	112
— hydrochloride	236 237	..	..	..	..	..	112
Dihydrodesoxythebaizonic acid methine	D. 195	..	..	..	..	..	112
— methiodide	156–158	..	..	..	..	..	112
Dihydrothebaizone	c. 140	..	..	..	..	..	112
— methiodide	D.239–240	..	..	..	..	..	112
Acetyldihydrothebaizone	..	..	..	..	..	..	112
— methiodide	D. 250	..	..	..	..	..	112
Isodihydrothebaizone	103–105	..	..	..	..	..	112
— methiodide	147–148	..	..	..	..	..	112
Isodihydrothebaizonic acid	248–249	MeOH	..	..	..	..	112
— hydrochloride	D. c. 130	..	..	..	..	..	112
— methiodide	D.179–180	..	..	..	..	..	112
Tetrahydrothebaizonic acid	230–235	..	..	..	..	..	112
Thebaine + NOCl + EtOH (*a*)	230–233	..	..	..	..	..	..
Thebaine + NOCl + EtOH (*b*)	238–240	..	..	..	..	..	115
Thebaine + NOCl + MeOH	240–242	..	..	..	.	..	115
Oripavine	200–201	..	..	−211·8	..	..	124
— hydrochloride	244–245	..	..	..	..	..	124
— methiodide	207–208	..	..	..	..	..	124

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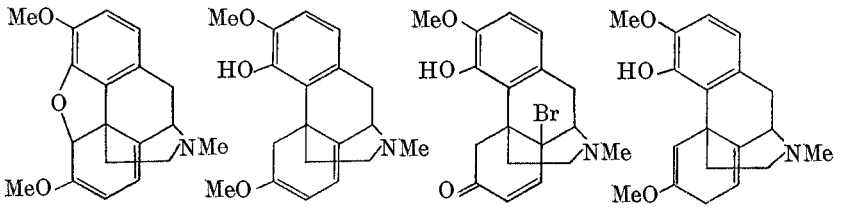
XII

THE REDUCTION OF THEBAINE

THE first reduction of thebaine [I] was achieved by sodium and boiling alcohol and resulted in the production of a phenolic dihydrothebaine in only moderate yield [1–3]. The same compound, now called dihydrothebaine-ϕ, is more conveniently prepared in yields of up to 95 per cent. by the reduction of thebaine with sodium in liquid ammonia without the addition of alcohol [4–5].

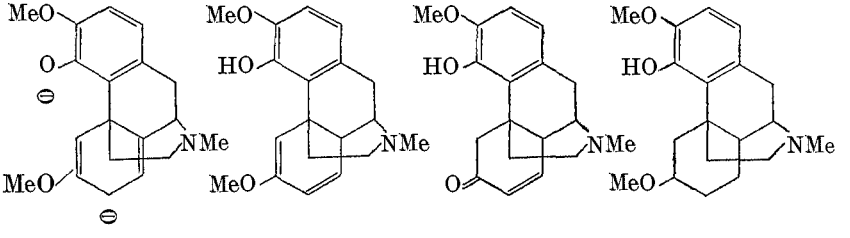
Dihydrothebaine-ϕ was originally given the structure [II], which was in accord with most of its chemical properties [3–4] except its failure to condense with benzoquinone or maleic anhydride and its failure to yield a derivative of 14-bromothebainone [III] on treatment with bromine [5]. However, the production of a conjugated diene as final product in a sodium-alcohol or sodium-ammonia reduction is contrary to general experience and examination of the infra-red and ultra-violet absorption spectra of dihydrothebaine-ϕ, thebaine, β-dihydrothebaine, several 1:4-dihydroanisole derivatives, and 1-alkoxy-1:3-dienes led to modification of the structure of dihydrothebaine-ϕ to [IV] [6], which structure is more in accord with its properties than is [II], and in particular explains why the hydrogenation of this base proceeds with absorption of only one mole of hydrogen (see Chap. XIV).



Dihydrothebaine-ϕ must arise from thebaine by addition of two electrons to the system —O—CH—CH=C— to give the transient ion [V], which immediately adds a proton from the ammonia to give the anion of [IV].

An isomer of dihydrothebaine-ϕ is obtained by the reduction of thebaine with lithium aluminium hydride [7] and was called by its discoverers β-dihydrothebaine, although it bears no relationship to the true, non-phenolic, dihydrothebaine (see below). It was originally thought to be a diastereoisomer, differing only at C-14, of thebainone-A enol methyl ether [VI] (prepared by the isomerization of codeine methyl

ether under the influence of hot sodium ethoxide [3]) as it yields β-thebainone [VII], having the 'abnormal' configuration at C-14, on hydrolysis [7]. However, the conditions required for the production of [VII] from β-dihydrothebaine are precisely those required for the production of the same ketone from dihydrothebaine-φ [3] and the reaction is of no structural significance. Moreover, β-dihydrothebaine readily absorbs two moles of hydrogen on reduction giving dihydrothebainol-6-methyl ether [VIII] [7], whereas thebainone-A enol methyl ether [VI] absorbs only one mole of hydrogen and gives an enol ether [3].



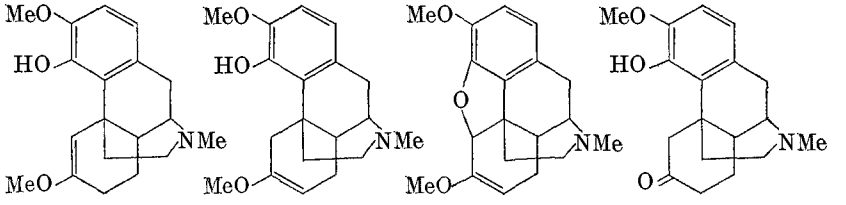
[V] [VI] [VII] [VIII]

Examination of the infra-red and ultra-violet absorption spectrum of β-dihydrothebaine indicated that it has in fact the structure [II] initially allotted to dihydrothebaine-φ [6]. Such a conjugated diene would be expected to undergo 1:4-addition of hydrogen with final production of [VIII], a reduction parallel to the production of tetrahydrothebaine from thebaine (see below).

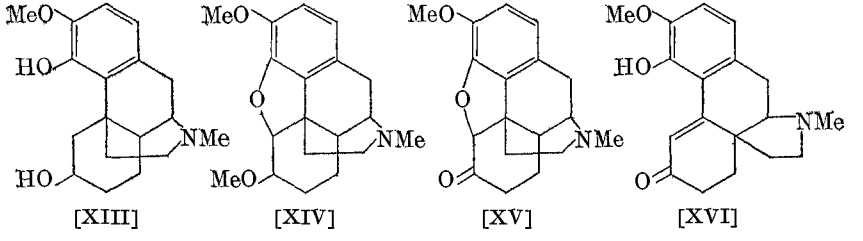
Catalytic or sodium and alcohol reduction of thebainone-A enol methyl ether [VI] affords a substance initially allotted the structure [IX] as it is different from an isomeric substance obtained by the catalytic reduction of dihydrothebaine-φ, at that time believed to be [II] [3]. It is now clear that this base is in fact dihydrothebainone Δ^6-enol methyl ether [X] and is formed from [VI] by 1:4-addition of hydrogen to the conjugated system. The product of catalytic reduction of dihydrothebaine-φ must therefore be the isomeric Δ^5-enol methyl ether [IX] produced by saturation of the 8:14-double bond of [IV]. Bentley, Robinson, and Wain [5] have in this way obtained a base different from that obtained by Small and Browning [3], but believe their product is the true dihydrothebainone-Δ^5-enol methyl ether [IX] as it can also be prepared in 98 per cent. yield by the sodium and liquid ammonia reduction of dihydrothebaine [XI] [5].

The catalytic hydrogenation of thebaine was first investigated by Oldenberg [8–9], who isolated a crude, amorphous substance to which he gave the name tetrahydrothebaine and which was doubtless a complex mixture of bases. The non-phenolic dihydrothebaine [XI] may be prepared in only moderate yield by the hydrogenation of thebaine

hydrochloride in presence of a platinum or colloidal palladium catalyst [10–14]. The main product of catalytic reduction of thebaine itself in dilute acetic acid with colloidal palladium or platinum catalysts is the phenolic ketone dihydrothebainone [XII] [10–11, 15]. Skita and his co-workers obtained this base together with a substance m.p. 143° C., thought to be tetrahydrothebaine but probably a mixture, and dihydrothebainol [XIII] which is formed by further reduction of dihydrothebainone [11].



Tetrahydrothebaine [XIV] was finally isolated by Schöpf and Winterhalder [13] and shown to be identical with dihydromorphine dimethyl ether. It is obtained in good yield by hydrogenation of thebaine in acetic acid over platinum oxide [16–17] or in ethanol over highly active (W 6) Raney nickel [18].



Catalytic reduction of thebaine in 2–2·5N hydrochloric acid results in hydrolysis of the dihydrothebaine [XI] first formed, the product being a mixture of dihydrothebainone [XII] and dihydrocodeinone [XV] [19–21]; in 5N hydrochloric acid migration of the side-chain occurs and metathebainone [XVI] is formed [19] (see below).

Hydrogenation of thebaine in neutral solution (alcohol containing suspended sodium bicarbonate) over palladized barium sulphate affords an oil that Wieland and Kotake [22] suggested was an enol ether of dihydrothebainone (actually a bridge-structure was used, in accordance with the thebaine formula current at that time) as it gave approximately 80 per cent. of dihydrothebainone on hydrolysis. Small and Browning [3] later resolved the oil into three crystalline components: dihydrothebainone Δ^6-enol methyl ether [X] (47 per cent.), tetrahydrothebaine [XIV] (31 per cent.), and dihydrothebainol-6-methyl ether

[VIII] (18 per cent.). The first of these was found to be identical with the product of reduction of thebainone-A enol methyl ether [VI], and dihydrothebainone obtained by Speyer and Freunds [15] by the reduction of thebaine in neutral solution doubtless arose from hydrolysis of this enol ether during isolation of the product. The dihydrothebainol-6-methyl ether from this reduction appears to be identical with that derived from β-dihydrothebaine. It can be methylated at the phenolic group (by Rodionov's method [23]), but none of the dihydrothebainols [11, 24–28] have yet been converted to a dimethyl ether for purposes of comparison [3].

Hydrogenation in neutral solution at 50–60° C. proceeds much more rapidly than at the room temperature. The activity of the various catalysts, which may vary greatly in different specimens prepared in apparently the same way, may markedly affect the course of reduction of thebaine [18].

The Mechanism of Reduction

The catalytic hydrogenation of thebaine evidently proceeds by four competing mechanisms that can be explained as follows. The conjugated system $-\overset{6}{O}-\overset{5}{C}-\overset{4}{C}=\overset{3}{C}-\overset{2}{C}=\overset{1}{C}-$ can undergo initially 1:2, 1:4, 1:6, or 5:6 addition of hydrogen, giving as final products dihydrothebaine, tetrahydrothebaine, dihydrothebainone Δ^6-enol methyl ether (dihydrothebainone in acid solution), and dihydrothebainol-6-methyl ether respectively. 3:6-addition of hydrogen occurs in the sodium and liquid ammonia reduction, giving dihydrothebaine-φ.

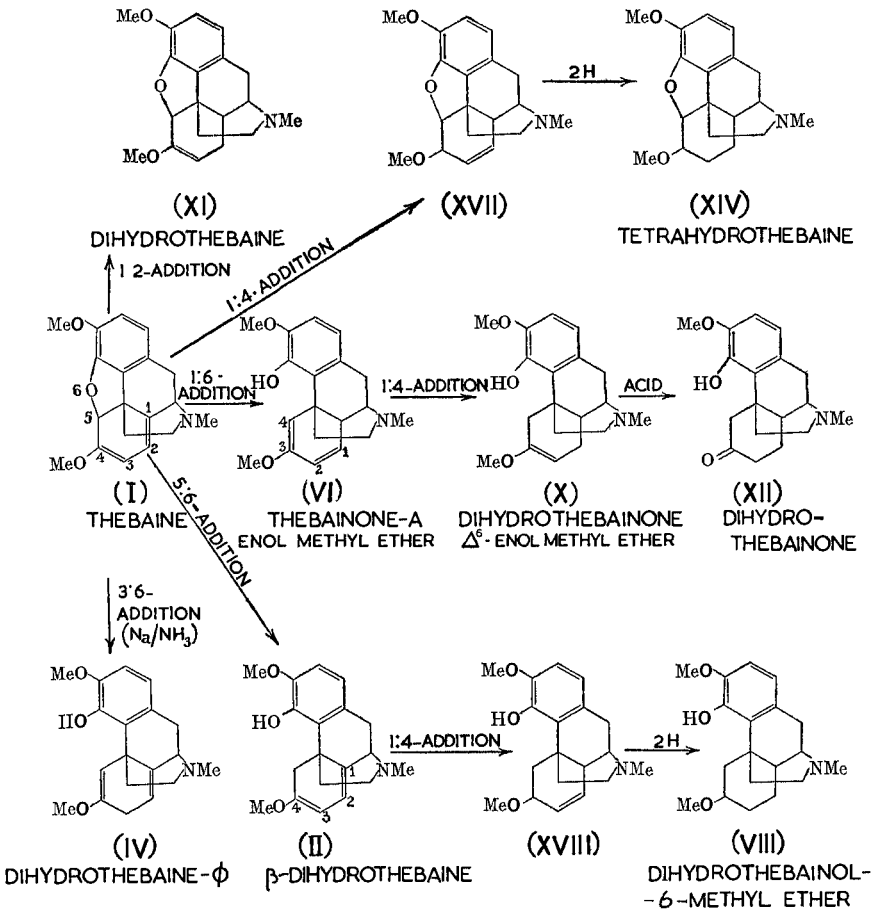
Dihydrothebaine [XI] results from 1:2-addition of hydrogen and is not further reduced under mild conditions, as hydrogenation ceases when a considerable amount of this still remains in the mixture.

Tetrahydrothebaine [XIV] arises as a result of 1:4-addition of hydrogen giving the intermediate [XVII], the isolated double bond of which is immediately further reduced.

As in the ψ- and allo-ψ-codeine series (Chap. IV), reduction of the double bonds of thebaine [I] without opening of the cyclic ether, giving [XI] and [XIV], is favoured by hydrogenation of the hydrochloride rather than of the base [10–14, 16–17].

Dihydrothebainone [XII] or its Δ^6-enol methyl ether [X] is produced in considerable quantity in all reductions of thebaine even under mild conditions, and cannot arise from further reduction of dihydrothebaine. It undoubtedly arises from 1:6-reduction of the conjugated system to give thebainone-A enol methyl ether [VI], which then suffers further 1:4-reduction to dihydrothebainone Δ^6-enol methyl ether [X], the latter being hydrolysed in acid solution to dihydrothebainone [XII]. This mechanism was suggested by Schöpf and Winterhalder [14], but Small

and Browning wished to modify it so as to make the Δ^5-enol ether [IX] the second intermediate on the basis of an erroneous concept of the nature of the reduction of thebainone-A enol methyl ether [3].



Dihydrothebainol-6-methyl ether is clearly formed as a result of 5:6-reduction of the conjugated system, i.e. addition of hydrogen to the cyclic ether with the 6:7-double bond merely exerting an activating influence, giving β-dihydrothebaine [II], which then undergoes 1:4 reduction of the diene system, yielding [XVIII] and finally [VIII]. Small and Browning [3] were unable to accept this explanation as they believed [II] to be the structure of dihydrothebaine-φ, which is reduced with absorption of only one mole of hydrogen to an enol ether. However, [II] is now known to correspond to β-dihydrothebaine [6], which is reduced catalytically to dihydrothebainol-6-methyl ether [VIII] [7].

An interesting point arises from the above. If β-dihydrothebaine is an

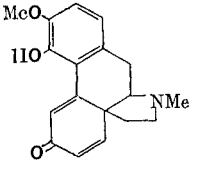
intermediate in the catalytic reduction of thebaine then, as it can be hydrolysed to β-thebainone [VII] which gives β-dihydrothebainone on hydrogenation, the latter would be expected to be formed in small amount during the hydrogenation of thebaine in acid solution. Schöpf and Borkowsky have in fact isolated from this reduction a small quantity of an 'epidihydrothebainone' as its oxime [29–30], the properties of which, so far as they are described, agree well with those of β-dihydrothebainone oxime.

When thebaine is dissolved in concentrated hydrochloric acid an intensely coloured orange-red solution believed to contain [XIX] [31–32] is obtained, and if thebaine is reduced with stannous chloride and concentrated hydrochloric acid at 100° C. [33] or catalytically in > 5N hydrochloric acid [19, 36] a reduced form of [XIX], namely metathebainone [XVI], is produced, the side-chain appearing at C-14. The true thebainone-A [VII] can be obtained in addition to metathebainone by modifying the conditions of the stannous chloride reduction [34].

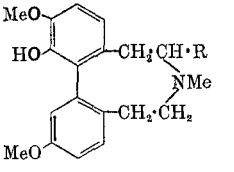
Reduction of the orange-red solution of thebaine in concentrated hydrochloric acid with zinc affords a yellow phenolic base about which little is yet known beyond the facts that it is dimolecular and contains no carbonyl group. Its ultra-violet absorption spectrum contains a band at about 3,800 Å, apparently indicating the presence of a highly conjugated system of double bonds such as

$$\phi\text{—CH=CH—CH=CH—CH=CH—}$$

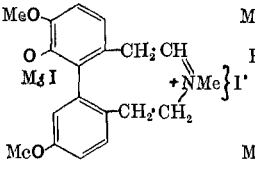
[5]. Presumably it is derived in some way from [XIX].



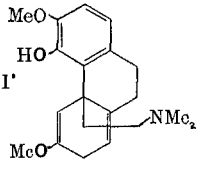
[XIX]



[XX]



[XXI]



[XXII]

The unsubstituted dihydrothebaine [XX, R = H] corresponding to phenyldihydrothebaine [XX, R = φ] would be a compound of great interest, and it was in the hope of obtaining it that the lithium aluminium hydride reduction of thebaine was investigated [7]. Now thebaine reacts with anhydrous magnesium iodide to give a very sensitive substance, possibly [XXI] [4, 35], that reacts with phenylmagnesium bromide to give phenyldihydrothebaine [XX, R = φ] and that reacts vigorously with lithium aluminium hydride when a gas (methane?) is evolved and what appears to be a sensitive, phenolic secondary amine [N-demethylated XX, R = H ?] is produced [35]. This reaction clearly warrants further investigation.

The nitrogen-containing ring of thebaine is stable to reduction, but that of the methiodide is readily opened on reduction with sodium in liquid ammonia when dihydrothebaine-ϕ dihydromethine [XXII] is obtained in about 70 per cent. yield [36].

The chemistry of the many reduction products of thebaine is fully considered in Chapters XIII, XIV, XV, and XVI.

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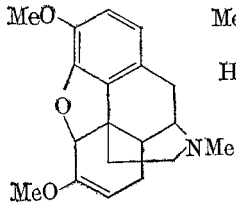
XIII

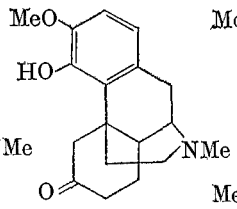
DIHYDROTHEBAINE AND TETRAHYDROTHEBAINE

DIHYDROTHEBAINE

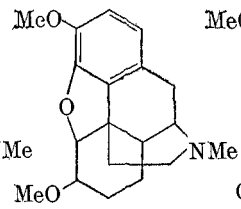
MILD catalytic reduction of thebaine hydrochloride in aqueous or dilute acetic acid solution using a platinum [1] or colloidal palladium catalyst [2–6] results in saturation of the 8:14-double bond and production of dihydrothebaine [I]. The yield is never high, as considerable amounts of dihydrothebainone [II] and tetrahydrothebaine [III] are produced simultaneously, not by further reduction of dihydrothebaine, which is stable under these conditions.



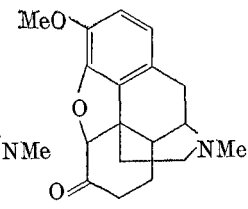
[I]



[II]



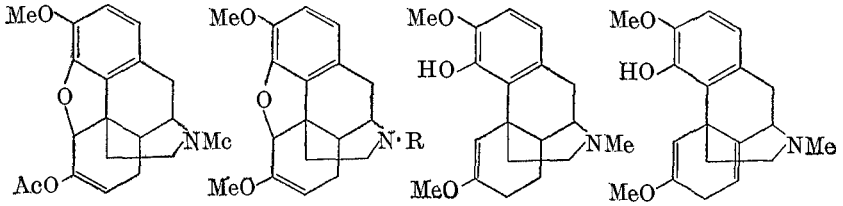
[III]



[IV]

Dihydrothebaine is a non-phenolic, tertiary base containing two methoxyl groups. It still contains the thebaine enol ether group, as is shown by its hydrolysis with hot mineral acid to dihydrocodeinone [IV] [1], a reaction that occurs when thebaine is reduced in 2–2·5N hydrochloric acid [7–9]. Dihydrocodeinone can be re-converted to dihydrothebaine by treatment with sodium tertiary butoxide and methyl sulphate [10] and can also be converted to an enol acetate [V] which is the drug 'acedicon' [11–13]. Unlike thebaine, dihydrothebaine reacts with cyanogen bromide simply with replacement of the N·Me group by N·CN, giving cyanonordihydrothebaine [VI, R = CN], which can be hydrolysed to nordihydrothebaine [VI, R = H]. The fact that no ring fission occurs during this reaction indicates that there is no double bond $\beta:\gamma$ to the nitrogen. Dihydrothebaine readily forms an amine oxide [1].

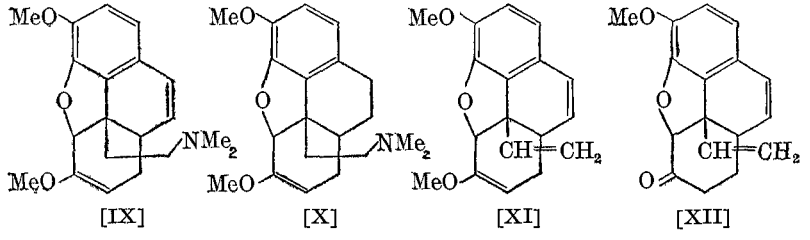
Vigorous reduction of dihydrothebaine with sodium and *iso*amyl alcohol or catalytically [1] results in opening of the cyclic ether link and production of dihydrothebainone [II]. The intermediate in this reaction is doubtless dihydrothebainone Δ^5-enol methyl ether [VII], which can



be prepared by the sodium and liquid ammonia reduction of dihydrothebaine (95 per cent. yield) or the catalytic hydrogenation of dihydrothebaine-ϕ [VIII] [14].

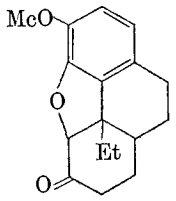
Degradation

Elimination of one of the double bonds of thebaine results in a compound more amenable to exhaustive methylation, and alkaline degradation of dihydrothebaine methiodide affords, in good yield, dihydrothebaine methine [IX] [1, 15–16], which can be hydrogenated to the dihydromethine [X] [1]. Further degradation of the methine [IX] methiodide results partly in regeneration of the base and partly in production of 6-methoxy-13-vinyltetrahydromorphenol methyl ether [XI] [15–16], which can be hydrolysed to 6-keto-13-vinylhexahydromorphenol methyl ether [XII].

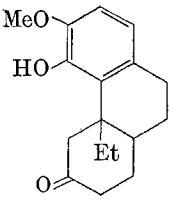


Catalytic hydrogenation of [XII] affords 6-keto-13-ethyloctahydromorphenol methyl ether [XIII], and this may be reduced with aluminium amalgam in wet ether, when scission of the cyclic ether occurs and 6-keto-13-ethyloctahydromorphol methyl ether [XIV] is formed [15]. The latter substance is obtainable in other ways, viz.: (*a*) Degradation of dihydrothebaine dihydromethine [X] to 6-methoxy-13-vinylhexahydromorphenol methyl ether [XV] followed by reduction in acid solution with a colloidal palladium catalyst [3]. An oily isomer of [XIV] is also formed in this way [3, 17]. (*b*) By hydrogenation of [XI] to 6-methoxy-13-ethylhexahydromorphenol methyl ether [XVI] followed by sodium and alcohol reduction of the latter to 3-methoxy-4-hydroxy-13-ethyloctahydrophenanthrene Δ^5-enol methyl ether [XVII], which yields [XIV] on hydrolysis [16]. (The Δ^5 structure for [XVII] is here

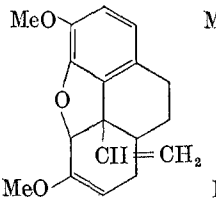
adopted by analogy with dihydrothebaine-ϕ.) [XVII] is presumably the phenolic substance formed by catalytic reduction of [XV] in absence of acid [17].



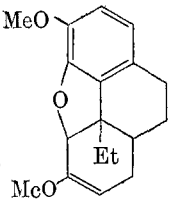
[XIII]



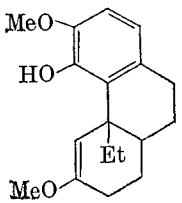
[XIV]



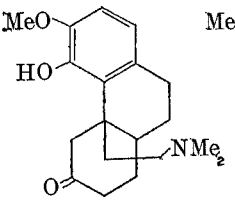
[XV]



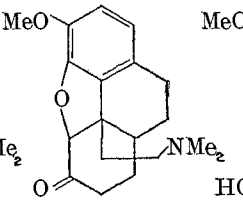
[XVI]



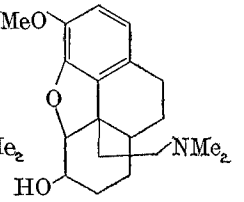
[XVII]



[XVIII]



[XIX]

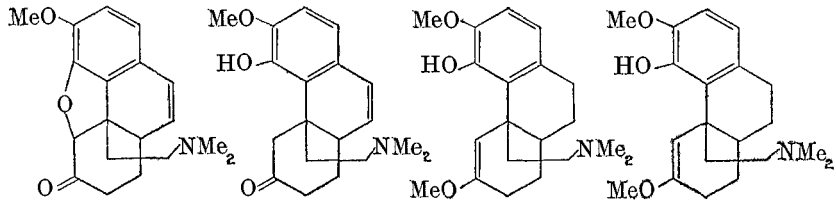


[XX]

Catalytic hydrogenation of dihydrothebaine methine [IX] with colloidal palladium in dilute acetic acid causes saturation of the 9:10 double bond, scission of the cyclic ether, and hydrolysis of the enol ether group giving dihydrothebainone dihydromethine [XVIII] [3], and this is the most satisfactory method of preparing the latter. The dihydromethine [X] may be reduced to [XVIII] under the same conditions [3]. [XVIII] can also be prepared by hydrolysis of dihydrothebaine dihydromethine [X] to dihydrocodeinone dihydromethine [XIX] (also accessible by the chromic acid oxidation of α-tetrahydrocodeimethine [XX] [3]) followed by aluminium amalgam reduction [3].

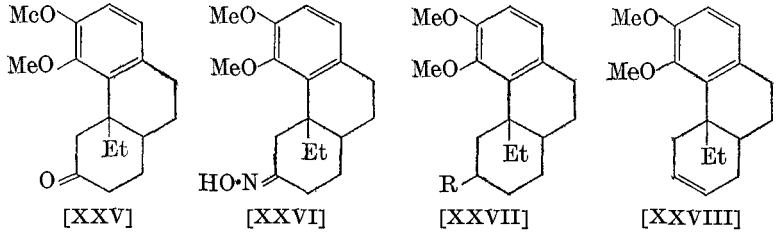
Hydrolysis of dihydrothebaine methine [IX] affords dihydrocodeinone methine [XXI], which can be reduced catalytically to the dihydromethine [XIX] or with aluminium amalgam to dihydrothebainone methine [XXII]. The nitrogen-free product of degradation of dihydrocodeinone methine [XXI] has not been isolated [3]. It was hoped to prepare the Δ^5-enol methyl ether [XXIII] of dihydrothebainone dihydromethine by the sodium and liquid ammonia reduction of dihydrothebaine methiodide, but only a complex mixture of products was obtained in this way. Sodium ammonia reduction of the methiodide of [VII] yielded only the original base, but [XXIII] was finally obtained by the catalytic reduction of dihydrothebaine-ϕ dihydromethine [XXIV] [18].

The degradation of dihydrothebaine has been pursued further by Sargent and Small [16, 19] as follows. The methyl ether [XXV] of [XIV] was converted to the oxime [XXVI], which yielded 6-keto-13-ethyloctahydromorphenol methyl ether [XIII] when subjected to

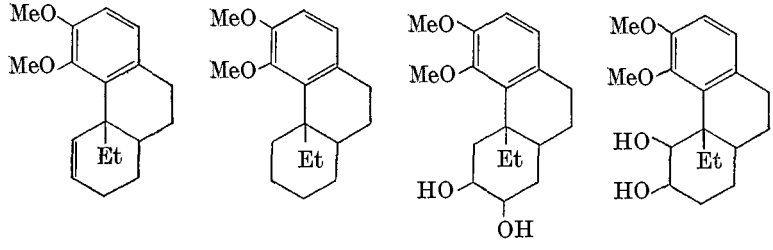


[XXI] [XXII] [XXIII] [XXIV]

Beckmann transformation. Reduction of the oxime, however, afforded a 2:1 mixture of α- and β-3:4-dimethoxy-6-amino-13-ethyloctahydrophenanthrene [XXVII, R = NH_2]. Methylation of the latter gave the corresponding 6-dimethylamino compound [XXVII, R = NMe_2] the methiodide of which was degraded to 3:4-dimethoxy-13-ethyl-9:10:5:13:8:14-hexahydrophenanthrene [XXVIII] or the 7:8:9:10:13:14-hexahydro isomer [XXIX]. This was reduced to 3:4-dimethoxy-13-ethyl-5:6:7:8:9:10:13:14-octahydrophenanthrene [XXX], a crystalline, optically active substance, having the structure assigned by Ghosh and Robinson [20] to an oil obtained by synthesis.

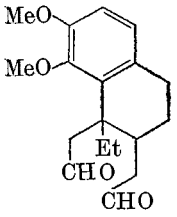


[XXV] [XXVI] [XXVII] [XXVIII]

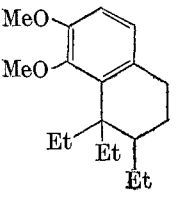


[XXIX] [XXX] [XXXI] [XXXII]

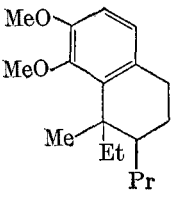
Two isomeric (presumably both *cis*) dihydroxy compounds, either [XXXI] or [XXXII] result from the osmium tetroxide oxidation of the hexahydrophenanthrene [XXVIII] or [XXIX], and these were further oxidized by lead tetra-acetate to aldehydes [XXXIII ?], the thioacetals of which were reduced over Raney nickel when both gave the same oil, believed to be either [XXXIV] or [XXXV], together with a by-product of unknown nature having the same composition as [XXXII]. Internal aldol condensation of the aldehyde could have occurred during the



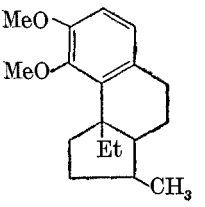
[XXXIII]



[XXXIV]



[XXXV]



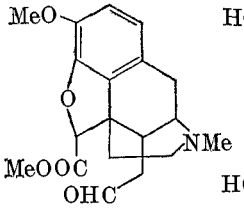
[XXXVI]

reaction, giving as final product a substance such as [XXXVI], but the physical and analytical data suggest that the product is either [XXXIV] or [XXXV] [16].

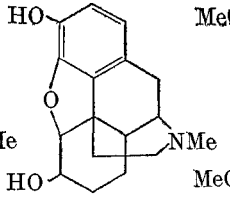
Dihydrothebaine [I] reacts with Grignard reagents with opening of the cyclic ether and entry of an alkyl group into ring C to give alkyldihydrothebainones [6]. The location of the entering group is uncertain [6, 13], but as the products can be converted to alkyldihydrocodeinones and thence to alkyldihydrothebaines [16] elucidation of their structures should be possible by a degradation similar to the above degradation of dihydrothebaine to [XXXIV] or [XXXV]. These compounds are considered in detail in Chapter XIX.

The ozonolysis of dihydrothebaine gives isodihydrothebaizone [XXXVII] [21] (see Chap. XI).

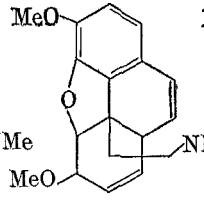
Demethylation of dihydrothebaine has been noticed during the reaction with Grignard reagents (see Chap. XIX) [13].



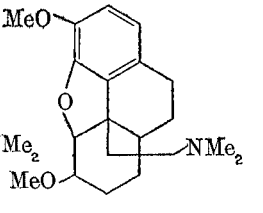
[XXXVII]



[XXXVIII]



[XXXIX]



[XL]

TETRAHYDROTHEBAINE

Tetrahydrothebaine [III] was first prepared by Schöpf and Winterhalder [5] and shown to be identical with dihydromorphine dimethyl ether. It is best prepared from thebaine by hydrogenation of the hydrochloride in glacial acetic acid over platinum oxide [22–23], or of the base in ethanol over W. 6 Raney nickel [24]. It can be demethylated to dihydromorphine by hydriodic acid or aluminium chloride [22–23]. The Hofmann degradation has not been studied, but hydrogenation of α-codeimethine methyl ether [XXXIX] affords α-tetrahydrocodeimethine methyl ether [XL], which is tetrahydrothebaine dihydromethine [25].

Oldenberg [26] prepared a substance that he believed was tetrahydrothebaine, but it was a mixture of substances. The action of cyanogen bromide on this mixture gave an ill defined substance, m.p. approximately 200° C. [27].

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Dihydrothebaine	162–163	EtOAc	(plates) prisms	−266·9	20	benzene	1–3, 5–6
— hydrochloride	..	..	cryst.	..	..	..	1
— picrate	235	EtOH	rods	..	..	..	1
— acid citrate	D. 88–90	EtOH+ benzene	..	..	..	..	2
— methiodide·2H_2O	231	H_2O	prisms	..	..	..	2
— methiodide (anhyd).	257	EtOH	prisms	..	..	..	2
— N-oxide	..	..	oil	..	..	..	1
— N-oxide picrate	209–210	..	needles	..	..	..	1
Cyanonordihydrothebaine	258–259	HOAc	..	..	..	..	1
Dihydrothebaine methine	134–135	EtOH	..	..	..	..	1, 16
— methiodide	243	..	..	..	..	..	1
Dihydrothebaine dihydromethine	..	..	oil	..	..	..	17
— hydrochloride	..	..	cryst.	..	..	..	17
— methiodide	217–222	..	..	..	..	..	17
6-methoxy-13-vinyltetrahydromorphenol methyl ether	123–124·5 120–121	.. EtOH	.. plates	..	..	..	16 15
6-keto-13-vinylhexahydromorphenol methyl ether	149	EtOH	prisms	..	..	..	15
6-keto-13-ethyloctahydromorphenol methyl ether	113	EtOH	rods	..	..	..	15
— semicarbazono	191	EtOH	..	..	..	..	15
6-methoxy-13-vinylhexahydromorphenol methyl ether	119	..	prisms	..	..	..	3
6-methoxy-13-ethylhexahydromorphenol methyl ether	65–66·5	petrol	prisms	−134·0	20	EtOH	16
methyl ether	..	..	..	..	..	..	16
6-keto-13-ethyloctahydromorphol methyl ether	154–155 148–150	.. EtOH	.. prisms	−48·0	20	EtOH	16 3, 15
— isomer	..	..	oil	..	..	..	3, 17
— methyl ether	114–116	subl.	..	−54·2	20	EtOH	16
3-methoxy-4-hydroxy-13-ethyl-octahydrophenanthrene-$\Delta^{5:6}$-methyl enolate	171–173	MeOAc	prisms	+23·8	20	EtOH	16
3:4-dimethoxy-6-amino-13-ethyloctahydrophenanthrene							
— α-base	..	..	oil	..	..	..	16
— α-hydrochloride	138–144 and 211–213	PrOH	prisms	+12·4	20	EtOH	16
— α-perchlorate	197–199	Et_2O+ MeOAc	plates	+8·4	20	EtOH	16
— β-base	..	..	oil	..	..	..	16
— β-hydrochloride	253–255	PrOH	needles	−58·9	20	EtOH	16
— β-perchlorate	..	Et_2O+ Et_2CO	prisms	−63·8	20	EtOH	16
3:4-dimethoxy-6-dimethylamino-13-ethyloctahydrophenanthrene							
— α-base	76·5–78	subl.	..	..	..	..	16
— α-perchlorate	224–225·5	Et_2O+ acetone	needles	+18·8	20	EtOH	16
— α-methiodide	242–244	..	..	..	..	..	16
— β-base	..	..	oil	..	..	..	16
— β-perchlorate	230–231·5	Et_2O+ acetone	prisms	−64·3	20	EtOH	16
— β-methiodide	263–264	..	..	..	..	..	16
3:4-dimethoxy-13-ethyl-9:10:5:13:8:14-octahydrophenanthrene, or isomer	110·5–112	petrol	prisms	+6·8	20	EtOH	16
3:4-dimethoxy-13-ethyl-5:6:7:8:9:10:11:14-octahydrophenanthrene	78·5–80	subl.	..	−32·3	20	..	16

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
3:4-dimethoxy-5:6 (or 6:7)-dihydroxy-13-ethyloctahydrophenanthrene							
—α-	150·5–152 137–142	dry Et_2O petrol	..	−47·6	20	EtOH	16
—β-	119–121	dry Et_2O	..	−11·7	20	EtOH	16
[XXXIV] or [XXXV]?	..	..	oil	−53·0	20	..	16

Tetrahydrothebaine: *see* dihydrocodeine methyl ether, Chap. IV.
Dihydrocodeinone derivatives: *see* Chap. X.
Dihydrothebainone derivatives: *see* Chap. XV.

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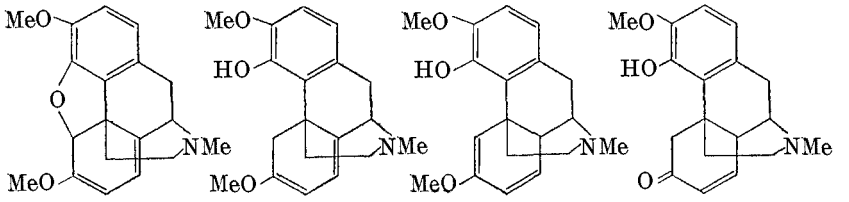
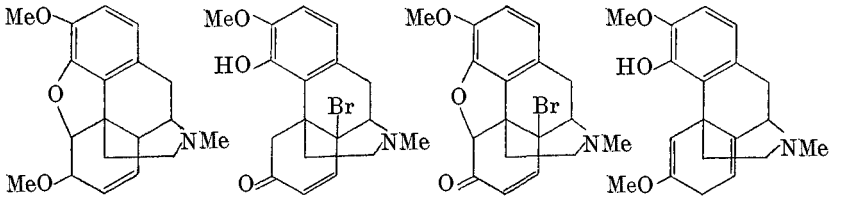
XIV

DIHYDROTHEBAINE-ϕ AND β-DIHYDROTHEBAINE

WHEN thebaine [I] is reduced by sodium and boiling alcohol [1–3], or best by sodium in liquid ammonia [4–5], scission of the 4:5-oxygen bridge occurs with the addition of two atoms of hydrogen and production of a phenolic dihydrothebaine, for which the name dihydrothebaine-ϕ has now been adopted [5]. The sodium-ammonia reduction is rapid, simple, and results in excellent yields of product. Reduction of thebaine with lithium aluminium hydride also yields a phenolic base, β-dihydrothebaine, which is isomeric with dihydrothebaine-ϕ [6]. Dihydrothebaine-ϕ was first allotted the structure [II] on the basis of its reactions [3], and β-dihydrothebaine the structure [III] with the 'abnormal' configuration at C-14 on the basis of its hydrolysis to β-thebainone-A [IV] [6]; thebainone-A enol methyl ether [III] with the 'normal' configuration at C-14, which results from the isomerization of codeine methyl ether [V] under the influence of hot sodium ethoxide, is known to give thebainone-A [IV, C-14 epimer] on hydrolysis [3].



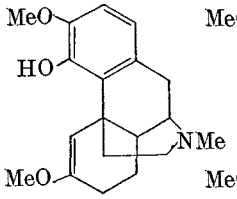


However, the production of a conjugated diene as final product in a sodium-alcohol or sodium-ammonia reduction is contrary to general experience and moreover structure [II] fails to account for the failure of dihydrothebaine-ϕ to condense with maleic anhydride or benzoquinone, or to react with bromine to give a derivative of 14-bromotho-

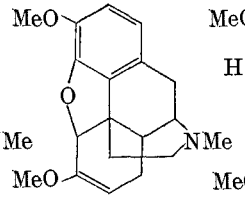
bainone [VI] under conditions under which thebaine [I] is converted to 14-bromocodeinone [VII] [5]; furthermore, it is difficult to reconcile the difference in behaviour on hydrogenation of β-dihydrothebaine (which gives a tetrahydro-derivative) and thebainone-A enol methyl ether (which gives a dihydro-derivative [3]) with the view that they differ only in stereochemistry at C-14. An examination of the infra-red and ultra-violet absorption spectra (Fig. 5) of thebaine, dihydrothebaine-ϕ, β-dihydrothebaine, and numerous 1:4-dihydroanisole derivatives and 1-alkoxy-1:3-dienes led to the allocation of structure [VIII] to dihydrothebaine-ϕ and [II] to β-dihydrothebaine [7], structures in agreement with all the known properties of these bases.

Reduction

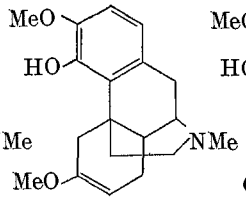
Dihydrothebaine-ϕ absorbs only one mole of hydrogen on catalytic reduction, yielding dihydrothebainone Δ^5-enol methyl ether [IX], which is identical with the product of sodium and liquid ammonia reduction of the non-phenolic dihydrothebaine [X] [5]. (A compound of different melting-point and specific rotation was prepared by Small and Browning [3] by the catalytic reduction of dihydrothebaine-ϕ and allotted the structure [XI] owing to a misconception of the structure of the latter. It is probably a mixture [5].) Dihydrothebainone [XII] is produced by the hydrolysis of [IX] showing that no rearrangement of the thebaine skeleton occurs during sodium and alcohol reduction [5].



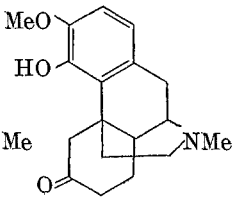
[IX]



[X]



[XI]



[XII]

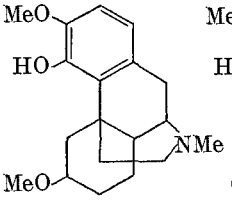
β-Dihydrothebaine [II] absorbs two moles of hydrogen on reduction over platinum oxide, the product being dihydrothebainol-6-methyl ether [XIII] [6], identical with the compound obtained in the reduction of thebaine in neutral solution [3]. The configuration at C-14 in [XIII] is not known. A dihydro-derivative, dihydrothebainone Δ^6-enol methyl ether [XI], can also be isolated from the products of reduction [12].

Thebainone-A enol methyl ether [III] can be reduced catalytically or with sodium and alcohol to dihydrothebainone Δ^6-enol methyl ether [XI] [3, 12] (erroneously given the Δ^5 structure [IX] at first [3]) and from the catalytic reduction dihydrothebainol-6-methyl ether, identical with the compound obtained from β-dihydrothebaine, is also obtained [12]. The fact that thebainone-A enol methyl ether and β-dihydrothebaine

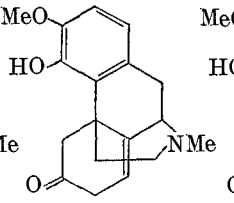
give identical dihydro- and tetrahydro-derivatives serves to confirm the structure [II] for β-dihydrothebaine [12].

HYDROLYSIS

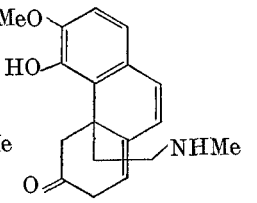
The hydrolysis of dihydrothebaine-ϕ is complicated and four different products have been isolated.



[XIII]



[XIV]



[XV]

(*a*) Mineral acid hydrolysis, first stated to give an ill defined substance called 'isocodeine' [1] (a bad name) and later 'a coloured, varnish-like substance' [3], has been shown to give thebainone-B [XIV] [8]. This compound is only stable as a dry salt; the free base and the damp salts readily degenerate to tars. It is a $\beta:\gamma$-unsaturated ketone and gives dihydrothebainone [XII] on reduction [8] (see Chap. XV).

(*b*) Hydrolysis with aqueous potassium bisulphate gives mainly β-thebainone-A [IV] with the 'abnormal' configuration at C-14, together with a small amount of thebainone-A [IV, C-14 epimer] and a small amount of thebainone-C [XV] [3]. Thebainone-β is doubtless an intermediate in this hydrolysis, as it is converted to β-thebainone-A on standing in aqueous potassium bisulphate [8].

(*c*) Hydrolysis with sulphurous acid affords a poor and erratic yield of thebainone-C, first tentatively allotted the formula [XIV] [3], but now known to have suffered fission of the nitrogen-containing ring and to be a secondary amine [XV] [8].

The hydrolysis of β-dihydrothebaine has not been extensively studied; with aqueous potassium bisulphate it is converted to β-thebainone-A [IV] [6], but as dihydrothebaine-ϕ also gives β-thebainone-A under the same conditions the reaction cannot be regarded as having any structural significance.

Thebainone-A enol methyl ether gives thebainone-A on hydrolysis so readily that no salts of the enol ether can be prepared even in anhydrous media [3].

Dihydrothebaine-ϕ methiodide undergoes hydrolysis with fission of the nitrogen-ring on boiling with sulphurous acid [1, 5] or mineral acid [5] giving thebainone-B methine [XVI] (the melting points of the hydrolysis product and its derivatives as recorded by Freund and Holtoff [1] differ widely from those observed by the author [5]). This has been given the structure [XVI] on account of the similarity of its ultra-violet

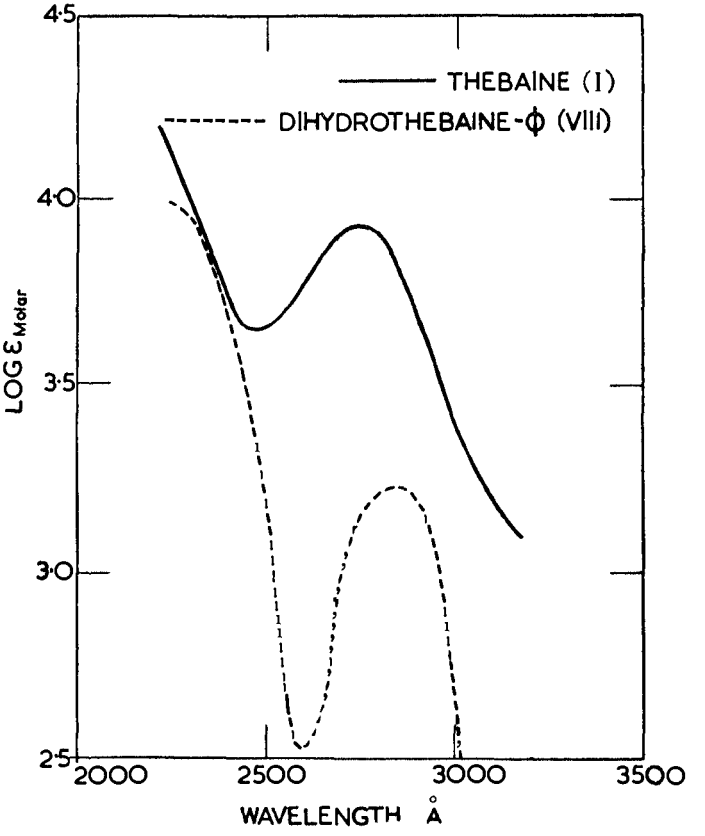
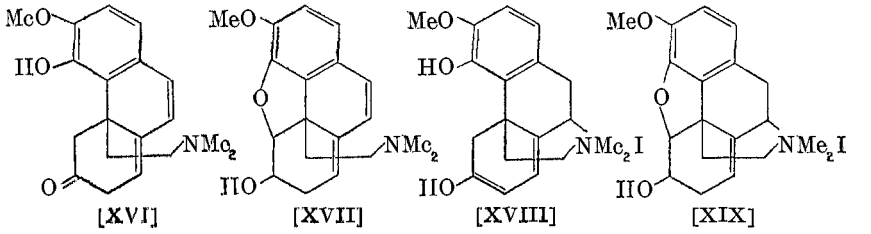


FIG. 5.

absorption spectrum to that of β-codeimethine [XVII] [5] (Fig. 6). It is also obtained by the hydrolysis of β-dihydrothebaine methine (see below), thebainone-B methiodide, and possibly β-dihydrothebaine methiodide [5]. The intermediate in all these reactions is doubtless thebainone-B methiodide which, in its enolic form [XVIII], allows the formation of a conjugated system by fission of the nitrogen ring with the introduction of a 9:10-double bond. Neopine methiodide [XIX], which cannot develop a similar conjugated system, is unaffected by hot acids [5].



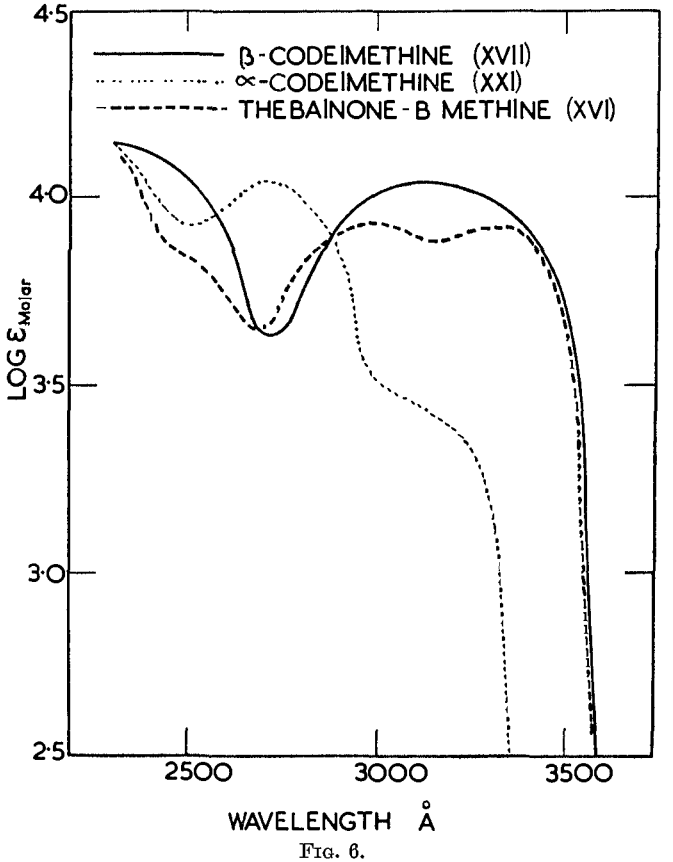


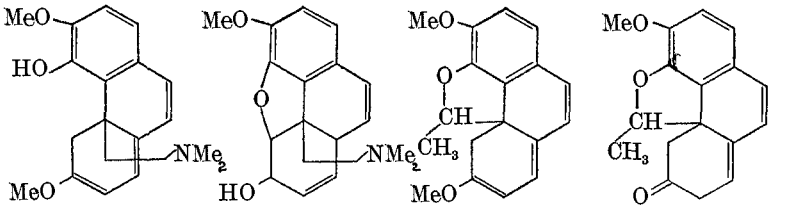
FIG. 6.

The methyl ether of [XVI] arises from acid hydrolysis of dihydrothebaine-ϕ methyl ether methiodide and β-dihydrothebaine methyl ether methine [5].

HOFMANN DEGRADATION

Contrary to the statement of Freund and Holtoff [1], dihydrothebaine-ϕ methiodide readily undergoes alkaline degradation with production of a methine base [4–5], which is allotted the structure [XX] and the name β-dihydrothebaine methine, as its ultra-violet absorption spectrum clearly indicates the conjugation of more than two double bonds with the aromatic nucleus [5, 8] (Fig. 7). Migration of the 5:6-double bond into conjugation with those at 8:14 and 9:10 doubtless occurs under the influence of the hot alkali (compare the conversion of α-codeimethine [XXI] to β-codeimethine [XVII], Chap. VI). Mineral acid hydrolysis of [XX] yields [XVI], and catalytic hydrogenation affords a tetrahydroderivative [4–5]. Hofmann degradation of dihydrothebaine-ϕ methyl ether methiodide gives the methyl ether of [XX] [5, 9], which is

very unstable and spontaneously loses amine on standing [5]; it can be hydrolysed to thebainone-B methyl ether methine [5].



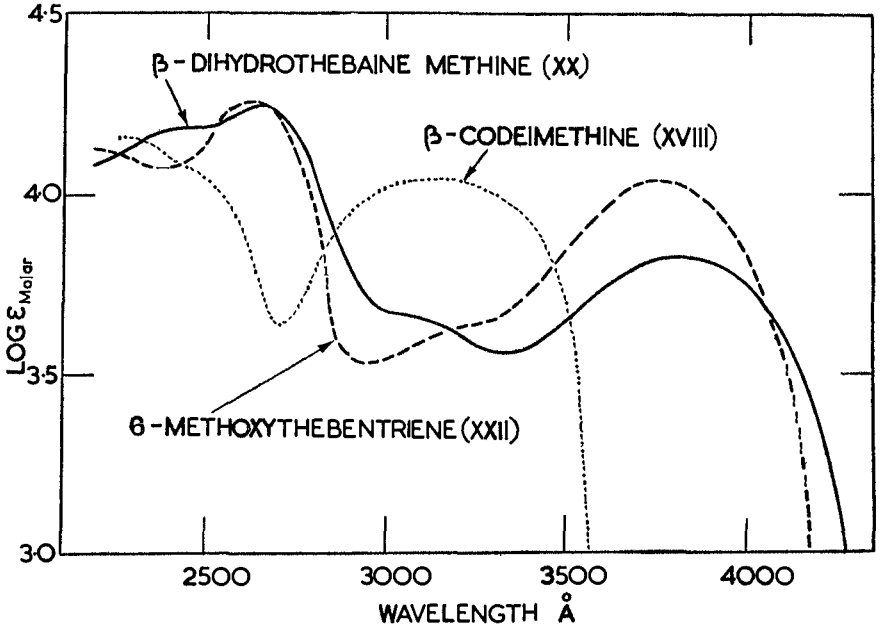
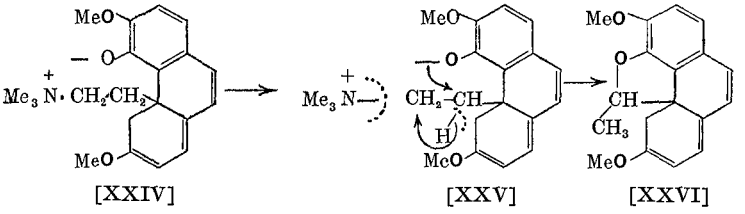


FIG. 7.

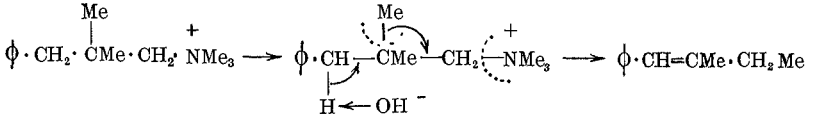
Further degradation of β-dihydrothebaine methine proceeds with ease, cyclization of the residue of the side-chain with the phenolic hydroxyl group occurring, the product being 6-methoxythebentriene [XXII] [5]. When this cyclization cannot occur, in the methyl ether, the entire side-chain is lost and 3:4:6-trimethoxyphenanthrene is formed [9]. It is reasonable to suppose that a vinyl group does not appear as such at C-13 during the degradation of [XX] as it would immediately be lost as ethylene, there being no feasible mechanism by which such a group could undergo cyclization with the phenolic hydroxyl group in alkaline solution. The ease of loss of trimethylamine in all degradations resulting in this type of cyclization suggests that the same

mechanism is operative in all cases, and this is probably as set out in [XXIV] to [XXVI] below. In a similar manner [XXVII] degrades to [XXIX] [10].



[XXIV] [XXV] [XXVI]

Migration of H^-

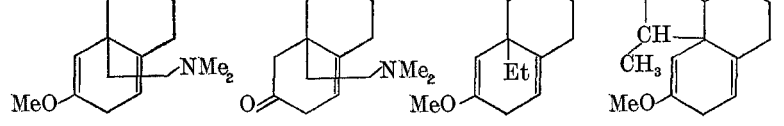


[XXVII] [XXVIII] [XXIX]

Migration of Me^-

Acid hydrolysis of 6-methoxythebentriene affords 8:14:9:10-tetradehydrothebenone [XXIII] [4–5].

The reduction of thebaine methiodide with sodium in liquid ammonia leads to dihydrothebaine-ϕ dihydromethine [XXX], also accessible by the reduction of dihydrothebaine-ϕ methiodide; the methyl ether can be prepared in the same way from dihydrothebaine methyl ether methiodide. [XXX] can be hydrolysed by mineral acids to thebainone-B dihydromethine [XXXI], and reduced with difficulty to dihydrothebainone dihydromethine Δ^5-enol methyl ether. Its methiodide on reduction with sodium and ammonia yields 4-hydroxy-3:6-dimethoxy-13-ethyl-7:13:9:10-tetrahydrophenanthrene [XXXII] and on alkaline degradation gives $\Delta^{5,8}$-6-methoxythebendiene [XXXIII] [11].



[XXX] [XXXI] [XXXII] [XXXIII]

The hydroxyl group of dihydrothebaine-ϕ is unreactive and cannot be methylated with diazomethane [5], though the methyl ether methiodide can be formed by heating the base with sodium ethoxide and methyl iodide [9]; the acetyl ester can be obtained by the prolonged action of ketene on the phenol; other acetylating agents give only intractable products [5].

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Dihydrothebaine-ϕ	154	EtOAc+ petrol	prisms	+25·5 +31·4	27 18	EtOH EtOH	3 5
— picrate	176d.	EtOH+ benzene	needles	..	..	..	5
— methiodide·EtOH	155–160	EtOH	prisms	..	..	..	1
— methiodide·$3H_2O$	75–80	H_2O	needles	..	..	..	1
— methyl ether methiodide	192	EtOH	..	..	..	..	9
O-acetyldihydrothebaine-ϕ	139	petrol	prisms	..	..	..	5
- picrate	180d.	β-ethoxy-ethanol	prisms	..	..	..	5
β-dihydrothebaine	171–172	Et_2O+ EtOH	..	+307·0	18	..	6
— picrate	..	..	..	..	..	..	6
— methiodide	..	Et_2O+ pyridine	..	..	..	..	6
Thebainone-A enol methyl ether	154–156	EtOH	granules	+9·6	22	EtOH	3
β-dihydrothebaine methine	99	MeOAc or petrol	cubes	..	..	..	5
— picrate	159	(decomp.)	scarlet prisms	..	..	..	5
— methiodide	..	.	oil	..	..	..	5
— methoperchlorate	134	H_2O+ EtOH	apple-green needles	..	..	..	5
β-dihydrothebaine methyl ether methine	..	..	oil	..	..	..	5, 9
Tetrahydro-(β-dihydrothebaine methine)	..	..	oil	0·0	20	EtOH	5
6-methoxythebentriene	88	petrol	yellow prisms	..	..	..	5
Dihydrothebaine-ϕ dihydromethine	88–89	Et_2O	leaflets	+94·5	17	EtOH	11
— methiodide	.	.	oil	.	..	..	11
— methoperchlorate·$\frac{1}{2}H_2O$	253	H_2O	needles	.	..	..	11
Dihydrothebaine-ϕ methyl ether dihydromethine	..	..	oil	..	..	..	11
4-hydroxy-3:6-dimethoxy-13-ethyl-7:13:9:10-tetrahydrophenanthrene	..	..	oil	..	..	..	11
$\Delta^{5,8}$-6-methoxythebendiene	..	..	oil	..	..	..	11
Thebainones and their derivatives. Dihydrothebainone and its derivatives. Tetradehydrothebenone	*see* Chap. XV.						

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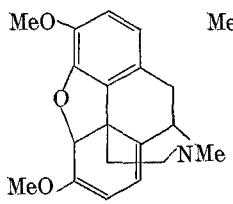
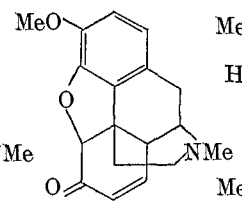
XV

THE THEBAINONES AND THEIR DERIVATIVES

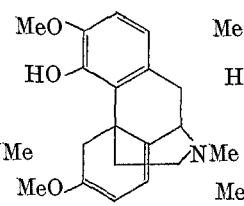
THE term 'thebainone' is applied to ketones of the morphine group having a phenolic hydroxyl at position 4 and a carbonyl group and one double bond in ring C. Strictly they are not ketones related to thebaine [I], which is an enol ether of codeinone [II], but to β-dihydrothebaine [III] and dihydrothebaine-φ [IV]. Four thebainones are known, not including metathebainone which is the product of a rearrangement of the thebaine skeleton and has the basic side-chain attached to C·14; it is discussed separately in Chapter XVI. References to 'thebainone' in the literature prior to 1927 refer to metathebainone.



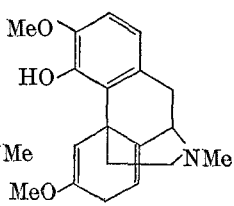
[I]



[II]



[III]



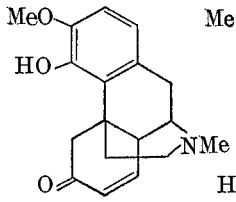
[IV]

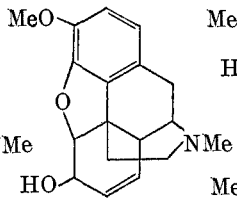
THEBAINONE-A

Thebainone-A [V] results from thebaine or codeinone when these bases are reduced with stannous chloride and concentrated hydrochloric acid under conditions different from those required for the preparation of metathebainone, which nevertheless is formed at the same time in small amount [1]. (A small amount of a by-product m.p. 156–158° C. was also obtained during one reduction of thebaine [1].) Thebaine hydrochloride and stannous chloride in acetic acid at 160° C. yield methebenine [1] (see Chap. XXV).

Thebainone-A can also be prepared by the catalytic rearrangement of codeine [VI] under the influence of palladized charcoal at 80° C. [2]; by the hydrolysis of thebainone-A enol methyl ether [VII] (prepared by the rearrangement of codeine methyl ether on heating with sodium ethoxide) [3]; by the hydrolysis of β-ethylthiocodide [VIII] (obtained by the action of sodium ethoxide on bromo- or β-chlorocodide) [4–8] (see Chap. XVII) and, in small amount, by the hydrolysis of dihydrothebaine-φ [IV] [3].

Catalytic reduction of thebainone-A proceeds readily with formation of dihydrothebainone [IX], which is formed in considerable quantity in


[V]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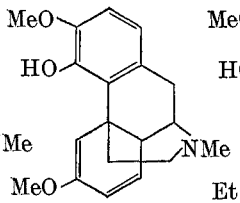
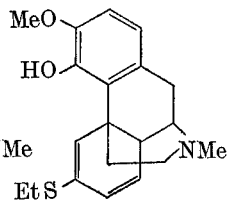
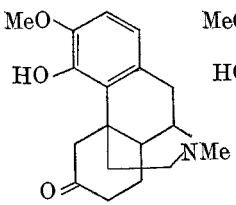
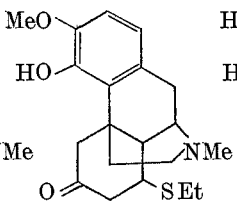

[VII]

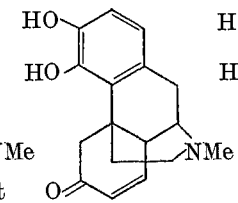

[VIII]

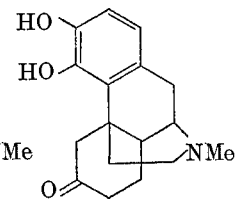
the mild catalytic hydrogenation of thebaine [9–12], so the basic thebaine skeleton must be intact in thebainone-A [1]. It behaves in general as an $\alpha:\beta$-unsaturated ketone, suffering addition of ethyl mercaptan in acid solution to give ethylthiodihydrothebainone [X], which is also obtainable from β-ethylthiocodide [8]. Its infra-red absorption spectrum is also consistent with an $\alpha:\beta$-unsaturated ketone structure [13] (see below). The nitrogen ring of thebainone-A is less stable than that of metathebainone and on heating with sodium acetate and acetic anhydride the methiodide is degraded to 3:4:6-triacetoxyphenanthrene [1]. The demethylation of the 3-methoxyl group under these conditions is unusual.

Thebainone-A enol methyl ether [VII] is described in Chapter XIV. It is the enol ether directly related to thebainone-A, which it yields so readily on hydrolysis that no salts of the enol ether can be prepared even in anhydrous media [3].


[IX]


[X]


[XI]


[XII]

O-Desmethylthebainone-A

O-desmethylthebainone-A [XI], the morphine analogue of thebainone-A, results from the catalytic rearrangement of morphine in the presence of palladized charcoal at 80° C. [2]; it is doubtless identical with the ketone obtained by the hydrolysis of β-ethylthiomorphide [14–15]. Although it cannot be methylated to thebainone-A, on reduction it yields O-desmethyldihydrothebainone [XII], which gives dihydrothebainone on treatment with diazomethane [2].

β-Thebainone-A

This substance is the main product of hydrolysis of dihydrothebaine-ϕ [IV] [3] and β-dihydrothebaine [III] [16] with potassium bisulphate

solution. The isomerism of thebainone-A and β-thebainone-A is not due to the difference in position of the double bond, as the infra-red absorption spectra show that both are α:β-unsaturated ketones [13], and moreover the isomerism persists after hydrogenation and when β-dihydrothebainone, the product of hydrogenation of β-thebainone-A, is degraded to a nitrogen-free product, at each stage of which compounds are obtained that are isomeric with those derived from dihydrothebainone [3].

The cause of the isomerism is the asymmetric carbon atom C-14, which in thebainone-A and its derivatives is configured as in codeine but has the opposite configuration in β-thebainone-A. Although the latter could arise from β-dihydrothebaine [III] by a 1:4-hydrolysis of the system MeO·C=C—C=C, such a mechanism seems unlikely as it cannot be operative in the hydrolysis of dihydrothebaine-φ [IV] during which β-thebainone-A must be formed by the isomerization of thebainone-B, a reaction that has been independently realized [13] (see below).

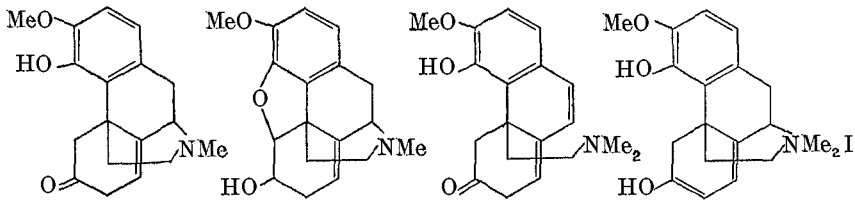
No enol ether of β-thebainone-A epimeric with thebainone-A enol methyl ether [VII] has been prepared; β-dihydrothebaine was first thought to be such a compound [16] but subsequently was shown to have the structure [III] [17].

THEBAINONE-B

Thebainone-B [XIII] is best prepared as its hydrobromide by the hydrolysis of dihydrothebaine-φ [IV] with alcoholic hydrobromic acid [13], but it is also formed by the hydrolysis of the same base with mineral acid in aqueous solution [13], a reaction first reported to give an ill-defined substance, 'isocodeine' [18], and later said to give a 'coloured, varnish-like substance' [3]. Thebainone-B appears to be stable only as its salts in the dry state, the damp salts and free base readily degenerating to brown tars [13]. The ultra-violet spectra of thebainone-A, β-thebainone-A, and thebainone-B closely resemble those of dihydrothebaine-φ and codeine, whilst that of thebainone-C is widely different (Fig. 8) and the frequencies of the carbonyl-absorption in the infra-red indicate that whereas thebainone-A and β-thebainone-A are α:β-unsaturated ketones, the unsaturation is β:γ- in thebainone-B and thebainone-C [13]. On this evidence thebainone-B is allotted the structure [XIII]. It can be catalytically reduced to dihydrothebainone [IX], in which the configuration at C-14 is the same as in codeine [13] (cf. the production of dihydrocodeine on reduction of neopine [XIV] [19]).

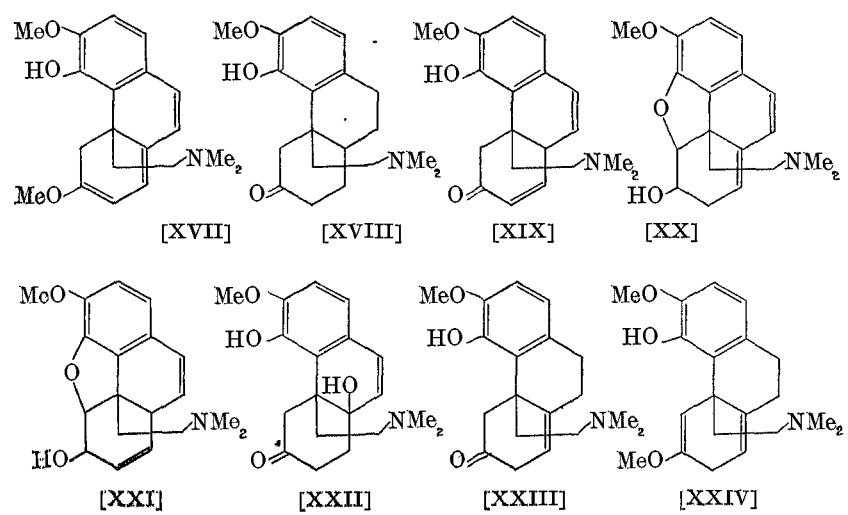
Thebainone-B is doubtless an intermediate in the hydrolysis of dihydrothebaine-φ to β-thebainone-A, to which it is converted on standing in aqueous potassium bisulphate for twenty hours [13].

Hofmann degradation of thebainone-B has not been attempted, but thebainone-B methine [XV] is formed when dihydrothebaine-φ meth-



iodide or thebainone-B methiodide is heated with sulphurous acid or mineral acid [20–21]. The intermediate in this reaction is doubtless thebainone-B methiodide which, in its enolic form [XVI], allows the formation of a conjugated system by fission of the nitrogen ring with the introduction of a 9:10 double bond. The methiodide of neopine [XIV], which cannot develop a similar conjugated system, is unaffected by hot acids [5]. Thebainone-B methine can also be prepared by the hydrolysis of β-dihydrothebaine methine [XVII], and its methyl ether by the hydrolysis of dihydrothebaine-φ methyl ether methiodide or of β-dihydrothebaine methyl ether methine [21].

Hydrogenation of thebainone-B methine proceeds rapidly, with the absorption of two moles of hydrogen and production of β-dihydrothebainone dihydromethine [XVIII] [20–21]; this is the only case in morphine series in which reduction of an 8:14 double bond results in configuration of the asymmetric carbon atom C-14 in the 'abnormal' manner. The possibility of thebainone-B methine having the isomeric structure [XIX] is ruled out by the ultra-violet absorption spectrum, which is closely similar to that of β-codeimethine [XX] and dissimilar from that of α-codeimethine [XXI] (Fig. 9) [21].



A compound allotted the structure [XV] was reported by Schöpf and Borkowsky [22] to result from the dehydration of 14-hydroxydihydrothebainone methine [XXII], but whereas [XV] gives β-dihydrothebainone

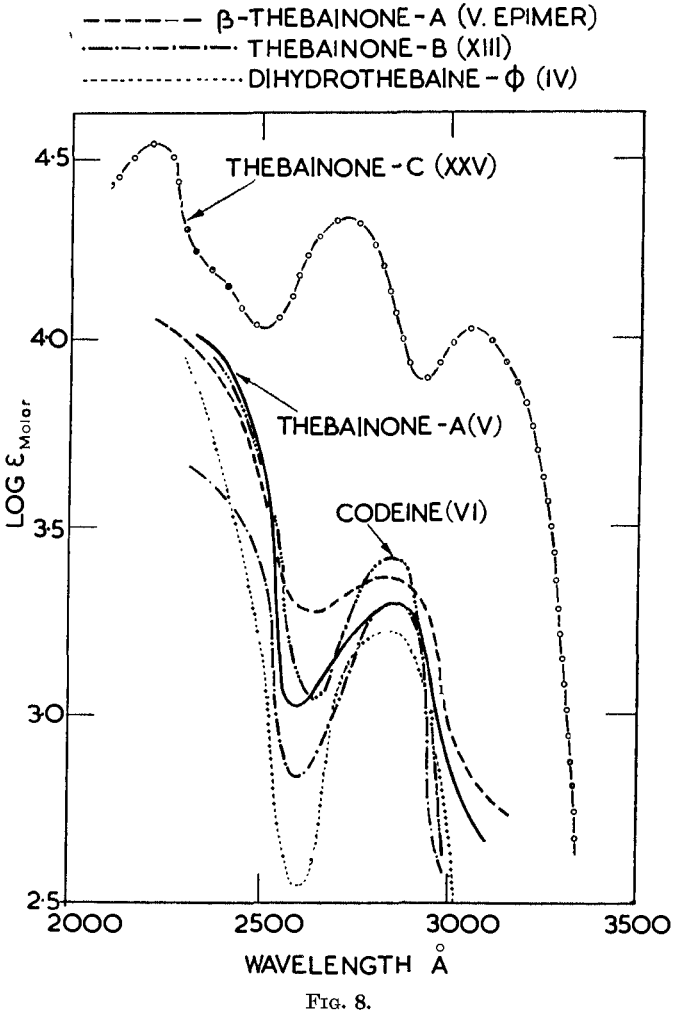


FIG. 8.

dihydromethine [XVIII] on hydrogenation, the base of Schöpf and Borkowsky gave a different substance that was not analysed.

Thebainone-B dihydromethine [XXIII] may be obtained by the hydrolysis of dihydrothebaine-ϕ dihydromethine [XXIV], which is formed from thebaine methiodide by reduction with sodium in liquid ammonia [23].

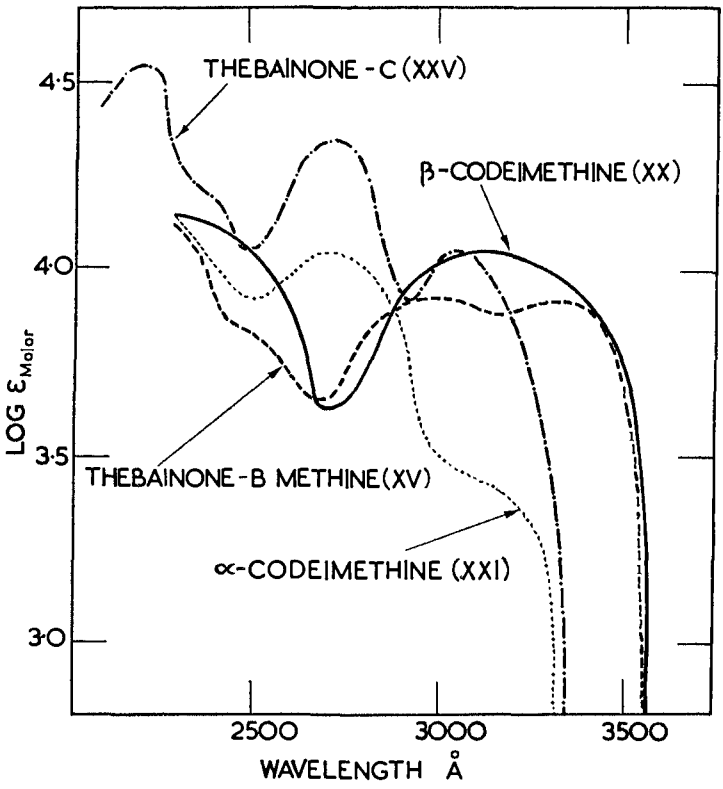
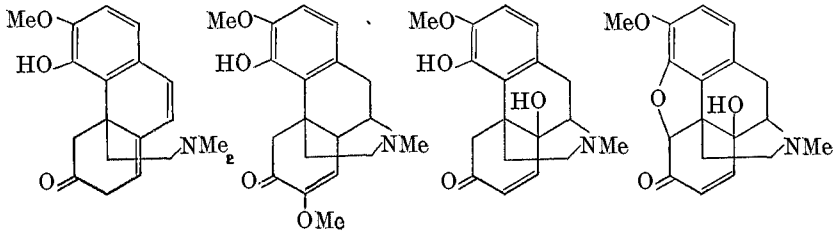


FIG. 9.

THEBAINONE-C

This isomer is obtained in erratic yield by the hydrolysis of dihydrothebaine-ϕ by sulphurous acid. It was initially allotted the structure [XIII] [3], but has since been shown to have the structure [XXV], which is allotted to the base on account of the ultra-violet absorption spectrum, which indicates a highly conjugated system (Figs. 8 and 9), and the infra-red absorption, which indicates that the compound is a $\beta:\gamma$-unsaturated ketone [13]. It is apparently formed during the hydrolysis



[XXV] [XXVI] [XXVII] [XXVIII]

of dihydrothebaine-ϕ independently of thebainone-B, which cannot be isomerized to thebainone-C by sulphurous acid [13].

Sinomenine

This alkaloid, which can be obtained from the plant *Sinomenium acutum*, is now recognized as the optical antipode of 7-methoxythebainone [XXVI]. It can be converted to the antipode of dihydrothebainone. Sinomenine and its derivatives are fully discussed in Chapter XXVI.

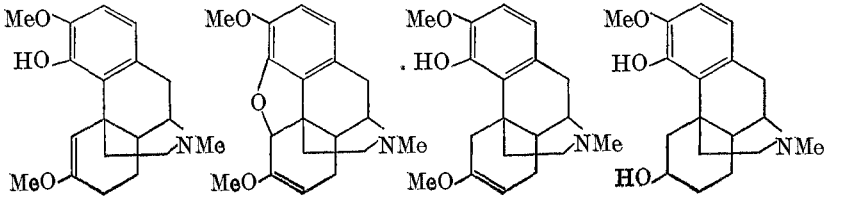
14-Hydroxythebainone [XXVII], which results from the stannous chloride reduction of 14-hydroxycodeinone [XXVIII] [24], is discussed in Chapter XVIII.

Dihydrothebainone

Dihydrothebainone [IX], obtained by the catalytic reduction of thebainone-A [V] [1] and thebainone-B [XIII] [13], can be most conveniently prepared by the catalytic reduction of thebaine in acid solution [9–12, 25], and it can also be obtained by the hydrolysis of its two enol ethers (see below). It is a phenolic, ketonic, base, that shows the diazo-reaction in dilutions up to 1 in 2,000,000 [26–27], gives a methyl ether [28], oxime [9], semicarbazone [29], and a benzylidene [30] and piperonylidene [25] derivative. The optical antipode is produced by the sodium amalgam reduction of sinomenine [XXVI] and is known as desmethoxydihydrosinomenine [31].

Dihydrothebainone Δ^5-enol Methyl Ether

This compound [XXIX] is produced by the catalytic reduction of dihydrothebaine-ϕ and is obtained as large prisms, m.p. 145–146° C., $[\alpha]_D^{17} = -61{\cdot}5°$ (alcohol) [21]. Small and Browning [3] in this way obtained a base as plates, m.p. 127–128° C., $[\alpha]_D^{27} = -8{\cdot}0°$ (alcohol), but it is believed that the compound m.p. 145–146° C. is in fact the authentic Δ^5-enol ether as it is obtained in 95 per cent. yield by the sodium and liquid ammonia reduction of dihydrothebaine [XXX] [21]. This substance, which is very readily hydrolysed to dihydrothebainone [IX] [21], is no doubt the intermediate in the production of the latter by the reduction of dihydrothebaine [XXX] catalytically or with sodium



[XXIX] [XXX] [XXXI] [XXXII]

and amyl alcohol [9], being hydrolysed during the isolation of the product.

Dihydrothebainone Δ^6-enol Methyl Ether

This enol ether [XXXI] is the product of catalytic or sodium amalgam reduction of thebainone-A enol methyl ether [VII] [3], from which it arises by 1:4-addition of hydrogen to the conjugated system, and it can also be prepared by the hydrogenation of thebaine in neutral solution [3]. It is very readily hydrolysed to dihydrothebainone, which doubtless arises from this during the reduction of thebaine in acid solution. (Dihydrothebainone was prepared by Speyer and Freunds [10] by the reduction of thebaine in neutral solution and no doubt arose from the enol ether by hydrolysis during the isolation of the product.)

β-Dihydrothebainone

β-Dihydrothebainone, the C-14 epimer of dihydrothebainone, can be obtained by the catalytic reduction of β-thebainone-A [3]. The physical properties of its oxime agree well with those reported for 'epidihydrothebainone' oxime isolated in very small yield from the products of reduction of thebaine [22, 32] (see Chap. XII).

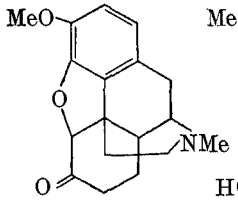
Reduction of the Dihydrothebainones

(*a*) Catalytic hydrogenation of dihydrothebainone affords the alcohol dihydrothebainol-B [XXXII] [11], which also results from the catalytic reduction of codeinone [II] [33] (see Chap. X). The optical antipode of this compound has been prepared in the sinomenine series [34–35], and the C-14 epimer by the catalytic reduction of β-dihydrothebainone [36].

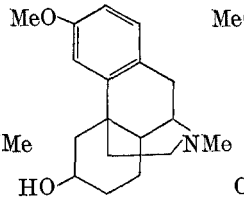
(*b*) The C-6 epimer of dihydrothebainol-B results from the sodium amalgam [35, 37] and sodium and liquid ammonia [38] reduction of dihydrothebainone [IX], and the sodium amalgam reduction of dihydrocodeinone [XXXIII] [34]; it is also obtained as a by-product during the electrolytic reduction of dihydrothebainone [39]. Its optical antipode, desmethoxydesoxydihydrosinomeninol, has been prepared from sinomenine [34–35, 40–42].

(*c*) The electrolytic reduction of dihydrothebainone was reported by Speyer and Siebert [39] to give 'dihydrothebacodine', which was alkali-insoluble, reacted with phosphorus pentachloride to give chlorodihydrothebacodide, reduction of which afforded desoxydihydrothebacodine. On this evidence dihydrothebacodine was allotted the structure [XXXIV] and the chloro- and desoxy-compounds structures [XXXV] and [XXXVI] respectively.

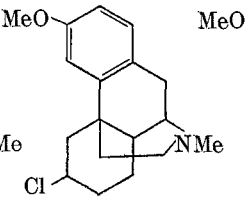
(*d*) Clemmensen reduction of dihydrothebainone and of dihydrocodeinone [XXXIII] yields a compound of the same composition as, and having the same physical properties as, dihydrothebacodine [34, 42–43].



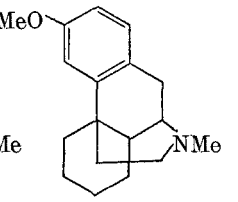
[XXXIII]



[XXXIV]



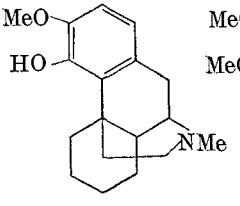
[XXXV]



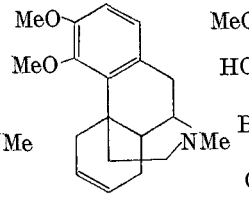
[XXXVI]

It is very probable that the latter is in fact tetrahydrodesoxycodeine [XXXVII], in which the phenolic group is inert. All preparations having the properties of dihydrothebacodine that have been directly compared with tetrahydrodesoxycodeine have been found to be identical with the latter [34, 43–44]. Speyer and Siebert claimed that a smooth reaction occurs between 'dihydrothebacodine' and phosphorus pentachloride [39], but tetrahydrodesoxycodeine is recovered in 90 per cent. yield on treatment with this reagent, and Small and Cohen were unable to isolate from the products of electrolytic reduction of dihydrothebainone any compound that reacts with phosphorus pentachloride [44].

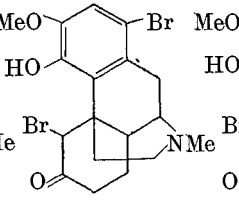
The high-melting dihydrothebainol-B [XXXII] (from the catalytic reduction of dihydrothebainone) and its C-14 epimer can be dehydrated through the toluene sulphonyl esters to two isomers of dihydrodesoxycodeine-B methyl ether [XXXVIII], one of which, having the 'abnormal' configuration at C-14, is identical with a substance prepared as racemate by synthesis [36] (see Chap. XXVIII).



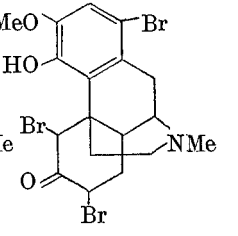
[XXXVII]



[XXXVIII]



[XXXIX]



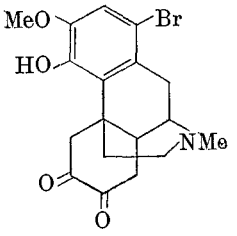
[XL]

Bromination of Dihydrothebainone

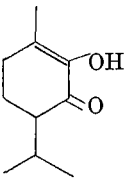
Bromination of dihydrothebainone proceeds with the formation of 1-bromodihydrothebainone with one mole of bromine, 1:5-dibromodihydrothebainone [XXXIX] with two moles of bromine [45], and 1:5:7-tribromodihydrothebainone [XL] with three moles of bromine [46]. Treatment of the 1:5-dibromo-compound [XXXIX] with alkali results in loss of hydrogen bromide and closure of the 4:5 ether bridge, the product being 1-bromodihydrocodeinone, reductive debromination of which affords dihydrocodeinone [XXXIII] [45, 47]; the latter can be converted

back to dihydrothebainone by reduction with zinc and alcohol [45]. Closure of the 4:5-oxygen bridge has also been effected in the sinomenine series [45].

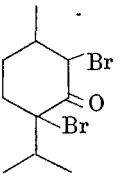
In the preparation of 1-bromodihydrocodeinone in this way small amounts of 1-bromodihydrothebainone and (—) 1-bromosinomeninone [XLI] are also obtained. The latter no doubt arises from 1:5:7-tribromodihydrothebainone [XL], from which indeed it can be made by treating



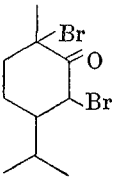
[XLI]



[XLII]

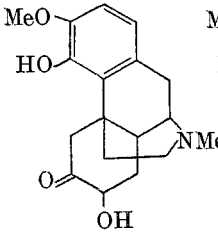


[XLIII]

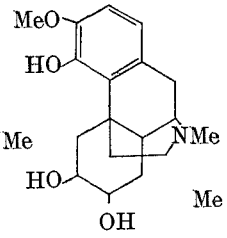


[XLIV]

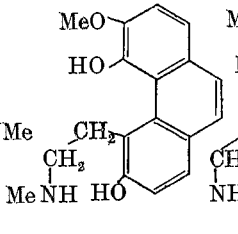
the latter with potassium carbonate in methanol [46]. The production of [XLI] from [XL] is analogous to the formation of buchucamphor [XLII] from dibromomenthone [XLIII] or dibromocarvomenthone [XLIV] [48]. (+) 1-Bromosinomeninone is available from sinomenine [49]. Catalytic reduction of (—) 1-bromosinomeninone gives α- and β-7-hydroxydihydrothebainone [XLV] [50] and 7-hydroxydihydrothebainol [XLVI] [51]; acetic anhydride degradation gives 1-bromo-4:6-diacetoxy-3-methoxyphenanthrene and 1-bromotri*acetyliso*thebenine (*iso*thebenine is probably either [XLVII] or [XLVIII]) [46].



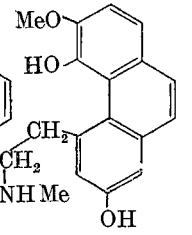
[XLV]



[XLVI]



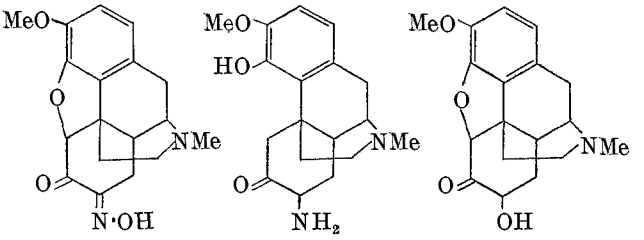
[XLVII]



[XLVIII]

1-Bromothebainone-A may be prepared by the bromination of thebainone-A [52].

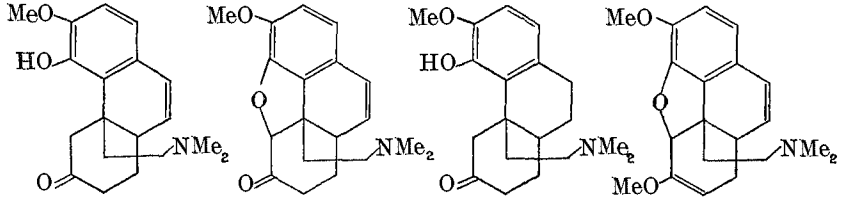
Closure of the 4:5-oxygen bridge in the dihydrothebainone series may be effected in another way as follows. 7-*iso*nitrosodihydrocodeinone [XLIX] yields 7-aminodihydrothebainone [L] on reduction, and the benzyl ether of this on diazotization in N sulphuric acid undergoes ring closure with loss of the benzyl group, the product being 7-hydroxydihydrocodeinone [LI] [53–54].



[XLIX] [L] [LI]

HOFMANN DEGRADATION OF DIHYDROTHEBAINONE

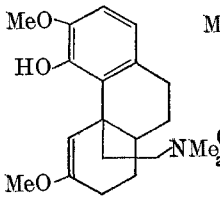
The alkaline degradation of dihydrothebainone methiodide affords dihydrothebainone methine [LII] [9], also accessible by the aluminium amalgam reduction of dihydrocodeinone methine [LIII] [25]. It can be reduced catalytically to dihydrothebainone dihydromethine [LIV] [9], which is best prepared by the catalytic reduction of dihydrothebaine methine [LV] in dilute acetic acid [25]. β-Dihydrothebainone can in the same way be converted to β-dihydrothebainone methine and β-dihydrothebainone dihydromethine [3], the latter being most conveniently prepared by the hydrogenation of thebainone-B methine [XV] [20–21].

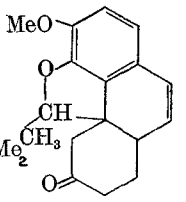


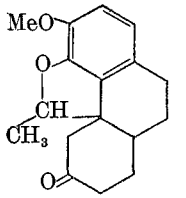
[LII] [LIII] [LIV] [LV]

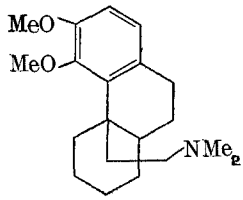
Dihydrothebainone dihydromethine Δ^5-enol methyl ether [LVI] results from the hydrogenation of dihydrothebaine-φ dihydromethine [XXIV] [23].

Further Hofmann degradation of dihydrothebainone methine has not been carried out, but its optical antipode, desmethoxydihydrosinomenine methine, has been degraded to (—) 9:10-dehydrothebenone [LVII] [55]. Dihydrothebainone dihydromethine [LIV] and its β-isomer have been degraded to thebenone [LVIII] [25] and β-thebenone [3] respectively and the antipode of the first of these can be prepared from desmethoxydihydrosinomenine dihydromethine [55]. Such a cyclic ether structure is invariably obtained by the exhaustive methylation of a morphine alkaloid derivative having a free hydroxyl group at position 4. The methyl ethers of [LII] and [LIV] resist further degradation [28], as does tetrahydrodesoxycodeine methyl ether dihydromethine [LIX], which results from the Clemmensen reduction of [LIV] methyl ether [28].

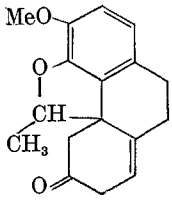

[LVI]

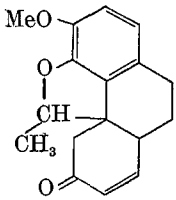

[LVII]

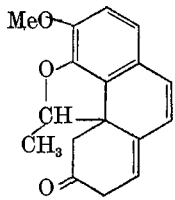

[LVIII]

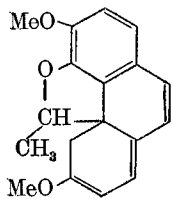

[LIX]

Thebainone-B dihydromethine [XXIII] was expected to give 8:14-dehydrothebenone [LX] on degradation, but partial isomerism probably occurred in alkaline solution as the product was clearly a mixture, doubtless of [LX] and [LXI] [23]. 8:14:9:10-Tetradehydrothebenone [LXII] is produced by the hydrolysis of 6-methoxythebentriene [LXIII] [21] (see Chap. XIV).


[LX]

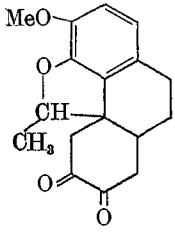

[LXI]

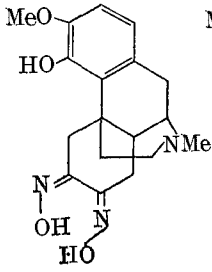

[LXII]

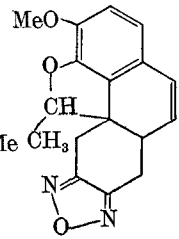

[LXIII]

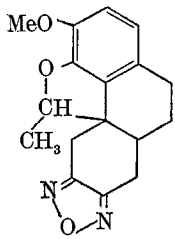
Bromination of thebenone gives a mixture of products that cannot be separated, but degradation of the corresponding derivatives of 1-bromodihydrothebainone or 1-bromodesmethoxydihydrosinomenine affords enantiomorphic forms of 1-bromothebenone and 1-bromo-9:10-dehydrothebenone; an isomer of the latter, (+) 9?-bromo-9:10-dehydrothebenone, results from the bromination of (+) 9:10-dehydrothebenone [56].

(+) and (−) thebenone on oxidation with chromic acid are converted into (+) and (−) thebenone ketone [LXIV?] respectively [25, 57]. Sinomeninone dioxime [LXV] can be exhaustively methylated to give


[LXIV]


[LXV]

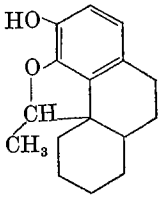

[LXVI]


[LXVII]

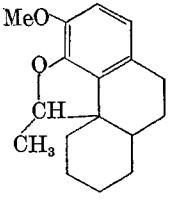
(—) 9:10-dehydrothebenone ketone furazan [LXVI]; this is too sparingly soluble to be reduced, but (—) thebenone ketone furazan [LXVII] can be obtained by reducing the 9:10 double bond before final elimination of the nitrogen atom [57]. Brominated derivatives of [LXVI] and [LXVII] can also be prepared [58–59] (see Chap. XXVI).

Reduction of thebenone and β-thebenone under the drastic conditions of Huang-Minlon's modification [60] of the Wolff–Kishner method results in simultaneous demethylation, the products being morphorane and β-morphorane [LXVIII], epimeric at C-14, respectively [20–21]. In one reduction of thebenone a small amount of thebenane [LXIX] was also isolated [21]. Thebenane has also been prepared by the exhaustive methylation of tetrahydrodesoxycodeine [61] and by the reduction of a compound (5:6 or 6:7-dehydrothebenane) derived from the desoxycodeimethine series [28]. (+) and (—) 9:10-dehydrothebenane [LXX] have also been prepared by the degradation of (+) and (—) tetrahydrodesoxycodeine [61].

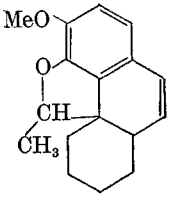
Dihydrothebainol-A has been degraded to a methine base and finally to a nitrogen-free product [39].



[LXVIII]



[LXIX]



[LXX]

Dimolecular Derivatives

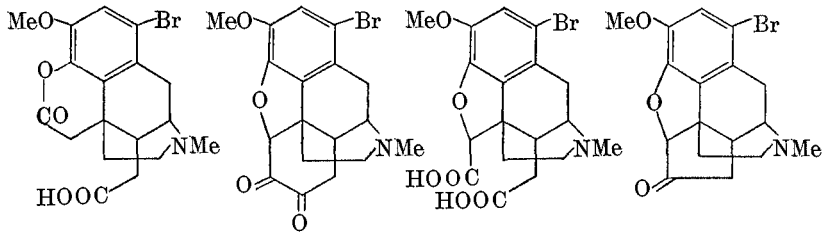
The thebainones and their derivatives are phenols and can be oxidized to dimolecular substances by gold or silver salts or potassium ferricyanide (compare the oxidation of morphine to pseudomorphine, Chap. III).

Thebainone-A may be oxidized to bis-1:1′-thebainone-A by 10 per cent. gold chloride in 10 per cent. hydrochloric acid. This may be hydrogenated to bis-1:1′-dihydrothebainone, which is also obtained by the oxidation of dihydrothebainone with silver nitrate [52]. Bis-1:1′-dihydrothebainone yields bis-1:1′-dihydrothebainone methine and dihydromethine, (+) bis-1:1′-(9:10-dehydrothebenone) and (+) bis-1:1′-thebenone, the antipodes of which may all be prepared from bis-1:1′-desmethoxydihydrosinomenine [62], on degradation.

Oxidation of sinomenine by potassium ferricyanide affords a mixture of two bases, disinomenine and ψ-disinomenine, the first of which also occurs with sinomenine in nature [63–65] (see Chap. XXVI).

A second type of dimolecular derivative has also been prepared. Reduction of thebainone-A with sodium amalgam in alkaline solution affords bis-8:8'-dihydrothebainone [52], the antipode of which results from the sodium amalgam reduction of sinomenine in alkaline solution [31, 42].

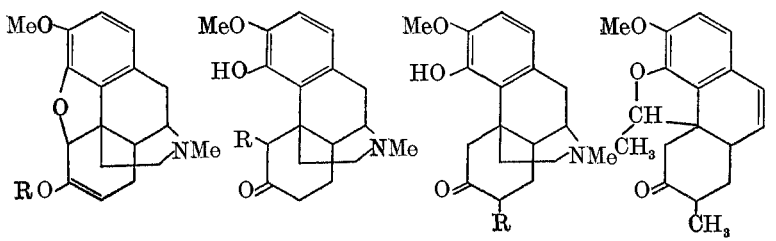
Further degradation of (+) and (−) 1-bromosinomeninone [XLI] to (+) and (−) 1-bromosinomeninic acid [LXXI], (+) and (−) 1-bromosinomeneine ketone [LXXII], (+) and (−) 1-bromosinomeneinic acid [LXXIII], and (+) and (−) 1-bromosinomenilone [LXXIV] is discussed in Chapter XXVI.



[LXXI] [LXXII] [LXXIII] [LXXIV]

ALKYLDIHYDROTHEBAINONES

When dihydrothebaine [LXXV, R = Me] and dihydrocodeinone enol acetate [LXXV, R = Ac] are treated with Grignard reagents alkyldihydrothebainones and *iso*alkyldihydrothebainones are obtained [66–67]. The location of the new alkyl group in these is uncertain, but may be either C-5 [LXXVI] or C-7 [LXXVII]. The products can be converted to alkyl and *iso*alkyldihydrocodeinones, the enol acetates of which react again with Grignard reagents to give, if the two alkyl groups introduced are identical, the same dialkyldihydrothebainone [67]. These compounds are discussed in detail in Chapter XIX, but it may here be stated that methyldihydrothebainone and *iso*methyldihydrothebainone have been degraded to the corresponding methine bases and to methyl-9:10-dehydrothebenone [LXXVIII ?] and *iso*methyl-9:10-dehydrothebenone [68].



[LXXV] [LXXVI] [LXXVII] [LXXVIII]

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Thebainone-A	145–147	..	..	−46·6	24	EtOH	3
	151–152	EtOAc	..	−42·5	20	EtOH	1, 6
— hydriodide·H_2O	165 and	..	..	..	..	..	6
	258–259	H_2O	needles	..	..	..	1
— perchlorate	149–150	H_2O	plates	−28·2	21	50% EtOH	13
— methiodide	251	H_2O	leaflets	..	..	..	6
	223	EtOH	needles	..	..	..	1
— oxime·½H_2O	175–177	..	..	..	..	..	6
	185–186	96% EtOH	..	..	..	..	1
— oxime hydrochloride	285–287	H_2O	needles	..	..	..	1, 3, 6
— semicarbazone	D.247–248	EtOAc	..	..	..	..	6
Acetylthebainone-A hydriodide	D. 269	..	needles	..	..	..	6
1-bromothebainone-A	196	acetone	prisms	−53·7	16	EtOH	52
— methiodide	200d.	H_2O	prisms	..	..	..	52
— oxime	235d.	..	prisms	..	..	..	52
— oxime hydrochloride	261	..	..	..	..	..	52
Bis-1;1'-thebainone-A	265d.	..	prisms	−219·8	15·5	$CHCl_3$+ MeOH	52
— hydrochloride	295	..	needles	..	..	..	52
— methiodide	250d.	..	prisms	..	..	..	52
— oxime	> 298	..	amorph.	..	..	..	52
1-benzeneazothebainone-A	152	MeOH	yellow prisms	..	..	..	27
Thebainone-A enol methyl ether	154–156	EtOH	granules	+9·6	22	95% EtOH	3
O desmethylthebainone-A	215–217d.	..	..	..	..	..	6
	220–221	pyridine	..	−34·3	24	10% HOAc	2
— oxime	260d.	..	..	..	..	..	6
	274–279	..	..	..	..	..	2
— oxime hydrochloride	varies	MeOH	..	..	..	..	2
— thiosemicarbazone hydrochloride	219–220	H_2O	..	..	..	..	2
Diacetyl-O-desmethylthebainone-A	183–184	$CHCl_3$+ Et_2O	needles	..	..	..	2
β-thebainone-A·H_2O	98–99	H_2O+ acetone	..	+114·9	27	EtOH	3
— hydrobromide	168–169	EtOH	rods	+61·1	27	H_2O	3
— hydriodide	150–155	EtOH	rods	+55·3	27	H_2O	3
— perchlorate	122–124	50%	prisms	..	..	..	13
	149–157	EtOH	plates	+67·3	27	MeOH	3
— picrate	172–183	50% EtOH	needles	+43·8	27	acetone	3
— oxime	..	..	not cryst.	..	..	..	3
— oxime fumarate	200·5	EtOH	needles	+46·0	27	H_2O	3
— semicarbazone	..	..	not cryst.	..	..	..	3
— semicarbazone picrate	203–204	EtOH	rods	..	..	..	3
Thebainone-B	..	..	gum	..	..	..	13
— hydrobromide	205–207	..	..	+15·8	20	H_2O	13
— picrate	183	β-ethoxy-ethanol	prisms	..	..	..	13
Thebainone-B methine·½EtOH	184	EtOH	needles	..	..	..	21
— hydrobromide	234d.	H_2O	needles	..	..	..	21
— hydriodide	214	H_2O	prisms	..	..	..	21
— perchlorate	230	H_2O	prisms	..	..	..	21
— methiodide	210	H_2O	needles	..	..	..	21
Piperonylidene thebainone-B methine	192–193	EtOH	brown plates	..	..	..	21
Thebainone-B methyl ether methine	..	..	..	..	..	..	..
— perchlorate	170	H_2O	prisms	..	..	..	21
Thebainone-B dihydromethine	164	60% EtOH	needles	..	..	..	23
— hydrobromide	256–257	EtOH	needles	..	..	..	23
— perchlorate	244–246	H_2O	prisms	..	..	..	23
— picrate	178–180	EtOH	needles	..	..	..	23
— methiodide·½H_2O	238	95% EtOH	needles	..	..	..	23
— oxime	180–187	50% acetone	needles	..	..	..	23
Thebainone-C	185–186	acetone	prisms	+158·5	27	$CHCl_3$	3
— perchlorate	200d.	H_2O	leaflets	..	..	..	13

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Dihydrothebainone·½EtOH	137–138 148–152	.. EtOH	.. ..	.. −80·1	.. 20	. EtOH	3, 9–13
— hydrochloride	..	..	needles	−50·7	20	H_2O	9
— hydrobromide	.. ..	H_2O EtOH	needles prisms	..	..	..	..
— hydriodide	262–263d.	..	..	..	..	..	9
— fumarate	> 220	..	..	..	..	..	3
— methiodide	116, 231* 150	.. H_2O	..	..	..	..	11, 31 9
— oxime	253–255	..	..	+6·6	20	10% HOAc	9, 32
— semicarbazone	226–227	..	..	..	..	..	29
Benzylidenedihydrothebainone	188	EtOH	pyramids	..	..	..	30
Piperonylidenedihydrothebainone	174–175	..	prisms	..	..	..	25
Dihydrothebainone methyl ether	..	..	oil	..	..	..	28
— methiodide	D.257–258	..	..	..	..	..	28
— methomethylsulphate	..	..	..	..	..	..	28
Bis-1:1′-dihydrothebainone	334* 258	EtOH* EtOH	prisms* ..	.. −161·0	.. 17	.. EtOH	52
— methiodide	278d.	..	prisms	..	..	..	52
— oxime	287d.	..	amorph.	..	..	..	52
Bis-8:8′-dihydrothebainone	307* 303	.. ..	prisms* ..	..	..	..	.. 52
— methiodide	310	..	prisms	..	..	..	52
— semicarbazone	283d.	..	..	..	..	..	52
1-bromodihydrothebainone	167	..	..	..	..	..	45
— hydrobromide	100–112 and 210–215	..	..	..	..	..	45
— oxime	178–180d.	..	..	..	..	..	45
1:5-dibromodihydrothebainone	..	..	..	..	..	..	45
1:5:7-tribromodihydrothebainone	..	..	..	..	..	..	46
(α)-7-hydroxydihydrothebainone	266* 127	..	..	.. −64·6	.. 20	.. $CHCl_3$	.. 50
— methiodide	276d.	..	..	..	..	..	50
— oxime	170	..	..	..	..	..	50
Dibenzoyl-(α)-7-hydroxydihydrothebainone	135–140	..	..	..	..	..	50
(β)-7-hydroxydihydrothebainone	105	..	..	..	..	..	50
— oxime	80	..	..	..	..	..	50
7-aminodihydrothebainone	245	..	..	..	..	..	53
— oxime	215–220d.	..	..	..	..	..	53
4-benzyl-7-aminodihydrothebainone	183–185d.	..	powder	..	..	..	53
Dihydrothebainone Δ^5-enol methyl ether	145–146	MeOAc	granular prisms	−61·5	17	EtOH	21
— methiodide	153	EtOH	prisms	..	..	..	21
Dihydrothebainone Δ^6-enol methyl ether	165·5–166	..	..	−118·4	22	EtOH	3
— fumarate	D.215–217	..	..	−64·4 extrapd.	22	H_2O	3
6-desacetyldihydrothebainone	274	..	..	−68·0	24	10% HOAc	2
— oxime hydrochloride·1½H_2O	318–320d.	..	..	..	..	..	2
— semicarbazone hydrochloride	D. c. 250	H_2O	..	..	..	..	2
β-dihydrothebainone	..	..	oil	−48·1	27	EtOH	3
— hydrochloride	183–190 and 245–248	EtOH	rods	−34·4	27	H_2O	3
— hydrobromide	182–185 and 225–228	EtOH	prisms	−31·5	27	H_2O	3
— perchlorate	254–255 ..	EtOH H_2O	prisms needles	.. −32·5	.. 24	.. H_2O	.. 3
— picrate	202–215	50% EtOH	needles	−16·5	27	acetone	3
— methiodide	149–154	EtOH	needles	..	..	..	3
— oxime	225–226	H_2O+ EtOH	needles	−100·4	21	EtOH	3
Dihydrothebainone methine	159* 183	.. EtOH	.. prisms	.. + 60·7	.. 20	.. dil. HOAc	62 9, 25

* Racemate

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Dihydrothebainone methine hydriodide	170–180	..	..	..	..	..	9
Bis-1:1′-dihydrothebainone methine.	240–243*	..	..	..	..	$CHCl_3$+	
	252	..	prisms	−45·1	19	MeOH	62
— methiodide	..	..	amorph.	..	19	..	62
Dihydrothebainone methyl ether methine	89·5	petrol	..	..	..	..	28
— hydriodide	211–212	H_2O	columns	..	..	..	28
— methiodide	c. 189	MeOH	..	..	..	..	28
— semicarbazone	184	EtOH	needles	..	..	..	28
— piperonylidene derivative	..	..	oil	..	..	..	28
1-bromodihydrothebainone methine.	189–192*	..	..	..	..	..	..
	200–201	MeOH	prisms	+8·0	17	..	46
— methiodide	243	H_2O	..	..	..	..	56
β-dihydrothebainone methine	183–184	H_2O+ EtOH	needles	−257·9	28	EtOH	3
— perchlorate	225·5–226	EtOH	..	..	..	..	3
— picrate	164–165	66% EtOH	..	−181·1	27	acetone	3
— oxime	160–162	50% EtOH	..	..	..	..	3
Dihydrothebainone dihydromethine	156·5†	Et_2O†	prisms†	+67·8†	18	MeOH	55
	154–156	H_2O+ EtOH	needles	..	..	..	9, 25
— perchlorate	233	..	..	..	..	..	28
— picrate	185–188	..	..	..	..	..	25
— methiodide	226–229	MeOH	prisms	..	..	..	9, 55
— piperonylidene derivative	179–181	..	..	..	..	..	25
— Acetyldihydrothebainone dihydromethine picrate	188–192	..	..	..	..	..	25
Bis-1:1′-dihydrothebainone dihydromethine	245–248*	..	prisms	− 32·5	20	$CHCl_3$+ MeOH	62
	249–250						
Dihydrothebainone methyl ether dihydromethine	70·5–72	petrol	..	..	..	..	28
— hydriodide	224–225	H_2O	needles	..	..	..	28
— perchlorate	216	..	..	..	..		28
— methiodide	..	..	oil	..	..	..	28
— methoperchlorate	185–186	H_2O	needles	..	..	..	28
— semicarbazone	176–178	EtOH	..	..	..	..	28
1-bromodihydrothebainone dihydromethine	175–177*	..	..	..	..	..	56
	192	MeOH	prisms	−62·7	17	..	56
— hydrobromide	257	..	..	..	..	..	56
— methiodide	273†	..	..	..	..	..	56
Dihydrothebainone dihydromethine Δ^5-enol methyl ether	..	..	oil	..	..	..	23
β-dihydrothebainone dihydromethine	177–178	EtOH	needles	+63·7	27	$CHCl_3$	3
— hydrobromide	260–260·5	EtOH	needles	+24·0	28	H_2O	3
— perchlorate	232·5–233·5	H_2O	rods	+23·8	28	MeOH	3
— picrate	203–207	EtOH	needles	+18·2	27	acetone	3
— oxime and salts	..	..	not cryst.	..	..	..	3
8:14:9:10-tetradehydrothebenone	248	dioxane	prisms	..	..	..	21
(−)9:10-dehydrothebenone	158*	..	..	..	..	..	62
	113	..	prisms	−206·9	18	..	55
(+)Bis-1:1′-(9:10-dehydrothebenone)	202–205*	..	..	..	..	..	62
	205–212	..	..	+201·5	20	$CHCl_3$+ MeOH	62
(+)1-bromo-9:10-dehydrothebenone	159–160*	MeOH*	..	..	..	..	..
	148–150	$CHCl_3$	prisms	+187·3	17	acetone	56
(+)9?-bromo-9:10-dehydrothebenone	156–158*	..	..	..	..	..	..
	127–130	..	..	+112·7	17	acetone	56
(−)9:10-dehydrothebenone ketone furazan and derivs.: *see* Chap. XXVI.							
Thebenone	120*	..	..	−78·6†	18	MeOH	55, 62
	134–136	EtOH	prisms	+64·6	22	EtOH	25, 69
— oxime	201–204	..	..	..	..	..	25
— 2:4-dinitrophenylhydrazone	228	dioxane	prisms	..	..	..	21
Isonitrosothebenone	165	..	..	..	..	..	25
Benzylidenethebenone	162	..	..	..	..	..	25
Piperonylidenethebenone	185–186	..	..	..	..	..	25
Bis-1:1′-thebenone.	250–254*	..	..	..	..	$CHCl_3$+	..
	233	..	..	+103·1	20	MeOH	62

* Racemate. † Antipode.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
1-bromothebenone	191–193* / 70	.. / MeOH	plates* / needles	.. / +23·3	.. / 17	.. / ..	.. / 56
Thebenone ketone	185–187	..	..	..	..	..	25
— dioxime	155–160 and 260	..	..	..	..	..	25
β-thebenone	189–190	EtOH	rods	+113·6	28	EtOH	3
— oxime	176–177	H_2O+ EtOH	cubes	+30·6	28	EtOH	3
Piperonylidene-β-thebenone	189	β-ethoxy-ethanol	plates	..	..	..	21
Morphirane	103	50% EtOH	plates	..	..	..	21
β-morphirane	148	50% EtOH	prisms	..	..	..	21
Thebenane·½H_2O	86	50% EtOH	prisms	0·0	20	MeOH	21
Thebenane	48–54	..	..	+3·2	22	EtOH	61
5:6(or 6:7)-dehydrothebenane	78	EtOH	..	..	..	..	70
9:10-dehydrothebenane	107–112	..	prisms	+175·5	22	EtOH	61
Derivatives of thebenone ketone furazan: *see* Chap. XXVI.							
Dihydrothebainol-A·½H_2O	D.138–142	..	..	−46·2	28	EtOH	35, 39
— hydrochloride	D. 268	..	..	..	..	..	39
— hydriodide	..	..	cryst.	..	..	..	39
— methiodide	280	H_2O+ EtOH	..	−24·3	29	MeOH	37
Dihydrothebainol-A methyl ether	181–182	..	..	..	..	..	39
— methiodide	284–285	..	..	..	..	..	39
Dihydrothebainol-A methine	..	..	oil	..	..	..	39
— hydriodide	179–180	..	..	..	..	..	39
— methiodide	281–282	..	..	..	..	..	39
Nitrogen free product from degradation of dihydrothebainol-A methine	..	..	oil	..	..	..	39
Dihydrothebainol-B	165	..	needles	−36·5	20	EtOH	11
— methiodide	273	EtOH	..	..	..	..	11
— bisphenylurethane	175	..	..	..	..	..	11
Dihydrothebainol-B methyl ether	..	..	oil	−28·0	27	EtOH	36
— hydrobromide	254·5–255	..	..	+34·0	28	EtOH	36
— methiodide	279–281	..	..	..	..	..	36
β-dihydrothebainol-B	165·5–166	..	..	−23·0	30	EtOH	36
β-dihydrothebainol-B methyl ether	152·5–153·5	..	..	−9·0	30	EtOH	36
— picrate	190–191	..	..	..	..	..	36
— methiodide	243–245	..	..	..	..	..	36
7-hydroxydihydrothebainol	..	..	..	..	..	..	51
Triacetyl-7-hydroxydihydrothebainol	..	..	..	..	..	..	51
Dihydrothebainol-6-methyl ether	140·5–142	subl.	needles	−23·4	27	EtOH	3, 16
— methyl ether	..	..	..	..	..	..	3
Alkyldihydrothebainones and their degradation products: *see* Chap. XIX.							

* Racemate.

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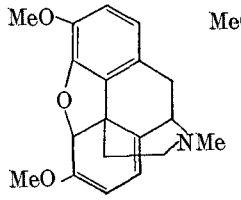
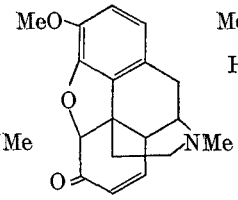
XVI

METATHEBAINONE

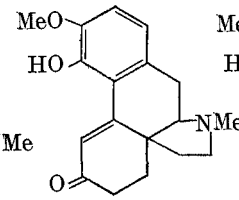
THE reduction of thebaine [I] [1–2] and codeinone [II] [3] with stannous chloride and hot concentrated hydrochloric acid and the catalytic hydrogenation of thebaine in > 5N hydrochloric acid [4, 24] results in migration of the carbon end of the basic side-chain from C-13 to C-14 and production of a phenolic ketone, metathebainone [III]. This ketone was originally called thebainone and was believed to be structurally related to thebaine, but Schöpf and Borkowsky realized that a migration of the side-chain must have occurred during its production and suggested the name metathebainone in 1927 [2]; this was finally generally adopted after the true thebainone-A [IV] had been discovered [5]. The conditions of the stannous chloride and hydrochloric acid reduction can be varied so that either [III] or [IV] is the main product [5].



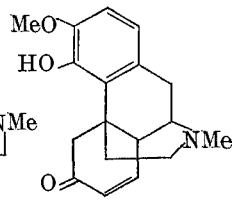
[I]



[II]



[III]

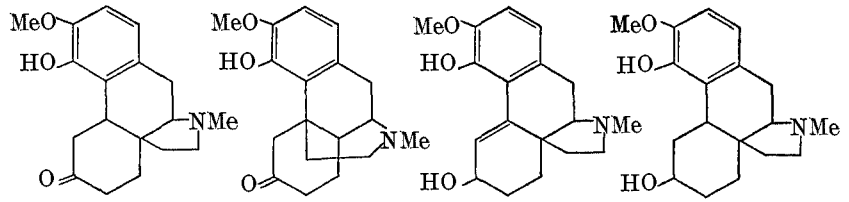


[IV]

Metathebainone gives a methyl ether [6] and an oxime [2], and formation of the latter may also be accompanied by the addition of hydroxylamine to the double bond, in the way observed with α:β-unsaturated ketones [2]. Structure [III] shows the ketone group to be conjugated with the double bond and, through the latter, with the guaiacol nucleus, and metathebainone exhibits halochromism in concentrated acid solution as do other substances having a similar conjugated system such as salicylideneacetone and salicylideneacetophenone [2].

REDUCTION

(*a*) Metathebainone may be reduced with sodium amalgam to dihydrometathebainone [V] [7–8], first thought by Pschorr [1] to be a secondary alcohol 'thebainol'. Dihydrometathebainone is a structural isomer of dihydrothebainone [VI], an isomerism first explained on the basis of a bridge-structure for thebaine, that was regarded as suffering fission of the bridge in either of two ways [7], later on the basis of a stereochemical difference at C-14 [9], and finally by the recognition of the migration of the side-chain in metathebainone [2, 10].

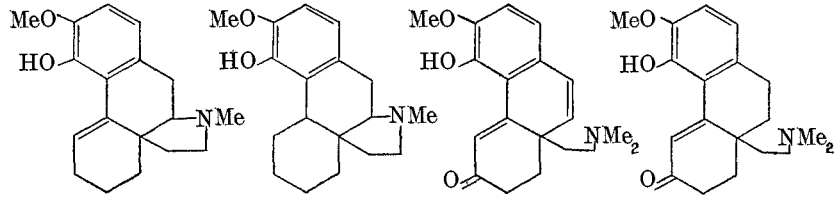


(*b*) Catalytic reduction of the base is difficult, presumably owing to the location of one end of the carbon-carbon double bond at the ring juncture. As saturation of the double bond generates a new asymmetric centre, a C-13 epimer of dihydrometathebainone [V] is theoretically capable of existence. In fact only one such dihydro-compound has been obtained. Hoek [11] claimed to have obtained an isomer, but Schöpf and Borkowsky [2] could find no evidence of this. Kondo and Ochiai [12–13] reported the production of a 'β-dihydrothebainone' by the catalytic reduction of metathebainone, but this product was subsequently identified as a mixture of dihydrometathebainone [V] and metathebainol [VII] [8]. The latter is the sole product when hydrogenation is carried out over platinum oxide at 2–3 atmospheres pressure [8].

(*c*) Dihydrometathebainone must be formed from metathebainone by initial 1:4-reduction of the α:β-unsaturated ketone system, as the isolated double bond of metathebainol is resistant to hydrogenation. Dihydrometathebainol [VIII] may, however, be prepared by further reduction of dihydrometathebainone over platinum oxide [8].

(*d*) Metathebainone and dihydrometathebainone afford dihydrodesoxymetacodeine [IX] and tetrahydrodesoxymetacodeine [X] respectively when reduced by Wolff and Kishner's method [8].

Metathebainol [VII] loses the elements of water on heating with alcoholic potassium hydroxide at 160° C., giving 'anhydrometathebainol', $C_{18}H_{21}O_2N$; this change, however, must involve more than simple dehydration of [VII] as the product can be hydrogenated to a dihydro-derivative that is different from dihydrodesoxymetacodeine [8].

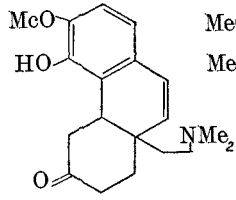


Diacetylmetathebainol readily loses the 4-acetyl group on treatment with hydroxylamine hydrochloride at room temperature. Metathebainol and its acetyl esters do not immediately give halochromic

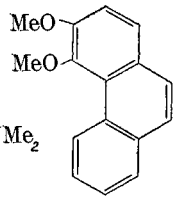
solutions in concentrated acids, but halochromism develops if the solutions are allowed to stand.

Degradation

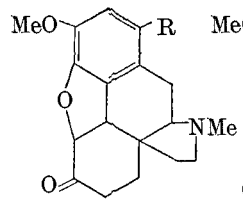
The nitrogen-containing ring of metathebainone is stable to acetic anhydride [14], but metathebainone methiodide on boiling with alkali is converted to metathebainone methine [XI], which is stable to further degradation, but can be reduced catalytically to metathebainone dihydromethine [XII] or by sodium amalgam to dihydrometathebainone methine [XIII]. Metathebainone methyl ether methine [2, 6, 15] behaves similarly on reduction [2] and can also be degraded by heating with acetic anhydride to 3:4-dimethoxyphenanthrene [XIV] and β-dimethylaminoethanol [6], showing that the latter can arise as a result of scission of a carbon-carbon link (see Chaps. I and XXVII).



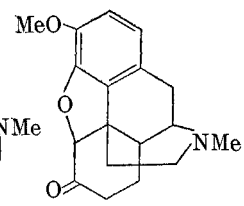
[XIII]



[XIV]



[XV]



[XVI]

Closure of the 4:5-ether bridge in dihydrometathebainone has been effected by bromination and the action of alkali on the dibromide thus formed. The product of this reaction was 1-bromodihydrometacodeinone [XV, R = Br], which was reduced to dihydrometacodeinone [XV, R = H], an isomer of dihydrocodeinone [XVI] [16–17].

Metathebainone condenses with benzaldehyde [7] and piperonal [7, 18], and dihydrometathebainone also gives an amorphous dipiperonylidene derivative [7]. Benzylidenemetathebainone can be reduced to two isomeric benzylmetathebainones [7]. A quinoline derivative, dianhydro-6-aminopiperonalmetathebainone, is produced by condensing metathebainone with 6-aminopiperonal [7].

Metathebainone methyl ether is unaffected by ozone [19].

Oxidation of metathebainone with silver nitrate according to Goto's method [20] gives the dimolecular base 1:1′-dimetathebainone, which occurs in two forms. It may be degraded to bis-1:1′-3-methyl-4-acetylmorphol (see Chap. XXVII) [21]. Both α- and β- forms of the parent base have been hydrogenated to tetrahydro-derivatives [21].

Treatment of metathebainone with silver nitrate also affords '*ψ*-metathebainone' [13, 22], stated to be different from 1:1′-dimetathebainone [21, 23]; it is assumed by Kondo and Ochiai to arise from inversion of an asymmetric centre in metathebainone. On catalytic reduction it yields dihydro-*ψ*-metathebainone [22].

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Metathebainone·1½H_2O	88–90	H_2O	..	−419	24	benzene	1–4, 7–8
Metathebainone·MeOH	115–118	MeOH	..	..	..	..	1
— picrate	250–253	..	..	..	..	..	2
— methiodide	255–256	..	..	..	..	..	1
— sodium salt	..	..	orange plates	..	..	..	1
— oxime·MeOH	200–201	MeOH	..	..	..	..	1
— phenylhydrazone	..	..	not cryst.	..	..	..	1
— semicarbazone	227	..	..	..	..	..	1
Acetylmetathebainone	100–101	Et_2O+ petrol	..	..	..	..	1
— methiodide	223–225	..	..	..	..	..	1
— phenylhydrazone	225–226	..	..	..	..	..	1
— semicarbazone	249	..	..	..	..	..	1
Metathebainone methyl ether	156	..	..	..	..	..	1
— methiodide	256	..	..	+182·5	7	..	15
Benzylidenemetathebainone	233	EtOH	needles	..	..	..	7, 18
— picrate	D. 194	..	..	..	..	..	7
— methiodide	195–197	..	..	..	..	..	7, 18
Piperonylidenemetathebainone	176	EtOH	..	..	..	..	7, 18
Dianhydro-6-aminopiperonalmetathebainone dihydrobromide·3H_2O	258–260	..	..	..	..	..	18
Benzylmetathebainone-A	229	..	needles	..	..	..	18
— sodium salt	..	..	orange	..	..	..	18
— semicarbazone	155–160	..	..	..	..	..	18
Benzylmetathebainone-B	179	EtOH	plates	..	..	..	18
— oxime	152	EtOH	columns	..	..	..	18
— semicarbazone	140–145	..	..	..	..	..	18
Metathebainone methine	170–171	MeOH	yellow needles	..	..	..	2
— methiodide	252	acetone	..	..	..	..	2
— oxime	210–211	EtOH	..	..	..	..	2
Metathebainone methyl ether methine	65–66	..	..	..	..	..	1
— methiodide·EtOH	171–172	EtOH	..	..	..	..	1
— oxime hydrochloride	271–272	..	..	..	..	..	1
— semicarbazone·MeOH	107–108	MeOH	..	..	..	..	1
Metathebainone dihydromethine	..	..	..	..	..	..	2
— hydriodide	258–259	..	..	..	..	..	2
Metathebainone methyl ether dihydromethine	..	..	..	..	..	..	2
— methiodide	154–155	..	..	..	..	..	2
Dihydrometathebainone	54–55 and 76–78	MeOH	..	..	..	..	1
Dihydrometathebainone	135–136	dry Et_2O	prisms	+67·1 +33·1	25 25	EtOH 5% HOAc	7
— perchlorate	245	EtOH	..	..	..	..	2
— methiodide	D. 243	..	..	+46·6	25	H_2O	1
— oxime	217–218	EtOH	..	+104·2	18	10% HOAc	2
— semicarbazone	232	..	..	+109·8	27	10% HOAc	8
	217–218	H_2O+ EtOH	..	..	..	..	7
Dihydrometathebainone methyl ether	..	..	not cryst.	..	..	..	1
— methiodide	260	..	..	..	..	..	2
	245	..	..	..	..	..	1, 7
Benzylidenedihydrometathebainone	100–102	..	needles	..	..	..	18
Dipiperonylidenedihydrometathebainone	..	..	non-cryst. powder	..	..	..	7
Piperonylidenedihydrometathebainone methyl ether	c. 156	..	not cryst.	..	..	..	7
Dihydrometathebainone methine	173–174	EtOH	..	..	..	..	2
Dihydrometathebainone methyl ether methine	..	..	oil	..	..	..	2
— perchlorate	193–194	..	..	..	..	..	2
Dihydrometathebainone dihydromethine	119–121	..	..	..	..	..	2
Dihydrometathebainone methyl ether dihydromethine	..	..	oil	..	..	..	2
— methiodide	117–118	..	..	..	..	..	2
— methoperchlorate	215	..	..	−44·0	18	acetone	2

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Metathebainol·$CHCl_3$	87–88	$CHCl_3$	..	−45·9	25	EtOH	8
Metathebainol·MeOH	92–93	MeOH	..	−61·2	27	EtOH	8
Metathebainol (anhyd.)	..	dist.	resin	..	..	..	8
— hydrochloride·EtOAc	162 and 220	EtOAc	..	..	..	..	8
— hydriodide·H_2O	..	H_2O	..	..	..	..	8
— methiodide	225	EtOH	..	..	..	..	8
6-acetylmetathebainol	150	EtOAc	..	..	..	..	8
Diacetylmetathebainol	140	H_2O+ MeOH	..	..	..	..	8
Dihydrometathebainol	c. 120	..	..	..	..	..	8
— hydrochloride	..	..	..	+16·4	30	H_2O	8
Anhydrometathebainol	106–107	MeOH	..	−201·0	25	EtOH	8
Acetylanhydrometathebainol	166	MeOH	..	..	..	..	8
Dihydroanhydrometathebainol	..	MeOH	..	..	..	..	8
Dihydrodesoxymetacodeine·MeOH	72	MeOH	..	..	..	..	8
Dihydrodesoxymetacodeine (anhyd).	..	dist.	resin	−93·8	24	EtOH	8
Tetrahydrodesoxymetacodeine	..	..	amorph.	..	..	..	8
— hydriodide	..	..	..	−12·5	28	H_2O	8
ψ-metathebainone	D. 227	..	..	−339·5	16	..	13
— semicarbazone	D. > 290	..	..	..	..	..	13
Dihydro-ψ-metathebainone	D. 270	..	needles	−71·8	25	..	13
α-1:1′-dimetathebainone	308–310	EtOH	needles	−532·6	23	$CHCl_3$	21
— methiodide	D. 274	..	..	..	..	..	21
Diacetyl-α-1:1′-dimetathebainone	272–273	EtOH	needles	−321·4	20	benzene	21
Tetrahydro-α-1:1′-dimetathebainone	D. > 300	MeOH	prisms	−390·6	23	EtOH	21
β-1:1′-dimetathebainone	235–237	..	..	−327·9	7	$CHCl_3$	21
— methiodide	D. 274	..	..	..	..	..	21
Tetrahydro-β-1:1′-dimetathebainone·3MeOH	266	MeOH	prisms	−223·9	24	$CHCl_3$	21

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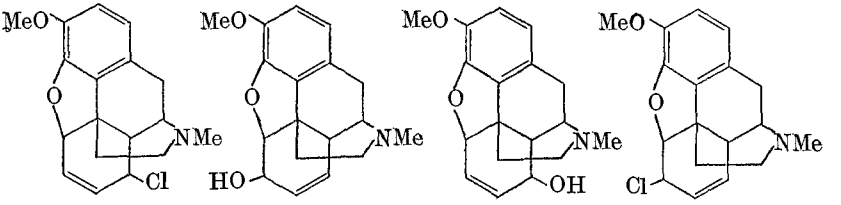
XVII

THE THIOCODIDES AND THIOMORPHIDES

REPLACEMENT of the chlorine atom of β-chlorocodide [I] by the hydroxyl group under suitable conditions gives rise to three isomers of codeine, namely isocodeine [II], ψ- and allo-ψ-codeine [III] (see Chap. VIII), but when replacement by the —SH group is attempted by heating β-chloro- or bromocodide with potassium hydrosulphide simultaneous oxidation occurs and the dimolecular bisthiocodide, $C_{36}H_{40}O_4N_2S_2$, is obtained. In this base two codeine units are linked by —S—S—, presumably in the 6:6′-position, as replacement of the halogen atom of bromo- and β-chlorocodide by groups other than hydroxyl always results, in other cases, in appearance of the new substituent at position 6 (see Chapter VIII). Bisthiomorphide, $C_{34}H_{36}O_4N_2S_2$, can be prepared in the same way from bromomorphide, and gives bisthiocodide on methylation [1]. Though the simple thiocodeines and thiomorphines are not known, their S-ethers, the alkylthiocodides and alkylthiomorphides, may be prepared by treating the halogenocodides and morphides with mercaptans under suitable conditions. The ethylthiocodides have been most extensively studied and are selected for discussion here; the methylthiocodides and methyl and ethylthiomorphides, as far as their properties are known, correspond in every way with the ethylthiocodides.



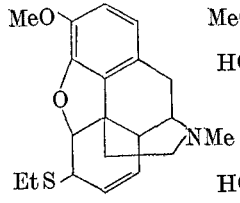
[I] [II] [III] [IV]

Four ethylthiocodides have been reported to exist. α-Ethylthiocodide results from heating bromo- or β-chlorocodide with ethyl mercaptan and aqueous sodium hydroxide at 100° C. [2]; it is isomerized to β-ethylthiocodide on heating with alcoholic sodium ethoxide, a reaction that occurs when bromo- and β-chlorocodide are heated with ethyl mercaptan and alcoholic sodium ethoxide [1–2]. From the latter reaction a small quantity of a substance named γ-ethylthiocodide was

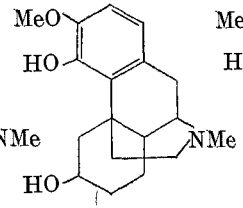
obtained [2]. δ-Ethylthiocodide may be obtained by heating α-chlorocodide [IV] with ethyl mercaptan and alcoholic sodium ethoxide in an atmosphere of hydrogen [2].

α-Ethylthiocodide

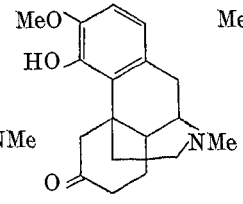
This undoubtedly corresponds to one of the epimeric pair codeine : isocodeine and is allotted the structure [V] for the following reasons. It cannot be reduced catalytically as sufficient ethyl mercaptan to poison the catalyst is immediately evolved, but it can be reduced by sodium and alcohol to dihydrothebainol-A [VI] identical [3] with the product of the parallel (sodium amalgam) reduction of dihydrothebainone [VII] [4–5] and dihydrocodeinone [VIII] [6]. This is only evidence for the location of the —SEt group at C-6 in so far as the relationship between α- and β-ethylthiocodide is known, as the conditions of reduction are precisely those known to cause the α → β isomerization.



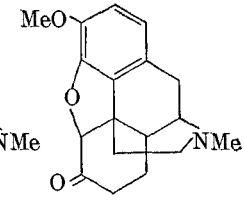
[V]



[VI]



[VII]



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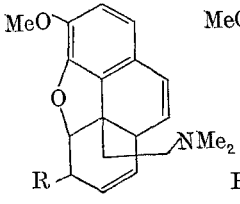
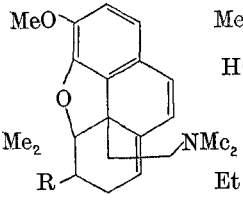
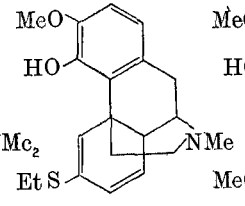


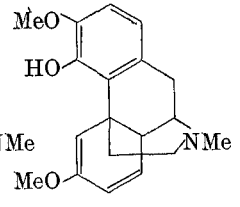
[IX]



[X]



[XI]



[XII]

Alkaline degradation of α-ethylthiocodide methiodide affords α-ethylthiocodeimethine [IX, R = SEt], which also results from the action of aqueous sodium hydroxide and ethyl mercaptan on bromocodide methiodide [2]. When this methine is heated with sodium ethoxide it undergoes isomerization to 'β-ethylthiocodeimethine', which results also from heating bromo- or chlorocodeimethines with sodium ethoxide and ethyl mercaptan [2]. This change was held to be analogous to the known isomerization of α-codeimethine [IX, R = OH] to β-codeimethine [X, R = OH] (see Chap. VI) and 'β-ethylthiocodeimethine' was accordingly allotted the structure [X, R = SEt] [2]. However, the conditions under which the isomerism occurs are those that cause the conversion of α-ethylthiocodide to the β-isomer, and the relationship between the

two methines is no doubt the same as that between the two parent bases; the correctness of this assumption is demonstrated by the fact that the β-methine can be prepared by degradation of β-ethylthiocodide [2, 7]. The name β-ethylthiocodeimethine which is applicable only to [X, R = SEt] is therefore misleading and will be replaced here by β-ethylthiocodide methine. Further degradation of α-ethylthiocodeimethine [IX, R = SEt] methiodide with sodium hydroxide yields trimethylamine, and with acetic anhydride yields the acetyl ester of β-dimethylaminoethanol, but the nitrogen-free substances have not been isolated [2].

β-Ethylthiocodide

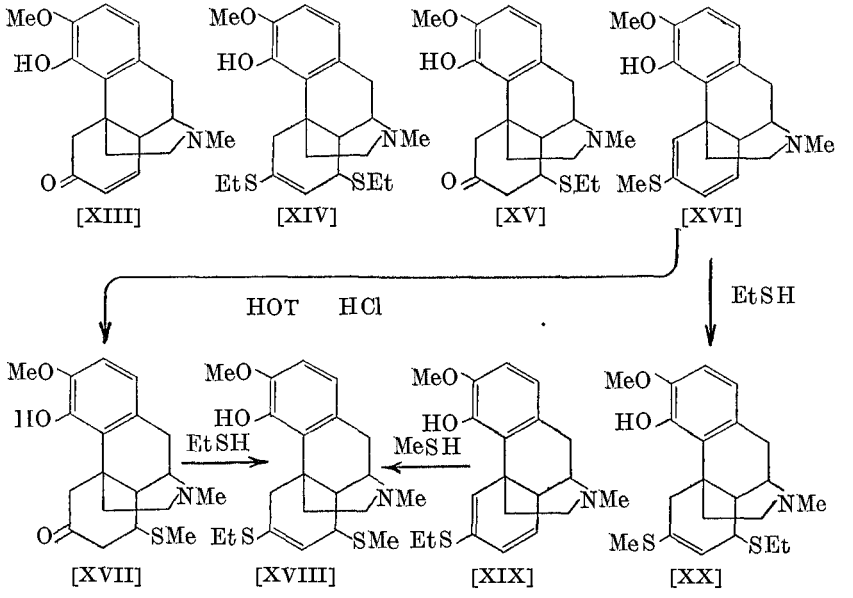
The early work on this compound was confused by Pschorr's failure to recognize its phenolic nature. He noted the alkali-soluble nature of the methiodide and the production of a mono-acetyl derivative, but concluded, on account of the apparent insolubility of the parent base in alkali, that fission of the cyclic ether link occurred during the reactions of the base with acetic anhydride and methyl iodide [7]. That β-ethylthiocodide is indeed a phenol was demonstrated by Morris and Small [3]; it gives coloured solutions with alcoholic ferric chloride and readily couples with diazonium salts in alkaline solution to give red dyes; moreover it is soluble in alkali, though not readily so, being a very weakly acidic phenol.

β-Ethylthiocodide [XI] results from α-ethylthiocodide [V] by migration of a hydrogen atom from C-6 to the oxygen of the cyclic ether with the introduction of a double bond at C-5:6 [3]. A precisely similar change occurs when codeine methyl ether is heated with alcoholic sodium ethoxide, the product being thebainone-A enol methyl ether [XII] [3, 8]. As isocodeine methyl ether is unaffected by sodium ethoxide [8], it is suggested that α-ethylthiocodide belongs to the codeine series. β-Ethylthiocodide contains two double bonds (it can be catalytically reduced without loss of sulphur to a tetrahydro-derivative) and its addition reactions point to the conjugation of these [3].

The hydrolysis of β-ethylthiocodide affords a sulphur-free ketone [7], which is identical with thebainone-A [XIII] [3, 9] despite a statement to the contrary by Schöpf and Hirsch [10]. The ethyl mercaptan liberated during the hydrolysis adds to unchanged β-ethylthiocodide to give dihydro-β-diethyldithiocodide [XIV], the product of hydrolysis being an equimolecular mixture of [XIII] and [XIV]. An equivalent mixture of these two bases, or β-ethylthiocodide itself, on heating with hydrochloric acid yields only 8-ethylthiodihydrothebainone [XV], the mercaptan produced by the hydrolysis of [XIV] adding to the thebainone-A. These additions and hydrolyses can be realized with the individual compounds concerned, e.g. ethyl mercaptan can be added to thebai-

none-A to give [XV] [7]. Addition of ethyl mercaptan to [XV] can also be accomplished, the product being dihydro-β-diethyldithiocodide [XIV], which is converted back to [XV] by acids [3].

The addition of mercaptans to thebainone-A is analogous to the addition of *iso*amyl and phenyl mercaptans to α:β-unsaturated ketones of the benzalacetone type, which has been reasonably explained as a 1:4-addition process [11–12]. The formation of [XIV] from β-ethylthiocodide no doubt occurs by 1:4-addition to the diene system, and from [XII] by addition of mercaptan to the carbonyl group followed by elimination of water, or by the condensation of mercaptan with the enol form of the ketone [3].



These formulae provide a satisfactory explanation of the results of Pschorr [7], who hydrolysed β-methylthiocodide [XVI] to a 'thioketone' (methylthiodihydrothebainone) [XVII] which underwent addition of ethyl mercaptan to give a compound (8-methylthiodihydro-β-ethylthiocodide) [XVIII], isomeric but not identical with the compound (8-ethylthiodihydro-β-methylthiocodide) [XX] obtained by treating β-methylthiocodide with ethyl mercaptan, but identical with that produced by treating β-ethylthiocodide [XIX] with methyl mercaptan [8].

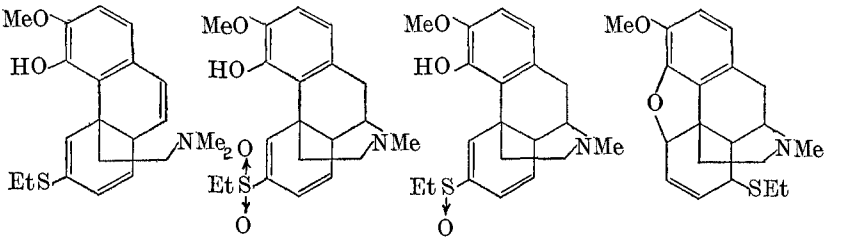
β-Ethylthiocodide methiodide is formed when the base is treated with methyl iodide in cold chloroform and may be hydrolysed to thebainone-A methiodide, which results directly when β-ethylthiocodide is treated with methyl iodide in aqueous alcohol. A phenol betaine is obtained by the action of cold sodium hydroxide on the methiodide and is converted

to β-ethylthiocodide methyl ether methiodide on boiling with alcoholic methyl iodide; if the latter reaction is carried out under pressure, thebainone-A methyl ether methiodide is obtained [7].

Acetylation of β-ethylthiocodide may be effected by heating the base with acetic anhydride, and the acetyl ester can be saponified by alkali, or hydrolysed to thebainone-A by hot acids; hydrolysis of acetyl-β-ethylthiocodide methiodide with warm acid gives acetylthebainone-A methiodide [7].

Hofmann degradation of β-ethylthiocodide gives β-ethylthiocodide methine [XXI], already mentioned [2, 7].

When β-ethylthiocodide is warmed with hydrogen peroxide it can be oxidized to β-ethylthiocodide sulphone [XXII], obtainable in the same way from α-ethylthiocodide [V] [13].



[XXI] [XXII] [XXIII] [XXIV]

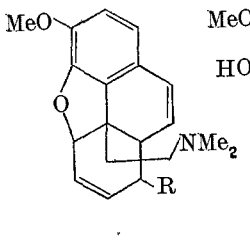
γ-Ethylthiocodide

This base was reported by Pschorr [2] as a by-product in the preparation of the β-isomer, and was stated to give. on degradation, a methine base that could not be isomerized, and was thus believed to have the —SEt group at C-8 and to be a stereoisomer of δ-ethylthiocodide. The production of this compound was verified by Morris and Small [3], who showed that it is in fact β-ethylthiocodide sulphoxide [XXIII] and that it can be prepared from β-ethylthiocodide by shaking this with oxygen in alcoholic solution.

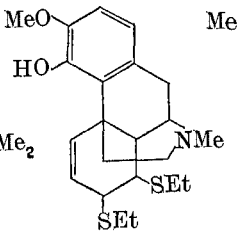
δ-Ethylthiocodide

The structure [XXIV] was suggested by Pschorr and Rollett [2] for this base as it can be degraded to a methine base [XXV, R = SEt] that cannot be isomerized, in this way resembling ε- and ζ-codeimethine [XXV, R = OH]. The formula has been confirmed by Morris and Small [3]. δ-ethylthiocodide has many properties characteristic of the system —O—CH—CH=CH— as found in other ψ-codeine-type compounds. It will suffer addition of ethyl mercaptan giving dihydro-δ-diethyldithiocodide [XXVI] (isomeric with [XIV]). In the same way desoxycodeine-C [XXVII] will give ethylthiodihydrodesoxycodeine-C [XXVIII]

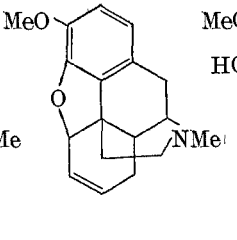
[3], and ψ-codeinone and ψ-codeine will also suffer addition of mercaptans [8].



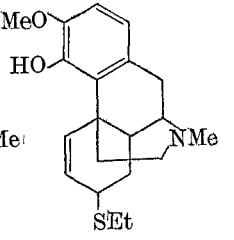
[XXV]



[XXVI]

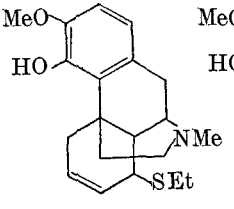


[XXVII]

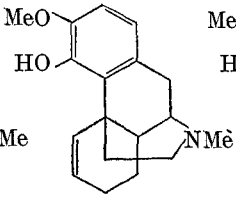


[XXVIII]

Catalytic reduction of δ-ethylthiocodide cannot be accomplished as the catalyst is immediately poisoned by liberated mercaptan. Electrolytic reduction furnishes dihydro-δ-ethylthiocodide-A [XXIX], together with a compound $C_{18}H_{23}O_2N$, apparently a dihydrodesoxycodeine, which has the properties of dihydrodesoxycodeine-C [XXX] but which gives a degradation product that depresses the melting-point of dihydrodesoxycodeine-C methine [8]. Reduction with sodium and alcohol affords dihydro-δ-ethylthiocodide-B [XXXI] together with the constant proportion mixture of dihydrodesoxycodeines B [XXXII] and C [XXX] known as 'dihydrodesoxycodeine-A' [3] that also appears in the parallel reduction of ψ-codeine [III] [14].



[XXIX]



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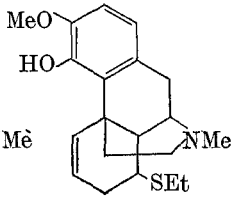
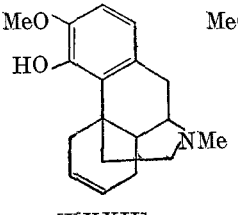


[XXXI]



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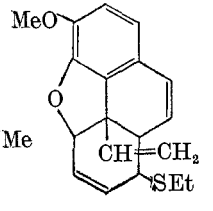
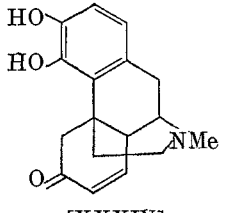


[XXXIII]



[XXXIV]

Hofmann degradation of δ-ethylthiocodide yields δ-ethylthiocodide methine [XXV, R = SEt] (the name δ-ethylthiocodeimethine would imply a relationship to δ-codeimethine, which has a hydroxyl group at C·6), which retains the residue of the basic side-chain on further

degradation, giving 8-ethylthio-13-vinyltetrahydromorphenol methyl ether [XXXIII] [2].

Ethylthiomorphides analogous to the codides have been prepared from bromomorphide [15]. β-Ethylthiomorphide on hydrolysis yields O-desmethylthebainone-A [XXXIV] [15], also obtainable by the catalytic rearrangement of morphine [16–17] (see Chap. XV).

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
α-ethylthiocodide (two forms)	77–79	*iso*propyl ether	..	−340·7	28	95% EtOH	3
	88–89	..	prisms	−344·6	27	95% EtOH	2, 3
— hydriodide	217	H_2O	leaflets	..	..	..	2
— perchlorate	191–192	EtOH	..	−249·0	20	acetone	13
— sulphate	185–190	H_2O	needles	−276·6	26	H_2O	3
— methiodide	236–237	..	..	−232·6	20	H_2O	2
— double compound + $AgNO_3$	..	EtOH	..	..	..	..	3
α-ethylthiocodeimethine	..	..	not cryst.	..	..	..	2
— hydriodide	204–206d.	..	..	..	..	..	2
— methiodide	235–236d.	..	..	..	..	..	2
β-ethylthiocodide	148	EtOH	..	−45·5	..	..	2, 3, 7
— methiodide	232	..	needles	..	..	..	7
— betaine from methiodide	170–172	..	..	..	..	..	7
Acetyl-β-ethylthiocodide	..	..	..	..	..	..	7
— methiodide	161	..	..	..	..	..	7
β-ethylthiocodide methyl ether methiodide	209–211	..	..	..	..	..	7
Tetrahydro-β-ethylthiocodide	..	..	oil	+15·3	26	EtOH	3
β-ethylthiocodide methine	173–174	EtOH	leaflets	..	..	..	2, 7
— methiodide	124–125	..	needles	..	..	..	2, 7
β-methylthiocodide	124–125	EtOH	prisms	..	..	..	7
Thebainone-A: *see* Chap. XV.							
— methyl ether methiodide	..	..	..	..	..	..	7
Acetylthebainone-A methiodide	..	..	..	..	..	..	7
Ethylthiodihydrothebainone ·H_2O	121–127	..	..	..	..	..	7
Ethylthiodihydrothebainone anhyd.	182	acetone	..	+55·4	20	H_2O	7
— hydriodide	222–223d.	..	needles	..	..	..	7
— methiodide	D. 241	..	..	..	..	..	7
— oxime	258	..	..	..	..	..	7
Methylthiodihydrothebainone (·H_2O)	95–97	..	..	..	..	..	7
Methylthiodihydrothebainone anhyd.	141–142	EtOH	prisms	..	..	..	7
Dihydro-β-diethyldithiocodide	..	..	not cryst.	..	..	..	7
— methiodide	212–213d.	H_2O	needles	..	..	..	7
8-methylthiodihydro-β-ethylthiocodide [XVIII]	71–73	MeOH	plates	..	..	..	7
— methiodide	D.146–147	..	..	+24	20	H_2O	7
8-ethylthiodihydro-β-methylthiocodide [XX]	112–115	..	prisms	..	..	..	7
— methiodide	D. 184	..	..	+33·6	20	H_2O	7
β-ethylthiocodide sulphone	192–193	H_2O + EtOH	..	+50·4	25	EtOH	13
β-ethylthiocodide sulphoxide (γ-ethylthiocodide)	..	..	amorph.	..	..	..	2
— methiodide	265d.	..	..	−119·2	20	H_2O	2, 3
— methine	..	..	oil	..	..	..	2
— methine hydriodide	179–180	..	..	−161·0	20	H_2O	2
δ-ethylthiocodide	..	..	oil	+57·7	28	EtOH	2, 3
— hydriodide	D. 255	..	..	+51·4	20	H_2O	2
— perchlorate	223–224	EtOH	..	+54·3 +40·5	28 28	H_2O EtOH	3
— methiodide	143–145	EtOH	..	..	..	..	3
	230–234	..	..	+55·0	20	H_2O	2
— double compound + $AgNO_3$	176–180d.	EtOH	needles	..	..	..	3
Dihydro-δ-ethylthiocodide-A	156–157	EtOH	needles	+167·6	25	EtOAc	3
— benzoate	151–154	EtOH	..	+119·8	26	MeOH	3
Dihydro-δ-ethylthiocodide-B	..	..	oil	..	..	..	3
— malonate	170·5–171·5	H_2O	..	+101·1	22	MeOH	3

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Dihydro-δ-diethyldithiocodide	125–126	EtOAc	plates	−100·0	25	EtOAc	3
δ-ethylthiocodide methine	..	..	oil	..	..	..	2
— hydriodide	196–197	..	..	+49·0	20	H_2O	2
— methiodide	193–195	..	..	+39·0	20	H_2O	2
8-ethylthio-13-vinyltetrahydromorphenol methyl ether	97–100	..	..	+689·0	20	EtOH	2
α- (or δ-) ethylthiomorphide	D. 180	..	leaflets	..	..	..	15
β-ethylthiomorphide	D.200–202	MeOH	..	..	..	..	15
Diacetyl-β-ethylthiomorphide	..	..	amorph.	..	..	..	15
— methiodide·EtOH	D. 153	EtOH	..	..	..	..	15
O-desmethylthebainone: *see* Chap. XV							
Ethylthio-O-desmethyldihydrothebainone	D.205–208	..	needles	..	..	..	15
— oxime hydrochloride·H_2O	..	..	cryst.	..	..	..	15
Dihydro-β-diethyldithiomorphide	252d.	..	prisms	..	..	..	15
Bisthiocodide	200	EtOH	leaflets	..	..	..	1
— methiodide	253	..	needles	..	..	..	1
Bisthiomorphide	201	$CHCl_3$	needles	..	..	..	1

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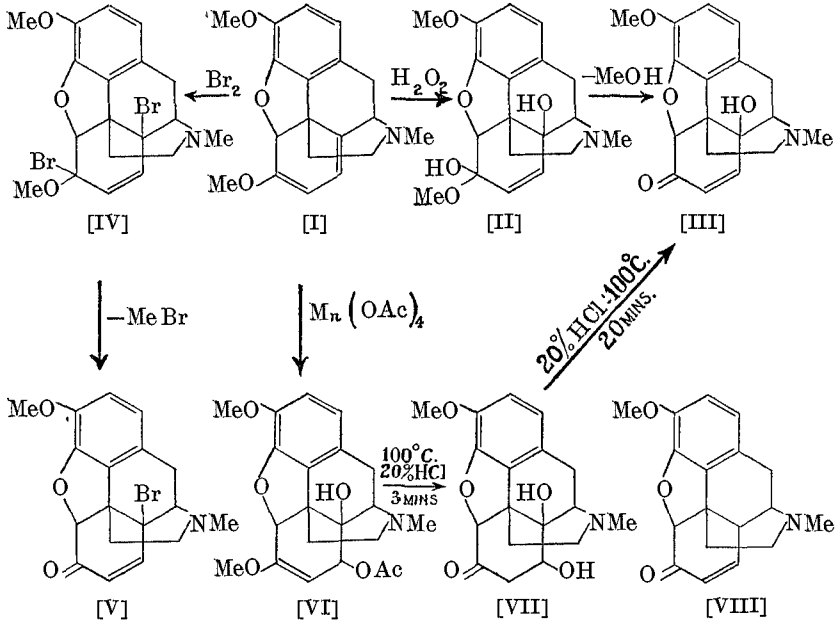
XVIII

14-HYDROXYCODEINONE, 14-BROMOCODEINONE, AND THEIR DERIVATIVES

THEBAINE-N-OXIDE is obtained when thebaine [I] is heated with 30 per cent. hydrogen peroxide alone [1–2], but when the alkaloid is heated with 30 per cent. hydrogen peroxide in glacial acetic acid a different substance, 14-hydroxycodeinone [III], is formed [3–7] (the maximum yield claimed for this reaction is 76·5 per cent. [7]). In the same way 14-bromocodeinone [V] results from the treatment of thebaine with bromine in glacial acetic acid [8]. These two compounds arise as a result of 1:4-addition of hydrogen peroxide and bromine to the conjugated diene system in thebaine to give, respectively, [II] and [IV], which then lose methyl alcohol and methyl bromide respectively, giving [III] and [V] [9].



14-Hydroxycodeinone has also been prepared by the oxidation of thebaine with sodium dichromate in aqueous acetic acid or sulphuric acid [3–5, 10–11]. The oxidation of thebaine with manganic acetate gives 8- (or 14-) acetyl-8:14-dihydroxydihydrothebaine [VI], which can

be hydrolysed by 20 per cent. hydrochloric acid at 100° C. to 8:14-dihydroxydihydrocodeinone [VII] after three minutes and 14-hydroxycodeinone [III] after twenty minutes [12]. These reactions indicate the structure [III] for 14-hydroxycodeinone.

STRUCTURE

That 14-hydroxy- and 14-bromocodeinone have the morphine skeleton intact is demonstrated by the reduction of the latter with ferrous hydroxide to codeinone [VIII] and catalytically to dihydrocodeinone [8, 13], and its conversion to 14-hydroxycodeinone oxime on treatment with hydroxylamine [8–9].

14-Hydroxycodeinone was first represented as an α-hydroxy-ketone, but such a formulation was rejected by Gulland and Robinson [9] on account of the stability of the base towards alkaline silver and cupric solutions, and, moreover, the base does not behave as an allylamine in its reaction with cyanogen bromide [4, 13–16]. A β-hydroxy-ketone structure was never seriously considered and is in any case at variance with the observed difficulty of dehydrating 14-hydroxycodeinone and its derivatives, but a γ-hydroxy-ketone formulation is compatible with all the experimental facts. 14 Hydroxycodeinone does not show the properties of a methylene-ketone, but its dihydro-compound does, facts best explained by postulating the presence of the system —CO—C=C—C—OH in the former [9].

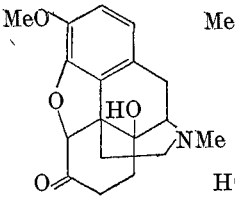
The location of the hydroxyl group at C-14 accounts for the stability of 14-hydroxycodeinone in acid solution; compounds of the morphothebaine and thebenine types are not formed, as aromatization would involve elimination of the group at C-14 as well as migration of the side-chain from C-13. The stability of 14-hydroxycodeinone and its derivatives to aromatizing dehydration is explained by the absence of a hydrogen atom on either C-13 or C-8. The loss of C-15 and C-16 during exhaustive methylation would not in itself render the structure aromatic and so retention of these two carbon atoms in the nitrogen-free product is not surprising.

REDUCTION

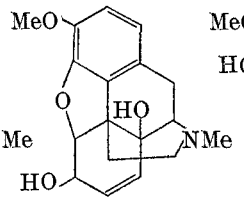
(*a*) Catalytic hydrogenation of 14-hydroxycodeinone [4, 10, 17–18] or reduction of this base with sodium hydrosulphite [1, 10, 19] affords 14-hydroxydihydrocodeinone [IX], which is marketed as the drug 'eukodal' [20–22].

(*b*) Reduction of 14-hydroxycodeinone with zinc-dust and acetic or formic acid [4, 10, 23], or zinc-dust and copper sulphate solution [23], yields '14-hydroxycodeine', which has been tentatively allotted the structure [X], though this is very unlikely in view of the work of Small and Lutz (see below).

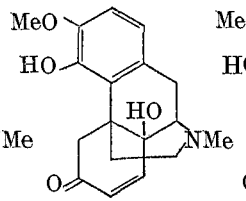
(*c*) Opening of the cyclic ether link occurs when 14-hydroxycodeinone is reduced with stannous chloride and hydrochloric acid, the product being 14-hydroxythebainone [XI] [3, 10, 23] (cf. the reduction of codeinone to thebainone-A). The formation of a substance of the metathebainone type by migration of the side-chain from C-13 to C-14 is blocked by the presence of a hydroxyl group at the latter position.



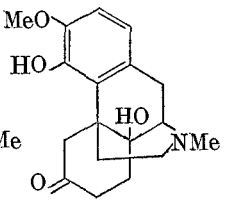
[IX]



[X]



[XI]



[XII]

(*d*) 14-Hydroxythebainone can be catalytically reduced to 14-hydroxydihydrothebainone [XII], which can be produced directly from 14-hydroxycodeinone by Clemmensen reduction [4], prolonged catalytic reduction [23], or reduction with sodium amalgam in alcohol [4].

(*e*) Clemmensen reduction was reported by Kondo and Ochiai [24–25] to give 'dihydrohydroxythebacodine', most probably 14-hydroxy-tetrahydrodesoxycodeine [XIII], but Small and Lutz were unable to detect this in any reduction of 14-hydroxycodeinone [6].

(*f*) 14-Hydroxythebainol [XIV] and a small amount of the above-mentioned '14-hydroxycodeine' result from the electrolytic reduction of 14-hydroxycodeinone [23].

(*g*) 14-Hydroxycodeinone is rapidly reduced by sodium in liquid ammonia to give an intractable mixture of phenolic bases the separation of which is still being attempted [26].

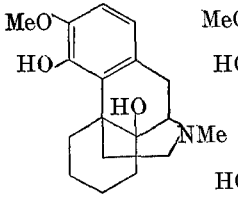
(*h*) Reduction of 14-hydroxycodeinone oxime in acid solution affords 14-hydroxydihydrocodeinone [IX] and in alkaline solution gives 14-hydroxydihydrothebainone [XII] [23]. This is further evidence for the α:β-unsaturated ketone structure of 14-hydroxycodeinone; the oximes of benzylidene- and dibenzylideneacetone are reduced to the saturated ketones under similar conditions, whilst dibenzylacetone oxime does not behave in this way [23].

(*i*) Catalytic reduction of 14-hydroxycodeinone hydrazone in aqueous acetone affords 14-hydroxydihydrocodeinone ketimine and 14-hydroxydihydrocodeinone dimethyl ketazine, formed by condensation of the hydrazone with acetone [27].

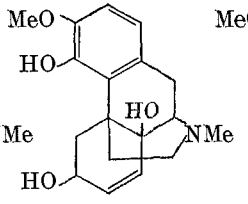
(*j*) Reduction of 14-bromocodeinone electrolytically or with ferrous sulphate yields codeinone [VIII] [8] and catalytic reduction gives dihydrocodeinone [13].

(*k*) Sodium hydrosulphite reduction of 14-bromocodeinone gives a

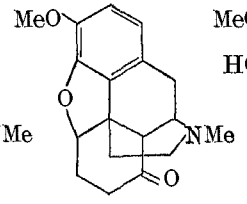
substance that Speyer and Rosenfeld suggested might be dihydro-ψ-codeinone [XV] [28], but the properties of the product do not agree with those of [XV] [29] (see Chap. X).



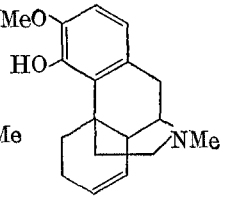
[XIII]



[XIV]



[XV]

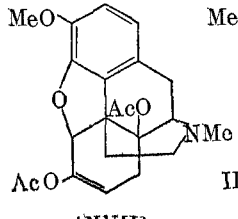


[XVI]

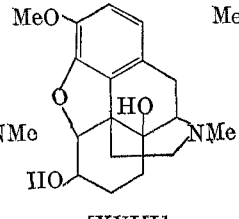
(*l*) Electrolytic reduction of 14-bromocodeinone also affords dihydrodesoxycodeine-E [XVI ?] [13, 30] (see Chap. IX).

14-Hydroxydihydrocodeinone [IX] forms an oxime [23] and a monoacetyl-derivative [4], indicating that the carbonyl and hydroxyl groups are still present in the molecule, and reacts with piperonal and 6-aminopiperonal as a methylene-ketone [9]. Prolonged treatment with acetic anhydride results in formation of acetyl-14-hydroxydihydrocodeinone enol acetate [XVII], gentle hydrolysis of which affords 14-acetoxydihydrocodeinone [6]. On warming with sodium amalgam 14-hydroxydihydrocodeinone is reported to be converted to an isomer of the same melting-point but differing in solubility; the salts of the two forms are identical [4].

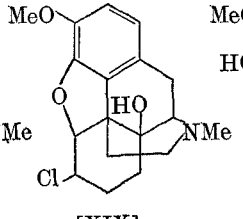
Catalytic hydrogenation of 14-hydroxycodeinone over platinum oxide affords mainly 14-hydroxydihydrocodeine-B together with a small amount of 14-hydroxydihydrocodeine-C. These are believed to have the structure [XVIII] and to differ only in the steric arrangement of the —CH·OH— group. Both are different from 14-hydroxydihydrocodeine-A which is formed by the catalytic hydrogenation of '14-hydroxycodeine' [6]. A rearrangement at C-14 during the catalytic reductions seems scarcely feasible, and it is most likely that a structural change occurs during the reduction of 14-hydroxycodeinone with zinc-dust and acetic acid, and this view is supported by pharmacological tests, which show that the 14-hydroxydihydrocodeines-B and C differ to about the extent expected for a pair of epimers, whilst the A-isomer differs widely from the other two [6].



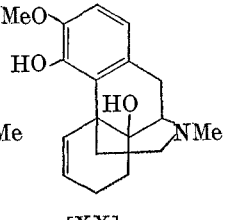
[XVII]



[XVIII]



[XIX]



[XX]

CHLORINATION

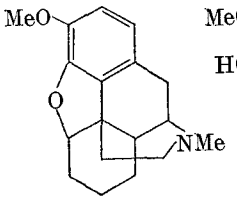
Treatment of 14-hydroxydihydrocodeine-B with thionyl chloride results only in chlorination of the aromatic nucleus (cf. the corresponding reaction with the four dihydrocodeine isomers, Chap. IV), but treatment with phosphorus pentachloride affords 14-hydroxy-6-chlorodihydrocodide [XIX]. That the hydroxyl group at C-6 is the one that is replaced by chlorine is revealed by the fact that reduction of [XIX] by sodium amalgam and alcohol is attended by rupture of the cyclic ether link, giving 14-hydroxydihydrodesoxycodeine-C [XX], which is readily reduced catalytically to 14-hydroxytetrahydrodesoxycodeine [XIII]. All attempts to reduce [XIX] to a non-phenolic base, or to secure elimination of hydrogen chloride with production of a substance of the desoxycodeine-C type failed [6].

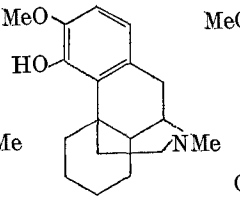
14-Hydroxydihydrocodeine-B on successive treatment with thionyl chloride and phosphorus pentachloride in either order is converted into 1-chloro-14-hydroxy-6-chlorodihydrocodide. It is surprising that only one of the two hydroxyl groups is replaced by halogen, and that this should be the secondary rather than the tertiary one; the reason for this may be that the latter is located at a ring juncture, but against this can be set the fact that neither the bromine of 14-bromocodeinone nor the similarly placed hydroxyl groups in certain toad poisons are inert [6].

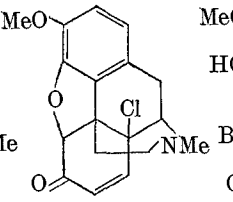
In contrast to 14-hydroxydihydrocodeine-B the C-isomer is converted by phosphorus pentachloride to substances containing phosphorus. The difference in behaviour of the two isomers is similar to that of the epimeric pair dihydrocodeine and dihydroisocodeine, and there is nothing about the chemical or pharmacological properties of the two isomers incompatible with the view that 14-hydroxydihydrocodeine-B has the codeine and the C-isomer the isocodeine arrangement of groups at C-6 [6].

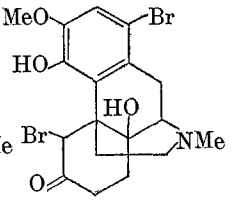
Compounds of the 14-hydroxycodeinone series yield mainly intractable substances on treatment with chlorinating agents. The most extensively studied of these reactions is that between 14-hydroxycodeinone and phosphorus pentachloride, which gives up to 20 per cent. of crystalline material. The product has been resolved into seven substances, namely, one monochloro-compound, two dichloro-compounds (believed to be ketochlorides), three trichloro-compounds (possibly ketochlorides with a chlorine atom at C-14), and a tetrachloro-compound [6, 31]. '14-chloroketochloride-A' can be catalytically reduced to dihydrodesoxycodeine-D [XXI] and tetrahydrodesoxycodeine [XXII] so must have the original skeleton intact [6]. The monochloro-compound is not identical with 14-chlorocodeinone [XXIII], which can be prepared in 80 per cent. yield by the action of iodobenzene dichloride on thebaine

[31]. Neither [XXIII] nor 14-bromocodeinone can be chlorinated with phosphorus pentachloride [31].


[XXI]


[XXII]


[XXIII]


[XXIV]

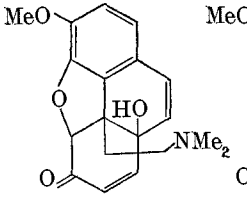
14-Hydroxythebainone [XI] gives only a monoacetyl-derivative, the phenolic hydroxyl group at C-4 being unreactive as in many similar compounds (e.g. tetrahydrodesoxycodeine [XXII]). It can be reduced catalytically to 14-hydroxydihydrothebainone [XII] [4, 23], which is also the product when 14-hydroxythebainone oxime is reduced in acid solution [23].

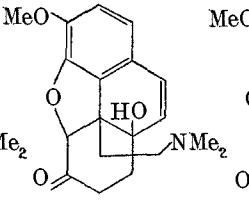
14-Hydroxydihydrothebainone [XII] can be brominated to give a 1:5-dibromo-compound [XXIV], which on treatment with alkali suffers the loss of hydrogen bromide and closure of the 4:5-ether bridge giving 1-bromo-14-hydroxydihydrocodeinone, which can be reductively debrominated to 14-hydroxydihydrocodeinone [32–33].

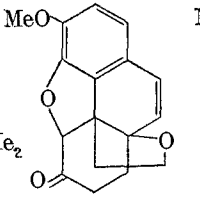
Hofmann Degradation

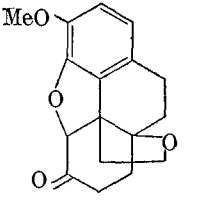
(*a*) The alkaline degradation of 14-hydroxycodeinone methiodide affords 14-hydroxycodeinone methine [XXV] [4, 3], further degradation of which affords no definite product [4].

(*b*) Hofmann degradation of 14-hydroxydihydrocodeinone affords 14-hydroxydihydrocodeinone methine [XXVI], further degradation of which proceeds with elimination of the nitrogen atom and cyclization of the residue of the side-chain with the hydroxyl group at C-14, the product being 'dihydrohydroxycodeone' [XXVII] [4, 34]. This may be roduced to 'tetrahydrohydroxycodeone' [XXVIII] [34]. These names are unsuitable as neither [XXVII] nor [XXVIII] contains a hydroxyl group.


[XXV]


[XXVI]

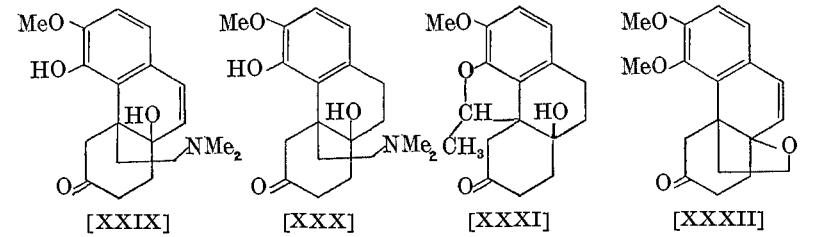

[XXVII]


[XXVIII]

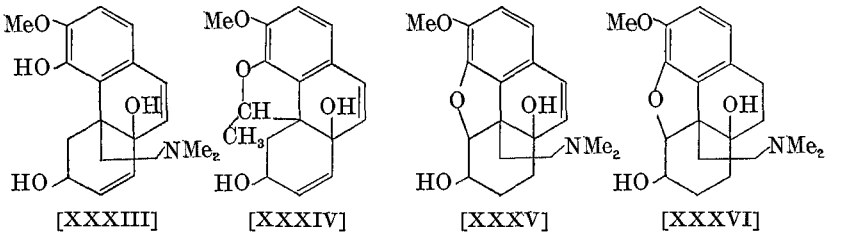
(*c*) 14-Hydroxydihydrothebainone can be degraded to 14-hydroxydihydrothebainone methine [XXIX] the resinous methiodide of which gives trimethylamine and a compound $C_{17}H_{16}O_4$ on degradation [3].

The dihydromethine [XXX] can be further degraded to 'tetrahydrohydroxythebaone' [4] which is most probably 14-hydroxythebenone [XXXI]; it is insoluble in alkali. 14-Hydroxydihydrothebainone methyl ether may be degraded to the methyl ethers of [XXIX] and [XXX] and also to nitrogen-free products, 'methyldihydrohydroxythebaone' [XXXII] and 'methyltetrahydrohydroxythebaone' [34].

(*d*) 14-Hydroxythebainol [XIV] has also been converted to a methine base [XXXIII] and nitrogen-free product [XXXIV ?] [23].



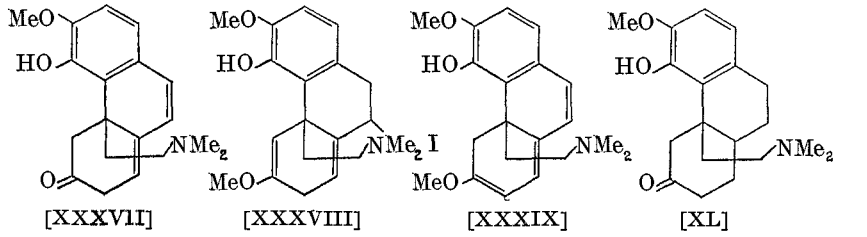
[XXIX] [XXX] [XXXI] [XXXII]



[XXXIII] [XXXIV] [XXXV] [XXXVI]

(*e*) Hofmann degradation of 14-hydroxydihydrocodeine-B affords 14-hydroxydihydrocodeine-B methine [XXXV] and 14-hydroxydihydrocodeine-B dihydromethine [XXXVI] [6].

The only recorded instance of the dehydration of a 14-hydroxycodeinone derivative is that recorded by Schöpf and Borkowsky, who claimed to have dehydrated 14-hydroxydihydrothebainone methine to [XXXVII] [34]. Now [XXXVII] has the structure assigned to thebainone-B methine obtained by the hydrolysis of dihydrothebaine-ϕ methiodide [XXXVIII] and β-dihydrothebaine methine [XXXIX] [35], and whereas thebainone-B methine can be hydrogenated to β-dihydrothebainone



[XXXVII] [XXXVIII] [XXXIX] [XL]

dihydromethine [XL] [35], the base of Schöpf and Borkowsky gives a different compound that was not analysed [34].

Miscellaneous Reactions

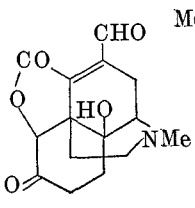
(i) Ozonolysis of 14-hydroxydihydrocodeinone yields 14-hydroxydihydrocodinal [XLI] [36].

(ii) 14-Hydroxycodeinone reacts with cyanogen bromide without scission of the nitrogen ring to give 14-hydroxycyanonorcodeinone [XLII] [4], which can be hydrolysed to 14-hydroxynorcodeinone [37]. Acetyl-14-hydroxydihydrocodeinone reacts similarly with cyanogen bromide.

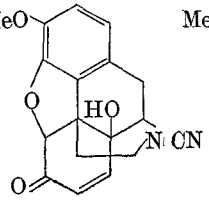
(iii) N-nitroso-14-hydroxydihydronorcodeinone [XLIII] is formed when 14-hydroxydihydrocodeinone is treated with nitrous acid [38].

(iv) 14-Hydroxycodeinone and 14-hydroxydihydrocodeinone are converted to -N-oxides by 30 per cent. hydrogen peroxide [4, 39] and 14-hydroxycodeinone-N-oxide can be sulphonated to two 14-hydroxycodeinone-N-oxide sulphonic acids, which may be reduced to 14-hydroxycodeinone sulphonic acid [17] or to 14-hydroxydihydrocodeinone sulphonic acid [40].

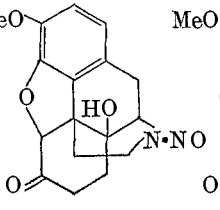
(v) 14-Hydroxydihydrocodeinone oxime sulphonic acid has been claimed to be formed by the action of sodium hydrosulphite on 14-hydroxycodeinone followed by conversion to the oxime [40].



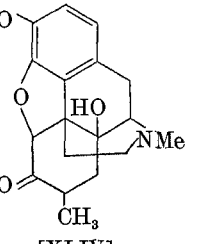
[XLI]



[XLII]



[XLIII]



[XLIV]

(vi) Bromination of 14-hydroxycodeinone affords 1-bromo, and 1:8 ?-dibromohydroxycodeinone, both of which may be catalytically reduced to 14-hydroxydihydrocodeinone [39]. Bromination of 14-hydroxydihydrocodeinone yields the 1:7:8-tribromocompound [39], which can be hydrolysed and reduced to 7:8:14-trihydroxydihydrocodeinone [39, 40].

(vii) Acetyl-14-hydroxydihydrocodeinone enol acetate [XVII] on treatment with methylmagnesium bromide gives two isomers of a phenolic base in unequal amounts, and these may be separated as their oxime hydrochlorides. Hydrolysis of the oxime of the major product apparently causes closure of the ether bridge, as the product is a new, non-phenolic base. Bromination, ether ring closure, and reductive elimination of bromine in an attempt to prepare a nuclear-methylated 14-hydroxydihydrocodeinone [e.g. XLIV] results in non-phenolic products, not obtained in a well-defined condition [6].

(viii) 14-Chlorocodeinone, like 14-bromocodeinone, gives the oxime of 14-hydroxycodeinone when treated with hydroxylamine [31].

Freund and Speyer [4] report that the prolonged action of 30 per cent. hydrogen peroxide at 100° C. on thebaine-N-oxide gives rise to 'dehydrothebaine', $C_{19}H_{19}O_3N$, about which nothing is known beyond the fact that it contains two methoxyl groups.

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
14-hydroxycodeinone	275–276	EtOH + $CHCl_3$	plates	−110·0	25	10% HOAc	4, 6, 7
— hydrochloride·H_2O	D.285–286	..	..	−149·7	20	H_2O	4
— hydrochloride·$2H_2O$	272–274d.	H_2O	..	−89·0	24	H_2O	6
— hydriodide	255–260d.	H_2O	..	−74·0	22	H_2O	6
— perchlorate	241–242d.	H_2O	plates	−80·0	25	H_2O	6
— methiodide	247	..	..	..	..	..	4
— oxime	D.279–280	..	..	..	..	..	4, 8
— oxime acetyl deriv.	214	..	..	..	..	..	4
— hydrazone	221–222	..	..	..	..	..	27
— dimethylketazine	171	..	..	..	..	..	27
— N-oxide	D. 243	..	needles	..	..	..	39
— N-oxide picrate	187–188	..	..	..	..	..	4
Acetyl-14-hydroxycodeinone	185	..	..	+21·0	25	10% HOAc	4, 6
— hydrochloride	260–261	H_2O	scales	+15·7	25	H_2O	4, 6
— oxime·H_2O	148	..	..	..	..	..	4
Benzoyl-14-hydroxycodeinone	245–247	..	..	..	..	..	4
— hydrochloride	..	..	cryst.	..	..	..	4
1-bromo-14-hydroxycodeinone	204–205	..	needles	−80·2	18	HOAc	39
— hydrobromide	D. 280	..	..	..	..	..	39
— phenylhydrazone	D. 250	..	..	..	..	..	39
Acetyl-1-bromo-14-hydroxycodeinone	238	..	..	..	..	..	39
1:8 ?-dibromo-14-hydroxycodeinone	194–195	..	..	−120·4	13	HOAc	39
— hydrobromide	265	..	..	..	..	..	39
— phenylhydrazone	D. 238	..	..	..	..	..	39
Acetyl-1:8 ?-dibromo-14-hydroxy-codeinone	219	..	..	..	..	..	39
Benzoyl-1:8 ?-dibromo-14-hydroxy-codeinone	216	acetone	plates	..	..	..	40
7:8:14-trihydroxycodeinone	..	..	..	..	..	..	40
Monobenzoyl-7:8:14:trihydroxy-codeinone	247	..	prisms	..	..	..	40
14-hydroxycodeinone sulphonic acid	D. 310	..	..	..	..	..	39
14-hydroxycodeinone-N-oxide sulphonic acid. 2 forms	D. 260 D. 270	.. H_2O	rods rods	.. ..	.. ..	.. ..	39 39
14-hydroxynorcodeinone	218	..	..	−123·3	13	HOAc	37
N-allyl-14-hydroxynorcodeinone	..	..	oil	..	..	..	37
— hydriodide	192	..	..	..	..	..	37
N-nitroso-14-hydroxynorcodeinone	234	..	..	..	..	..	37
Cyano-14-hydroxynorcodeinone	255	..	..	..	..	..	4
— oxime	..	..	..	..	..	..	4
14-hydroxycodeinone methine	..	..	amorph.	..	..	..	4
— methiodide	267d.	..	..	..	..	..	4
14-hydroxydihydrocodeinone	218	EtOH	..	−97·0	25	10% HOAc	4, 6
— hydrochloride	268–270	H_2O	..	−125·5	20	H_2O	4
— hydriodide	189–190	..	..	..	..	..	4
— camphorsulphonate·H_2O	180–183	H_2O	..	−76·7	..	H_2O	41
— methiodide	D. 251	..	..	..	..	..	4
— oxime hydrochloride	D.275–278	..	..	..	..	..	4
— oxime hydrochloride methiodide	D.275–278	..	..	..	..	..	4
— hydrazone	213–214	..	leaflets	..	..	..	27
— phenylhydrazone	204	..	..	..	..	..	4
— ketimine	216–217	..	..	..	..	..	27
— dimethylketazine	159	..	..	..	..	..	27
— N-oxide	D. c. 210	EtOH	prisms	..	..	..	40
Acetyl-14-hydroxydihydrocodeinone	215–216	EtOH	..	..	..	..	4
— oxime hydrochloride	170–180	..	..	..	..	..	4
— enol acetate	207·5	MeOH	..	−107·0	20	MeOH	6

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Benzoyl-14-hydroxydihydrocodeinone	275–276	..	..	..	..	..	4
1-bromo-14-hydroxydihydro-codeinone	182	EtOH	plates	..	..	..	32, 39
— hydrobromide	D.227–230	..	needles	−93·1	13	H_2O	39
— semicarbazone	249	..	..	..	..	..	39
Acetyl-1-bromo-14-hydroxydihydro-codeinone	217	EtOH	..	..	..	..	39
1:7:8-tribromo-14-hydroxydihydro-codeinone	D. 228	acetone	prisms	−225·6	13	HOAc	39
— hydrobromide	D. 255	..	..	..	..	..	39
Acetyl-1:7:8-tribromo-14-hydroxy-dihydrocodeinone	220	..	..	..	..	..	39
1-bromo-7:8:14-trihydroxydihydro-codeinone	D. 302	..	leaflets	..	..	..	39
Monoacetyl-1-bromo-7:8:14-tri-hydroxydihydrocodeinone	D. 267	..	..	..	..	..	39
Monobenzoyl-1-bromo-7:8:14-tri-hydroxydihydrocodeinone	128–129	H_2O	needles	..	..	..	40
— hydrochloride·$3H_2O$	215	H_2O	needles	..	..	..	40
— oxime·$3H_2O$	D. 344	..	..	..	..	..	40
— phenylhydrazone hydriodide	D. 256	..	..	..	..	..	40
7:8:14-trihydroxydihydrocodeinone	D. 320	..	prisms	..	..	..	39
Piperonylidene-14-hydroxydihydro-codeinone	..	..	amorph.	..	..	..	9
Dianhydro-6-aminopiperonal-14-hydroxydihydrocodeinone	282–283	..	prisms	..	..	..	9
14-hydroxydihydrocodeinone sul-phonic acid	D. > 280	H_2O	prisms	..	..	..	40
— oxime	> 340	H_2O	needles	..	..	..	40
14-hydroxydihydronorcodeinone	..	..	oil	..	..	..	38
— hydriodide	D. 295	..	..	−114·5	13	..	38
N-allyl-14-hydroxydihydronor-codeinone	..	..	oil	..	..	..	38
— hydrobromide	D. 182	..	..	..	..	..	38
N-nitroso-14-hydroxydihydronor-codeinone	D. 259	EtOH	..	..	..	..	38
Acetylcyano-14-hydroxydihydronor-codeinone	D. 256	..	..	..	..	..	37
14-hydroxydihydrocodeinone methine	115	..	..	..	..	..	4
— methiodide	255–256	..	..	..	..	..	4
— oxime	185–186	..	..	..	..	..	4
14-hydroxydihydrocodeinone dihydromethine	136–137	..	..	..	..	..	34
— methiodide	280	..	..	..	..	..	34
'Dihydrohydroxycodeone'	214–215	..	..	−140·8	20	$CHCl_3$	4, 23
'Tetrahydrohydroxycodeone'	150–153	..	..	..	..	..	23
'14-hydroxycodeine'	304–305	EtOH + $CHCl_3$	..	−143·0	25	10% HOAc	6
	293	..	..	−119·5	20	dil. HOAc	4, 23
— hydrochloride	269–275	dil. HCl	..	..	..	..	6
— hydrobromide	D. 290	..	..	..	..	..	4
Monoacetyl-14-hydroxycodeine	D. 265	..	..	..	..	..	4
— methiodide	D. 265	..	..	..	..	..	23
14-hydroxydihydrocodeine-A	301–302	$CHCl_3$ + EtOH	plates	−64·0	19	10% HOAc	6
14-hydroxydihydrocodeine-B	145–145·5	EtOAc	plates	−136·0	26	10% HOAc	6
— methiodide	223–224	EtOH	..	−87·0	21	H_2O	6
Diacetyl-14-hydroxydihydro-codeine-B	181–182	H_2O + EtOH	..	−127·0	22	10% HOAc	6
— acid tartrate·H_2O	181–182	H_2O	..	−82·0	29	H_2O	6
14-hydroxydihydrocodeine-C	166–167	40% EtOH	scales	−152·0	23	10% HOAc	6
Diacetyl-14-hydroxydihydrocodeine-C	203	80% EtOH	needles	−107·0	22	10% HOAc	6
— acid tartrate	209–210	H_2O	scales	−72·0	29	H_2O	6
14-hydroxydihydrocodeine-B methine	103	Et_2O	..	−70·0	21	10% HOAc	6
— acid tartrate·$4H_2O$	100–101	H_2O	..	−25·0	21	H_2O	6
14-hydroxydihydrocodeine-B dihydromethine	108	EtOAc	..	−44·0	22	10% HOAc	6

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
1-chloro-14-hydroxydihydro-codeine-B	..	..	oil	..	..	..	6
— hydrochloride	238–239	EtOH	..	−106·0	21	H_2O	6
1-chloro-14-hydroxy-6-chloro-dihydrocodide	163·5	EtOH	prisms	−141·0	22	10% HOAc	6
14-hydroxy-6-chlorodihydrocodide	213·5–214	EtOAc	..	−151·0	22	10% HOAc	6
14-hydroxydihydrodesoxycodeine-C	137–138	Et_2O	..	−19·0	22	10% HOAc	6
14-hydroxytetrahydrodesoxycodeine — perchlorate	242–244	H_2O	..	−28·0	21	H_2O	6
Phosphorus compd. from 14-hydroxy-dihydrocodeine-C + PCl_5	136–139	..	..	..	..	..	6
14-hydroxythebainone	D.104–106	Et_2O + EtOH	..	..	..	..	4, 23
— hydrochloride	D. 305	..	..	−68·8	18	H_2O	4
— methiodide	245	..	..	..	..	..	4, 23
— dibromide	258	..	..	..	..	..	4, 23
— oxime	D. 255	..	..	..	..	..	23
Acetyl-14-hydroxythebainone	197	EtOH	..	..	..	..	23
— methiodide	212–213	..	..	..	..	..	23
— oxime	216–218	..	..	..	..	..	23
14-hydroxydihydrothebainone	140–145	petrol	..	..	..	..	4, 23, 34
— hydrochloride	D. 310	..	..	−52·5	20	H_2O	34
— hydrochloride·$2H_2O$	270–272	95% EtOH	..	−123·0	25	H_2O	6
— perchlorate	170–180 / D. 270	H_2O / EtOH	..	..	..	..	4
— methiodide·H_2O	D. 210	..	..	..	..	..	4
— oxime	220–222	..	..	..	..	..	4
Acetyl-14-hydroxydihydrothe-bainone	214	EtOH	..	..	..	..	4
14-hydroxydihydrothebainone methyl ether	151–153	..	..	..	..	..	34
— perchlorate	134	..	..	..	..	..	4
— methiodide	206–208	..	..	..	..	..	34
14-hydroxydihydrothebainone methine	242–243	..	..	−81·9	20	dil. HOAc	4
— hydriodide	c. 158	..	..	..	..	..	4
14-hydroxydihydrothebainone methyl ether methine	131–133	..	..	..	..	..	34
— methiodide	209	..	..	..	..	..	34
14-hydroxydihydrothebainone dihydromethine	239–240	..	..	−45·2	20	dil. HOAc	4
— methiodide	..	..	..	..	..	..	4
14-hydroxydihydrothebainone methyl ether dihydromethine	83–85	..	..	..	..	..	34
'Tetrahydrohydroxythebaone'	143–144	..	..	..	..	..	4
'Methyldihydrohydroxythebaone'	87–89	..	..	..	..	..	34
'Methyltetrahydrohydroxythebaone'	74–76	..	..	..	..	..	34
14-hydroxythebainol	234	$CHCl_3$	prisms	..	..	..	23
— hydrobromide	252–253	..	..	..	..	..	23
— hydriodide·H_2O	247	H_2O	..	..	..	..	23
— picrate	204–205	..	..	..	..	..	23
— N-oxide	D. 237	..	..	..	..	..	23
— methyl ether methiodide	D. 233	H_2O	..	..	..	..	23
Formyl-14-hydroxythebainol	277	..	..	..	..	..	23
— hydriodide	D. > 305	..	..	..	..	..	23
Benzoyl-14-hydroxythebainol	D. 257	..	..	..	..	..	23
14-hydroxythebainol methyl ether methine	195–197	..	..	..	..	..	23
— hydriodide	255	..	..	..	..	..	23
— methiodide	D.239–240	..	..	+141·8	20	H_2O	23
— N-free product $C_{18}H_{20}O_4$	188–189	..	..	−29·0	19	$CHCl_3$	23
14-hydroxydihydrocodinal	285d.	..	..	..	..	..	36
14-bromocodoinone	156–157	..	..	..	..	..	8, 13
— hydrochloride·$2H_2O$	104	..	..	..	..	..	8
— hydrobromide·H_2O	197–198	..	..	..	..	..	8
— $Na_2S_2Cl_4$ redn. product	D.240–241	..	..	..	..	..	28
1-nitro-14-bromocodoinone	D. 210	..	prisms	..	..	..	40
14-chlorocodoinone	..	..	..	..	..	..	31

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Acetyl-8:14-dihydroxydihydrothebaine	196	Et_2O	..	..	..	..	12
8:14-dihydroxycodeinone	171	..	..	..	..	..	12
—chromate	..	..	needles	..	..	..	12
Dehydrothebaine	..	..	yellow cryst.	..	..	..	4

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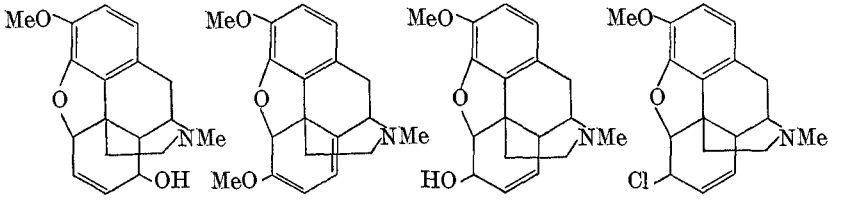
XIX

THE REACTION OF ψ-CODEINE AND THEBAINE DERIVATIVES WITH GRIGNARD REAGENTS

THE cyclic ether link and 6:7-double bond in derivatives of ψ-codeine [I] and thebaine [II] form a reactive conjugated system capable of undergoing a reaction with Grignard reagents that involves scission of the ether bridge and entry of an organic radical into the molecule. Activation of the 4:5-ether bridge by a 6:7-double bond appears to be necessary for reaction to occur, as derivatives of codeine [III], ψ-codeine, and thebaine that have no such double bond cannot be made to react with Grignard reagents. (The reaction between α-chlorocodide [IV] and methylmagnesium iodide is no exception to this, as in that case the Grignard reagent functions in a reducing capacity only; see Chap. VIII.)



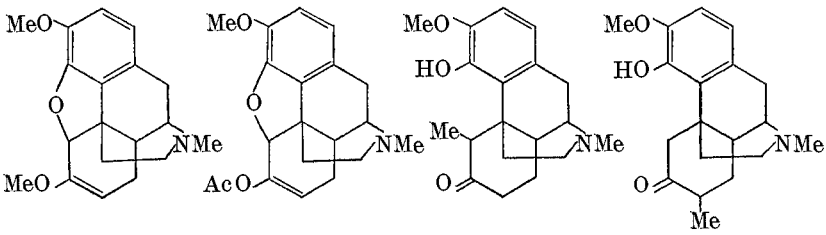
[I] [II] [III] [IV]

The reactions may be divided into two types: (*a*) those giving 'normal' products, and (*b*) those giving 'abnormal' products in which a marked change in the original molecular structure has occurred. Of these the former only are considered here, the latter being discussed in Chapter XX.

THE REACTION OF DIHYDROTHEBAINE WITH METHYLMAGNESIUM HALIDES

Methylmagnesium halides readily react with dihydrothebaine [V] [1–7] when this is slowly introduced into the reaction mixture, giving mainly the phenolic base methyldihydrothebainone together with 10 per cent. of an isomeric phenol *iso*methyldihydrothebainone, the enol ether group of [V] being hydrolysed during the reaction or, more probably, during the isolation of the products. A more convenient method of preparation of these bases is by the very vigorous reaction of methylmagnesium halides with dihydrocodeinone enol acetate [VI], which is more easily prepared than dihydrothebaine [8]. It has been

discovered that the enol acetates of any of the 6-ketodihydro-compounds in the morphine series will react similarly with Grignard reagents [8].



[V] [VI] [VII] [VIII]

Three reasonable explanations of the isomerism of methyl- and *iso*-methyldihydrothebainone may be envisaged:

(*a*) The two bases might be 5- [VII] and 7- [VIII] substituted substances, arising from competing 1:2 and 1:4-addition of the Grignard reagent to the system $-\overset{1}{O}-\overset{2}{C}-\overset{3}{C}=\overset{4}{C}-$.

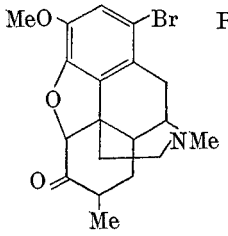
(*b*) The two bases might be stereoisomers at C-5 [VII].

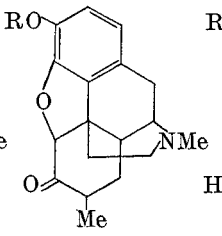
(*c*) The two bases might be stereoisomers at C-7 [VIII].

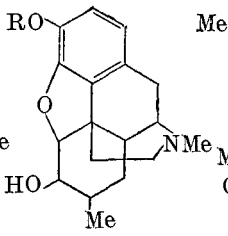
The cause of the isomerism remains obscure, but in this account, in order to simplify the formulation of further reaction products, methyldihydrothebainone is arbitrarily assigned the structure [VIII] and *iso*methyldihydrothebaine the structure [VII].

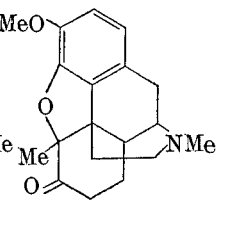
A compound of structure [VIII], and also possibly [VII], would be expected to undergo bromination and cyclization to give a derivative of dihydrocodeinone, a sequence of reactions that has been achieved with both isomers. Methyldihydrothebainone [VIII ?] on treatment with bromine yields a dibromo-compound (not isolated) which is converted by alkali to 1-bromomethyldihydrocodeinone [IX ?], and this may be reduced to methyldihydrocodeinone [X ?, R = Me]. Demethylation of the latter affords methyldihydromorphinone [X ?, R = H]. Catalytic hydrogenation of dihydrocodeinone yields only dihydrocodeine, with no trace of dihydroisocodeine, and reduction of methyldihydrocodeinone and methyldihydromorphinone under the same conditions gives methyldihydrocodeine [XI, R = Me] and methyldihydromorphine [XI, R = H] respectively [1].

*Iso*methyldihydrocodeinone [XII ?] may be prepared via the 1-bromo-derivative from *iso*methyldihydrothebainone [VII ?], but cannot be demethylated to the dihydromorphinone [1]. The conversion of [VII ?] to [XII ?] is accompanied by the production of *iso*methyl-7-ketodihydrothebainone (cf. the production of 1-bromo-7-ketodihydrothebainone, (—)-1-bromosinomeninone, in the conversion of dihydrothebainone to 1-bromodihydrocodeinone (Chap. XV)) [8]. This supports the structure [VII] for *iso*methyldihydrothebainone.

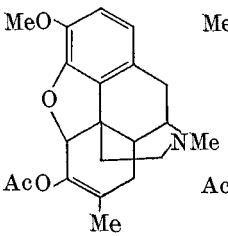

[IX]

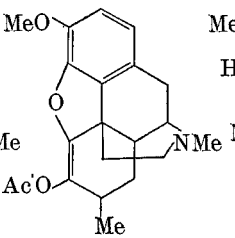

[X]

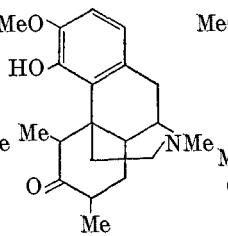

[XI]

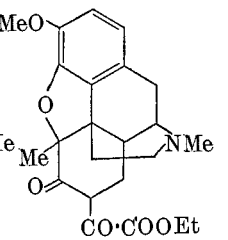

[XII]

The possibility of methyl and *iso*methyldihydrothebainone being diastereoisomers at C-7 is eliminated by the fact that the corresponding methyl and *iso*methyldihydrocodeinones do not give identical enol acetates; the possibility of the isomerism of the enol acetates arising from enolization in both of the two possible ways, [XIII] and [XIV], is discounted by the fact that each enol acetate reacts with methylmagnesium iodide, indicating that each has a 6:7-double bond in the molecule. The product of this second Grignard reaction is, in both cases, the same dimethyldihydrothebainone [XV ?] [8].


[XIII]


[XIV]


[XV]

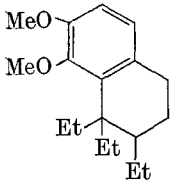

[XVI]

The possibility that the two methyldihydrothebainones are epimers at C-5 seems unlikely as stereochemical considerations appear to indicate that closure of the 4:5-oxygen bridge in such compounds would occur with the hydrogen at C-5 in one configuration only [9]. However, against this may be cited the fact that the only crystalline substance recovered after attempted closure of the 4:5-oxygen bridge in dimethyldihydrothebainone is the unchanged phenol, suggesting that in the latter C-5 is fully substituted [8].

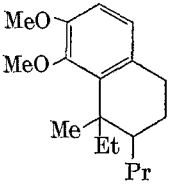
If the isomerism is the result of competing 1:2 and 1:4 addition of the Grignard reagent to dihydrothebaine, then the isomeric methyldihydrocodeinones resulting from closure of the ether bridge would have the structures [X, R = Me] and [XII], and of these only [XII] would be expected to condense with ethyl oxalate (to give [XVI]), as the latter condenses with —CO—CH_2— but not with —CO—CH— [10–12]. Both methyl- and *iso*methyldihydrocodeinone condense with ethyl oxalate and sodium ethoxide, but not with sodium ethoxide alone, giving

methyl- and *iso*methyldihydrocodeinone glyoxalic acid—reactions that tend to show that the two bases are diastereoisomers at C-5 [1].

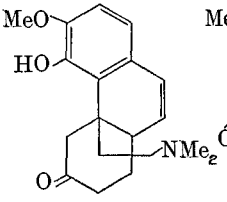
The structural problem remains unsolved, but as dihydrocodeinones can be converted into dihydrothebaines by sodium tertiary butoxide and methyl sulphate, it is possible that the problem will receive a solution by the degradation of methyl- and *iso*methyldihydrothebaines in a manner similar to the degradation of dihydrothebaine to [XVII] or [XVIII] [13–14] (see Chap. XIII).



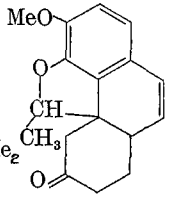
[XVII]



[XVIII]



[XIX]



[XX]

Methyl- and *iso*methyldihydrothebainone have been degraded by Hofmann's method to the corresponding derivatives of dihydrothebainone methine [XIX] and 9:10-dehydrothebenone [XX] [15].

The Reaction of Dihydrothebaine with other Grignard Reagents

(*a*) The reaction between dihydrothebaine and ethylmagnesium iodide affords ethyl- and *iso*ethyldihydrothebainone, the former of which has been converted to ethyldihydrocodeinone and ethyldihydromorphinone, reduction of which could not be effected [8].

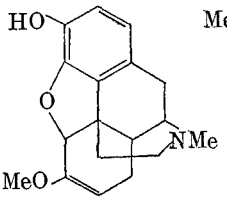
(*b*) Dihydrothebaine reacts with *iso*propylmagnesium iodide to give *iso*propyldihydrothebainone and dihydromorphinone Δ^6-enol methyl ether, the latter being formed by the demethylation of dihydrothebaine by the Grignard reagent. Ring closure of *iso*propyldihydrothebainone to *iso*propyldihydrocodeinone can be effected as before and the reverse change can be brought about by the Clemmensen reduction of the latter. Neither *iso*propyldihydrocodeinone nor *iso*propyldihydromorphinone can be reduced at the carbonyl group [8].

(*c*) *n*-Amyl- and benzyldihydrothebainones have been prepared and these have been converted to the corresponding substituted dihydrocodeinones and dihydromorphinones [8].

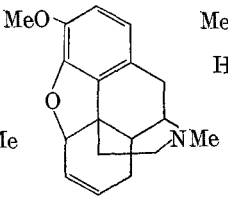
(*d*) Phenyl- and *iso*phenyldihydrothebainones, which result from the interaction of dihydrothebaine and phenylmagnesium bromide, can be converted to phenyldihydrocodeinone and *iso*phenyldihydrocodeinone, the first of which can be demethylated, when phenyldihydromorphinone is obtained. Vacuum-distillation of *iso*phenyldihydrothebainone methyl ether methochloride in an attempt to obtain the base affords a substance

having the composition of phenyl-3:4-dimethoxy-6-keto-5:6:7:8-tetrahydrophenanthrene; there is no obvious explanation of this reaction [8].

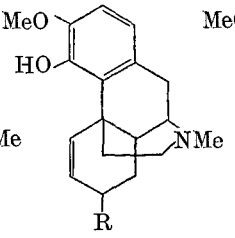
(*e*) As a by-product in the reaction between dihydrothebaine and *iso*propyl- and phenylmagnesium halides dihydromorphinone Δ^6-enol methyl ether is obtained. The identity of this base [XXI] was revealed by its conversion to dihydrothebaine on treatment with diazomethane [8]. The demethylating action of Grignard reagents has been noted at high temperatures [16–18], but is surprising at the temperature of boiling benzene.



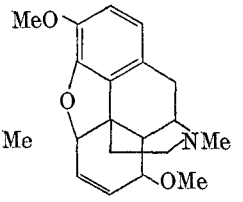
[XXI]



[XXII]



[XXIII]



[XXIV]

Desoxycodeine-C [XXII] also reacts with Grignard reagents. With methylmagnesium iodide it gives methyldihydrodesoxycodeine-C [XXIII ?, R = CH_3], but with ethylmagnesium iodide two isomers of the resulting product are obtained, one only after hydrogenating the reaction mixture. Both methyl and ethyldihydrodesoxycodeine-C can be hydrogenated to dihydro-derivatives with an ease compatible with structure [XXIII], and the same is true of *cyclo*hexyldihydrodesoxycodeine-C. Distillation of methyldihydrodesoxycodeine-C with zinc-dust afforded a colourless liquid that could be separated into two picrates having melting-points identical with those of the picrates of 2- and 4-methylphenanthrene, but both gave melting-point depressions when mixed with authentic specimens of the latter two picrates. A crystalline hydrocarbon was also obtained and shown to have a composition corresponding to that of a methylphenanthrene, but its physical properties differ from those of any of the five methylphenanthrenes [19].

With phenylmagnesium bromide desoxycodeine-C affords phenyldihydrodesoxycodeine-C and, after hydrogenation of the reaction mixture, a small amount of phenyltetrahydrodesoxycodeine-C, which must be derived from a compound other than the main product as the latter cannot be hydrogenated to a dihydro-derivative. Hydrogenation of phenyldihydrodesoxycodeine-C over platinum oxide in glacial acetic acid results in addition of eight atoms of hydrogen to the molecule and the product, octahydrophenyldihydrodesoxycodeine-C, is not identical with *cyclo*hexyltetrahydrodesoxycodeine-C [19]. Now, whereas Small

and Yuen identify the analytical data of phenyldihydrodesoxycodeine-C with the composition $C_{24}H_{27}O_2N$, they are equally compatible with $C_{24}H_{29}O_2N$; the double bond of [XXIII, R = ϕ] would on the latter formulation be reduced during the Grignard reaction, an unusual but not altogether impossible reaction. If this is so, the resistance of phenyldihydrodesoxycodeine-C to hydrogenation is hardly surprising and the addition of eight atoms of hydrogen when the reaction is forced can be explained by assuming saturation of the phenyl group and reductive scission of the nitrogen-containing ring [20].

ψ-Codeine methyl ether [XXIV] with methylmagnesium iodide yields methyldihydro-ψ-codeine methyl ether, a phenolic base that is very resistant towards hydrogenation [8]. The analytical data appear to exclude the possibility that the compound is really methyltetrahydro-ψ-codeine methyl ether, but it is conceivable that the compound has a structure analogous to phenyldihydrothebaine (see Chap. XX), though this would require two hydrogen atoms less than it appears to contain. In this connexion it is of interest to note that the reaction in *iso*propyl ether also affords a substance giving analytical data for, and no melting-point depression with tetrahydro-ψ-codeine methyl ether, though differing from this in certain physical properties [8].

The reaction between methylmagnesium iodide and acetyl-14-hydroxydihydrocodeinone enol acetate [21] is discussed in Chapter XVIII.

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Methyldihydrothebainone	192–193	95% EtOH / acetone	plates / rods	−20·5	25	EtOH	1
— hydrochloride	283–285*	EtOH	..	−6·8	25	H_2O	1
— methiodide	212–216*	acetone	..	+3·9	26	H_2O	1
— oxime	244*	H_2O+EtOH	..	+69·4	24	H_2O	1
— oxime hydrochloride	244*	H_2O	..	+38·9	24	H_2O	1
Acetylmethyldihydrothebainone	179–179·5	EtOAc	..	+13·1	26	EtOH	1
1-bromomethyldihydrothebainone	207–208	EtOAc	..	−33·2	24	EtOH	1
Methyldihydrothebainone methine	164–165	EtOAc	needles	+163·0	20	EtOH	15
— methiodide	246–249*	MeOH	..	+117·0	20	EtOH	15
Methyl-9:10-dehydrothebenone	183–184	EtOH	..	+262·0	20	acetone	15
*Iso*methyldihydrothebainone	168–168·5	acetone	needles	−57·0	24	EtOH	1
— hydriodide	259–260*	EtOH	..	−28·0	21	H_2O	8
— methiodide·H_2O	194–196*	acetone	needles	−18·6	21	H_2O	8
— oxime	191–192*	EtOH	needles	−82·4	24	EtOH	1
Acetyl*iso*methyldihydrothebainone	157–158	acetone	..	−9·9	24	EtOH	1
1-bromo*iso*methyldihydrothebainone	237–239*	EtOH	..	−66·2	21	EtOH	8
Isomethyl-7-ketodihydrothebainone	172 / 258–259*	EtOAc / subl.	..	−67·3 / −97·4	21	EtOH	8
Methyldihydrothebainone	190·5–191·5	EtOH	..	+10·9	25	EtOH	8
— hydrochloride	280–282*	..	needles	+17·8	21	H_2O	8
— hydriodide	253–255*	EtOH	..	+14·0	22	H_2O	8
1-bromomethyldihydrothebainone ·½EtOH	201·5–202·5	EtOH	..	−6·8	23	EtOH	8
Isomethyldihydrothebainone	188–189	EtOH	..	−36·2	22	EtOH	8
hydriodide·H_2O	191–193*	MeOH	..	−4·1	23	H_2O	8
— methiodide·½H_2O	237–240*	MeOH	..	−5·8	23	H_2O	8

* In evacuated tube.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Isopropyldihydrothebainone	217·5–219·5	EtOH	needles	−31·0	23	$CHCl_3$	8
— hydrochloride	273–275*	EtOH	rods	−18·3	25	H_2O	8
— hydrobromide	277–277·5*	H_2O	..	−12·6	24	H_2O	8
— perchlorate	236–238*	EtOH	..	−16·0	25	acetone	8
— salicylate	165–185*	EtOH	needles	−8·9	25	acetone	8
— oxime·$2H_2O$	199–201	EtOH	..	+13·5	25	EtOAc	8
— oxime hydrochloride	213–215*	..	..	+43·8	26	H_2O	8
1:5-dibromoisopropyldihydrothebainone hydrobromide	230–232*	EtOH	..	−2·7	24	EtOH	8
n-Amyldihydrothebainone	153–155	acetone	..	−12·8	26	EtOH	8
— hydrochloride·H_2O	203–205	H_2O	..	+2·8	24	EtOH	8
— hydrobromide	223–224·5*	H_2O	plates	+1·5	25	EtOH	8
— hydriodide	238–239*	50% EtOH	plates	−1·4	25	EtOH	8
— perchlorate·$\frac{1}{2}H_2O$	235–236*	25% EtOH	plates	−2·1	25	EtOH	8
— sulphate·H_2O	95–105	H_2O	rods	0	24	EtOH	8
— oxime	113–115	EtOH	plates	+18·6	25	EtOH	8
1-bromo-*n*-amyldihydrothebainone	241–242	EtOH	rods	−30·6	25	EtOH	8
Benzyldihydrothebainone	227–229	EtOH	needles	−51·6	25	$CHCl_3$	8
— hydrochloride	243–244*	EtOH	..	−29·0	25	H_2O	8
— oxime	135–142	benzene	..	+5·5	25	$CHCl_3$	8
1-bromobenzyldihydrothebainone	230–232*	EtOH	needles	−59·4	23	EtOH	8
Phenyldihydrothebainone	230–232	EtOH	..	−165·9	24	$CHCl_3$	8
— perchlorate	201*	95% EtOH	..	−97·6	25	acetone	8
— methiodide	245–248*	30% EtOH	..	−96·5	25	EtOH	8
— oxime	198–200	EtOH	..	−106·7	24	EtOH	8
*Iso*phenyldihydrothebainone	213–215	EtOH	needles	+34·8	24	$CHCl_3$	8
— methiodide	214–215	EtOAc+MeOH	..	0	24	EtOH	8
— oxime	230–232	EtOAc	needles	−157·0	24	EtOH	8
— methyl ether methiodide	264–265*	MeOH+EtOAc	..	+49·3	24	EtOH	8
— methyl ether methochloride	239–243	..	..	..	..	..	8
Phenyl-3:4-dimethoxy-6-keto-5:6:7:8-tetrahydrophenanthrene?	227–230	EtOAc	plates	−130·0	22	benzene	8
Dimethyldihydrothebainone	199–202	acetone	..	+3·5	26	EtOH	8
— oxime	c. 70–90	petrol	..	..	..	..	8
Methyldihydrothebainone methine	164–165	EtOAc	needles	+163·0	20	EtOH	15
— methiodide	246–249	MeOH	..	+117·0	20	EtOH	15
*Iso*methyldihydrothebainone methine	193	EtOAc	..	+231·0	20	EtOH	15
— methiodide	..	..	amorph.	..	..	..	15
Methyl-9:10-dehydrothebenone	183–184	EtOH	..	+262·0	20	acetone	15
*Iso*methyl-9:10-dehydrothebenone	116·5–117	EtOH	..	+252·0	20	EtOH	15
Methyldihydrocodeinone	144–144·5	EtOAc	needles	−146·9	23	EtOH	1
— methiodide	246–248	EtOAc	..	−74·2	24	H_2O	1
1-bromomethyldihydrocodeinone	143·5–145	EtOAc	..	−109·4	24	EtOH	1
Methyldihydrocodeinone enol acetate	191·5–194·5	EtOAc	..	−142·9	23	EtOH	1
Methyldihydrocodeinone glyoxalic acid hydrochloride	..	..	cryst.	..	..	..	1
*Iso*methyldihydrocodeinone	144–145	EtOAc	..	−179·4	24	EtOH	1
— hydrochloride	191–193*	EtOH	needles	−122·1	21	H_2O	8
— hydriodide·H_2O	209–210	EtOH	needles	−102·1	21	H_2O	8
*Iso*methyldihydrocodeinone enol acetate	123–124	EtOAc	..	−250·3	24	EtOH	1
*Iso*methyldihydrocodeinone glyoxalic acid	..	..	oil	..	..	..	1
Ethyldihydrocodeinone	163–164	EtOAc	needles	−100·9	25	EtOH	8
— methiodide·$\frac{1}{2}H_2O$	255–257*	EtOH	..	−48·8	21	H_2O	8
1-bromoethyldihydrocodeinone	..	..	oil	..	..	..	8
Ethyldihydrocodeinone enol acetate	120–130	50% EtOH	..	−124·1	25	EtOH	8
Isopropyldihydrocodeinone	175–177	EtOH	needles	−110·5	26	EtOH	8
— hydrobromide	202–203*	H_2O	needles	−58·3	25	H_2O	8

* In evacuated tube.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Isopropyldihydrocodeinone hydriodide·H_2O	196–198*	H_2O	rods	−67·2	25	EtOH	8
—methiodide	274–275*	H_2O+EtOH	..	−66·0	25	acetone	8
— oxime	224–226*	EtOAc	lozenges	−25·0	23	EtOH	8
1-bromoisopropyldihydrocodeinone	164–167	EtOAc	..	−79·0	24	acetone	8
n-Amyldihydrocodeinone	153–155	EtOAc+petrol	..	−9·3	26	EtOH	8
— picrate	174–177	EtOH	plates	−52·8	24	acetone	8
— salicylate	..	EtOH	needles	..	..	..	8
— styphnate·$\frac{3}{4}H_2O$	142–145	EtOH	plates	−45·4	25	acetone	8
1-bromo-*n*-amyldihydrocodeinone	143–145	EtOH	..	−76·7	24	EtOH	8
— oxime·$\frac{1}{2}H_2O$	121–123 and 170–174	MeOH	..	−29·7	24	EtOH	8
Benzyldihydrocodeinone	..	..	oil	−114·3	25	$CHCl_3$	8
1-bromobenzyldihydrocodeinone	167–168	EtOH	needles	−101·4	23	EtOH	8
Phenyldihydrocodeinone	149–151	EtOAc+petrol	..	−166·2	24	EtOH	8
1-bromophenyldihydrocodeinone	..	..	oil	..	..	..	8
Methyldihydrocodeine·H_2O	98–102	50% EtOH	..	−84·8	24	EtOH	1
Methyldihydrocodeine (anhyd.)	85–88	subl.	..	..	..	..	1
— hydrochloride	286–287*	EtOH	..	−64·5	23	H_2O	1
— methiodide	269–271*	EtOH	..	−47·9	24	H_2O	1
*Iso*methyldihydrocodeine·$\frac{1}{2}H_2O$	103–104	EtOH	..	−126·9	21	EtOH	8
— salicylate	235–237*	EtOH	..	−87·3	21	EtOH	8
— methiodide	252–254	75% EtOH	..	−56·8	21	H_2O	8
Methyldihydromorphinone	243–245*	EtOH	needles	−140·7	24	EtOH	1
— hydrochloride	315–318*	EtOH	..	−104·8	24	H_2O	1
Ethyldihydromorphinone	213–214*	EtOH	..	−103·5	25	EtOH	8
— hydriodide	285–286*	EtOH	needles	−49·1	22	H_2O	8
— methiodide·$\frac{1}{2}H_2O$	263–265*	EtOH	..	−42·2	22	H_2O	8
Isopropyldihydromorphinone	236–238	EtOH	..	−107·5	26	EtOH	8
— hydrochloride·H_2O	340–341*	acetone	prisms	−64·2	25	H_2O	8
— hydrobromide	215–220*	H_2O	needles	−56·4	23	H_2O	8
—hydriodide·H_2O	199–201*	H_2O	..	−61·5	25	acetone	8
— perchlorate·$1\frac{1}{2}H_2O$	168–170*	33% EtOH	plates	−69·0	25	EtOH	8
n-Amyldihydromorphinone·$\frac{1}{2}H_2O$	113–116	EtOAc	..	−97·3	25	EtOH	8
— hydrochloride	322–325*	H_2O	plates	−63·9	25	H_2O	8
—hydrobromide·H_2O	189–190*	EtOH	prisms	−66·0	25	EtOH	8,
—hydriodide·H_2O	182–184*	EtOH	needles	−59·8	25	EtOH	8
Benzyldihydromorphinone	166–167·5	EtOH	prisms	−439·0	24	$CHCl_3$	8
—hydrochloride·H_2O	241–242*	EtOH	prisms	−100·6	24	H_2O	8
Phenyldihydromorphinone	278–280*	EtOH	prisms	−164·5	24	acetone	8
— hydrochloride	334–337*	90% EtOH	needles	−126·9	24	H_2O	8
— hydrobromide	281–284*	90% EtOH	rods	−97·4	25	acetone	8
— hydriodide	273–276*	90% EtOH	prisms	−95·1	25	acetone	8
Dihydromorphinone Δ^6-enol methyl other	233–235	EtOH	rods and needles	−206·5	24	EtOH	8
—hydrochloride	309–310*	H_2O	prisms	−180·6	25	H_2O	8
— hydriodide	274–275*	H_2O	..	−140·5	25	H_2O	8
— benzoate	229–230	EtOH	rods	−150·7	25	EtOH	8
—salicylate	268–270*	H_2O+EtOH	needles	−130·8	25	acetone	8
— methiodide·H_2O	259–261*	MeOH	needles	−123·6	25	acetone	8
Methyldihydromorphine	206–207	EtOAc	..	−92·9	24	EtOH	1
— hydrochloride	316–317*	EtOH	..	−65·7	23	H_2O	1
—hydriodide	289–291*	EtOH	..	−50·5	23	H_2O	1
Methyldihydrodesoxycodeine-C	145–146	MeOH	..	+69·7	25	EtOH	19
— hydrobromide	245–246	H_2O	plates	+61·5	23	$CHCl_3$	19
— hydriodide	155–158	H_2O	..	+51·9	23	$CHCl_3$	19
— methiodide	289	acetone	..	+28·8	25	$CHCl_3$	19
Methyltetrahydrodesoxycodeine	128–129	MeOH	..	−47·8	25	EtOH	19
— hydrochloride	240·5	acetone	needles	−28·1	25	$CHCl_3$	19

* In evacuated tube.

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Methyltetrahydrodesoxycodeine hydrobromide	248–249	H_2O	..	−21·9	22	$CHCl_3$	19
— methiodide	254–255	EtOH	..	−34·9	25	$CHCl_3$	19
α-Ethyldihydrodesoxycodeine-C	156–164	acetone	..	−184·0	22	$CHCl_3$	19
— hydriodide	205–210	50% EtOH	..	−123·2	23	EtOH	19
— perchlorate	187–200	50% EtOH	prisms	−134·7	26	EtOH	19
— methiodide	210–215	H_2O	..	−111·4	26	EtOH	19
β-Ethyldihydrodesoxycodeine-C	..	..	oil	..	..	..	19
α-Ethyltetrahydrodesoxycodeine	168·5–169	subl.	..	−54·8	23	$CHCl_3$	19
— hydriodide	234	20% MeOH	..	−2·9	24	$CHCl_3$	19
β-Ethyltetrahydrodesoxycodeine	148–153	acetone	..	−37·6	26	$CHCl_3$	19
*Cyclo*hexyldihydrodesoxycodeine-C	131·5–132·5	MeOH+ *iso*Pr_2O	..	−51·0	26	$CHCl_3$	19
— perchlorate	250–251	..	..	−26·3	25	$CHCl_3$	19
*Cyclo*hexyltetrahydrodesoxycodeine	193–193·5	MeOH	..	−14·2	25	$CHCl_3$	19
— hydriodide	235–236	..	..	+14·8	23	$CHCl_3$	19
Phenyldihydrodesoxycodeine	184·5–185·5	EtOAc	..	+129·3	24	$CHCl_3$	19
— picrate·H_2O	c. 115	MeOH	..	..	..	..	19
— picrate (anhyd.)	129–132	..	..	+69·5	20	$CHCl_3$	19
— benzoate	203–204	Et_2O+ EtOH	..	+82·1	24	EtOH	19
— methiodide	257·5–258	EtOH	flakes	+105·0	25	EtOH	19
Octahydrophenyldihydrodesoxy-codeine	132–134	..	..	−48·4	24	$CHCl_3$	19
— perchlorate	255–256	..	..	−16·7	26	EtOH	19
— methiodide	250	EtOH	..	−28·0	25	$CHCl_3$	19
Phenyltetrahydrodesoxycodeine	218–220	H_2O+ MeOH	..	+16·1	26	$CHCl_3$	19
Methyldihydro-ψ-codeine methyl ether	182·5–183	EtOAc	..	+121·0	23	EtOH	8
— hydrochloride	247–251*	EtOH	needles	+125·9	25	H_2O	8
— hydriodide	256–257*	EtOH	needles	+91·5	25	EtOH	8
— perchlorate	285–287*	EtOH	..	+103·1	23	EtOH	8
— methiodide	273–276*	EtOH	needles	+98·1	25	EtOH	8
By-product in preparation of above in *iso*propyl ether	132–132·5	EtOAc	..	−57·4	25	EtOH	8

* In evacuated tube.

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XX

THE PHENYLDIHYDROTHEBAINES AND RELATED COMPOUNDS

In Chapter XIX it was shown how certain derivatives of thebaine and ψ-codeine having a double bond in the 6:7-position react with Grignard reagents with opening of the cyclic ether and introduction of an organic radical in ring C, the products in general behaving as anticipated. The presence of a second double bond in ring C, however, causes the reaction of Grignard reagents with thebaine and ψ-codeinone to take an entirely different course, which has only recently been elucidated.

THE PHENYLDIHYDROTHEBAINES

The reaction between thebaine and phenylmagnesium bromide was first investigated by Freund [1–2], who obtained in this way a phenolic base, the composition of which was $C_{25}H_{27}O_3N$ = thebaine+C_6H_6; the base was accordingly named phenyldihydrothebaine. The peculiar properties of this compound at once became evident. It was found to be strongly resistant to hydrogenation; to be so stable in concentrated acids that demethylation could be accomplished without structural change, though no hydrolysis of the 'enol-ether' methoxyl group could be effected. Furthermore, exhaustive methylation resulted in loss of trimethylamine only, and retention of the residue of the basic side-chain as a vinyl group, a reaction without parallel in a compound of the morphine series in a comparable state of unsaturation. These facts led Freund to postulate some unlikely formulae for thebaine. The reduction of phenyldihydrothebaine was subsequently accomplished, but was found to involve reductive scission of the nitrogen-containing ring, the product being a secondary amine, phenyltetrahydrothebaimine [3].

The problem was investigated by Small, Sargent, and Bralley [4], who, following work by Small and Fry on the methyldihydrothebaines (prepared by the interaction of thebaine and methylmagnesium iodide [5], see below), resolved the phenyldihydrothebaine obtained from the Grignard reaction into two enantiomorphic bases, designated (+)-α- and (+)-δ-phenyldihydrothebaine, in the ratio of approximately 10:1. That both are phenolic as well as basic was shown by their solubility in alkalis and ready coupling with diazonium salts. As with the corresponding methyldihydrothebaines, these bases were made to undergo isomerization by slow distillation in a high vacuum, or by heating in an evacuated sealed tube at 200° C., under which conditions (+)-α-phenyldihydrothebaine was recovered 75 per cent. unchanged together

with 16 per cent. of a new isomer termed by Small (—)-δ, identical with the (+)-δ form except for the opposite sign of optical rotation. A fourth isomer, (—)-α, equal and opposite in optical rotatory power to the (+)-α form, was prepared in the same way from (+)-δ-phenyldihydrothebaine. The existence of two centres of dissymmetry in the phenyldihydrothebaine molecule is thus evident; the equilibria reached from either side favour the α-forms [4].

Small clearly recognized these changes as partial racemizations, but appears to think it possible that a number of asymmetric centres can be inverted in a single step, for he calls the optical antipode of (+)-α (—)-α. It is preferable to term it (—)-δ, however, for then (+), (—), α, and δ can be taken as symbols representing left-hand or right-hand at two sources of dissymmetry and the partial racemization of (+)-α by heat then gives (—)-α [6, 7].

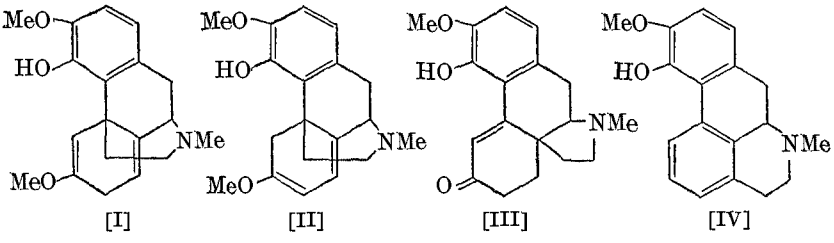
Examination of the products of exhaustive methylation of the phenyldihydrothebaines demonstrated convincingly that the difference between the α and δ series is due solely to asymmetry about a carbon atom joined directly to the nitrogen atom, the difference between the two series vanishing when the nitrogen atom is eliminated from the molecule. The (+):(—) isomerism, however, persisted in the nitrogen-free products.

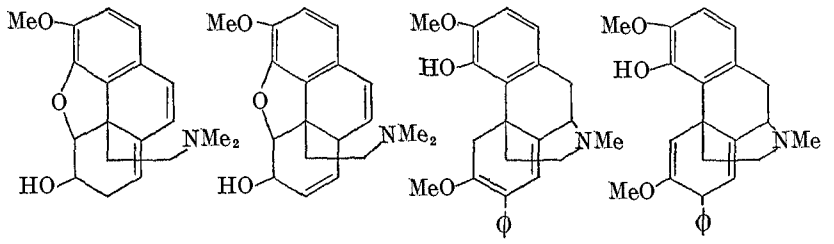
Any satisfactory formula for phenyldihydrothebaine must give an adequate explanation of the following:

(*a*) The resistance of the base to hydrogenation [1, 4].
(*b*) The stability of the base in acid solution [1, 4].
(*c*) The retention of the vinyl group during exhaustive methylation [4].
(*d*) Demethylation of phenyldihydrothebaine gives norphenyldihydrothebaine [1], which exhibits the properties of a trihydric phenol and can be methylated to phenyldihydrothebaine methyl ether [4, 8].
(*e*) Partial racemization about an asymmetric carbon atom attached directly to the nitrogen during the entry of the phenyl group [4].

In spite of (*a*), (*b*), (*c*), and (*d*) Small, Sargent, and Bralley rejected the obvious explanation that the near-aromatic nucleus of thebaine, which bears the hydrolysable methoxyl group, has become fully aromatic in phenyldihydrothebaine. If this ring is made aromatic, it was claimed, not only can no place be found for two hydrogen atoms, but the optical activity of phenyltetrahydrothebaimine cannot be explained [4–5]. Comparison was made between the ultra-violet absorption spectra of the phenyl- and methyl-dihydrothebaines and that of the most closely related thebaine derivative in which it is known that no deep-seated structural change has occurred, namely dihydrothebaine-ϕ [I] (at that time believed to be [II]). These compounds show

maxima and minima at almost identical wave-lengths, whereas the absorption spectra of metathebainone [III] and apocodeine [IV], in





which rearrangement has taken place are widely different (Fig. 10). Moreover, the absorption spectra of phenyldihydrothebaine methine and β-codeimethine [V] are closely similar, whilst that of α-codeimethine [VI], with the aliphatic double bond at C-7:8 out of conjugation, differs markedly (Fig. 11). The spectrum of phenyldihydrothebaine gave no indication of the appearance of a new aromatic nucleus in conjugation with that already present in thebaine, and Small regarded this as unsurmountable evidence against the postulate of aromatization of ring C in phenyldihydrothebaine [4].

In this way Small, Sargent, and Bralley advanced the structure [VII] for phenyldihydrothebaine, although it fails to explain any of the anomalous properties of the base, and at the same time questioned the validity of the Gulland and Robinson formulae for morphine and thebaine [4]. It is difficult to see how [VII] could arise from thebaine, as a 1:4-addition of the Grignard reagent to the allylic ether would give [VIII]; moreover, [VII] is not in agreement with the ultra-violet spectrum of phenyldihydrothebaine, which is not styrenoid. The original paper [4] must be consulted for the formulae of degradation products based on [VII], as here all degradations are interpreted on the basis of the structure [XI] for phenyldihydrothebaine proved by Bentley and Robinson [6–7, 9–10].

The one inescapable conclusion to be deduced from the properties of phenyldihydrothebaine outlined above is that in this base the near-aromatic nucleus of thebaine has become fully aromatic, and other

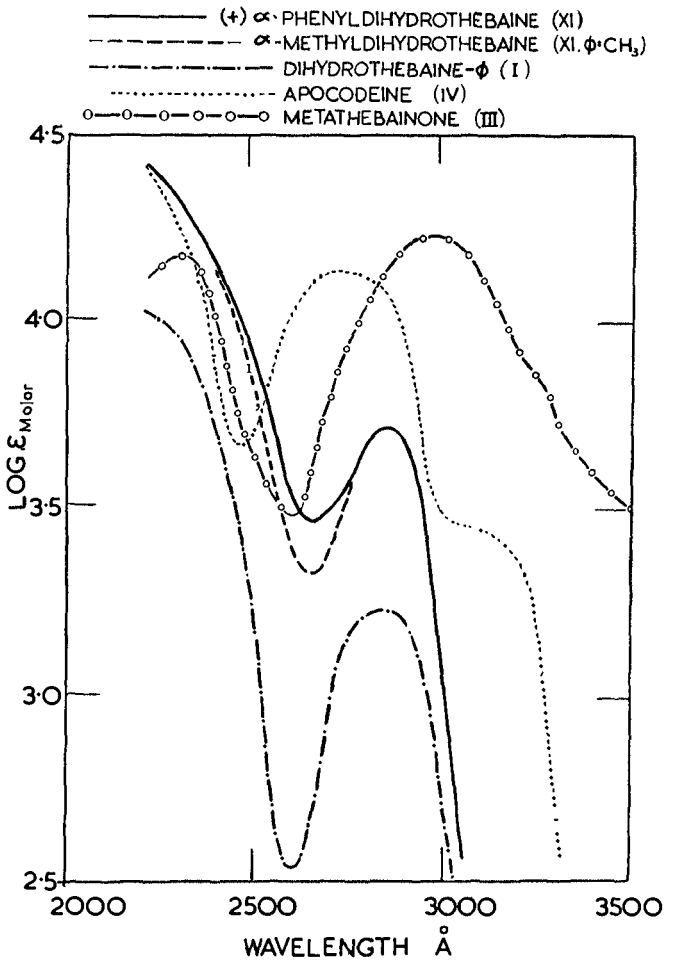


FIG. 10.

conclusions follow logically if this is accepted. The sequence of processes leading to the optically active nitrogen-free product may be represented essentially in the form

$$—C—C—NMe—C—C \longrightarrow —C{=}C + NMe_3 + C{=}C—$$

the presence of two double bonds in the end-product being easily demonstrated. Now phenyldihydrothebaine is a C_{25} base; of these carbon atoms one is present in an NMe group (now lost), two in OMe groups, and, by hypothesis, eighteen are present in three benzene rings, leaving only four for the two double bonds. Hence, exhaustively methylated phenyldihydrothebaine cannot contain an asymmetric carbon atom, and must owe its optical activity to an asymmetric molecule of a type

familiar to chemists but never before encountered in the study of a natural product.

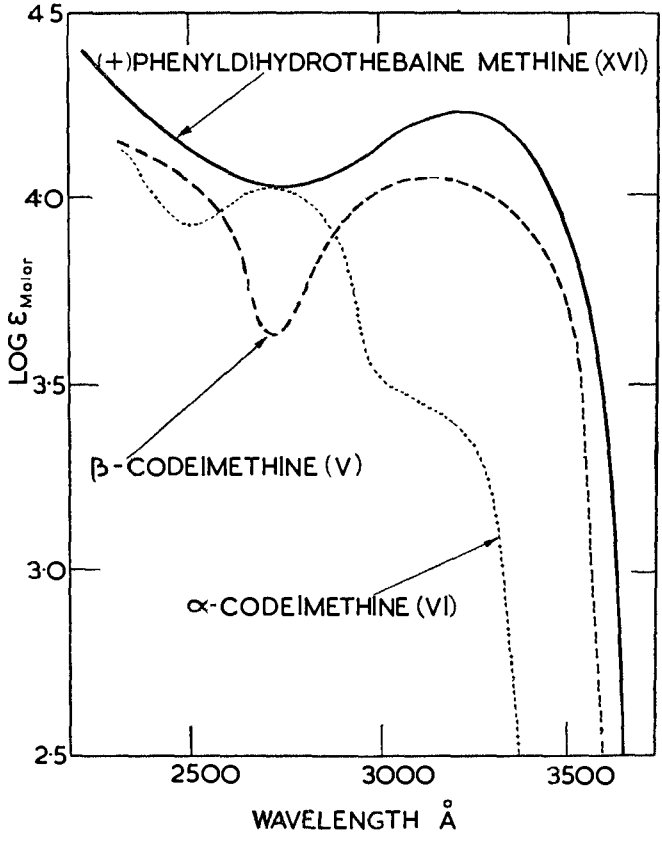
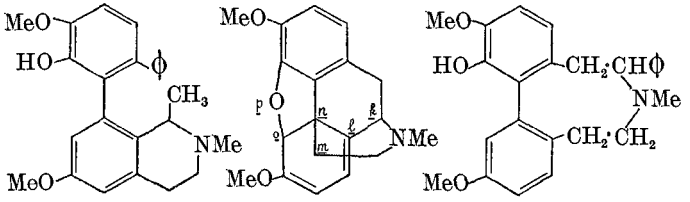


FIG. 11.

Thebaine is easily degraded to phenanthrene derivatives, which in turn are derived from diphenyl, certain derivatives of which exhibit optical activity, and it is well known that the hypothesis of restricted rotation of the phenyl groups in presence of ortho-substituents of sufficient size harmonizes all the experimental data.

This restricted diphenyl idea was arrived at as a plausible explanation of the optical activity of the end-product of exhaustive methylation, but there is strong evidence that it must be applied to phenyldihydrothebaine itself, in which the experimental facts suggest that there are two, and only two, centres of dissymmetry. One of these, represented by (+) and (−), is a non-coplanar diphenyl system and the other, represented by α and δ, is an asymmetric carbon atom, and phenyldihydrothebaine is the first substance in which both forms of dissymmetry have been proved to exist.

The structure first suggested on the basis of the above reasoning was [IX], which explained all the data then known (1945) except the formation of two isomers during the entry of the phenyl group. This view was not maintained, however, as phenyldihydrothebaine does not show diphenyl bands in its ultra-violet absorption spectrum and [IX] contains an unrestricted diphenyl system.



[IX] [X] [XI]

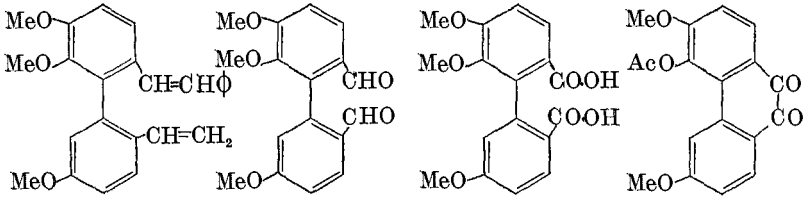
The structure finally adopted for phenyldihydrothebaine was [XI], and its formation from thebaine [X] is the result of a molecular change of quite a new type, first formulated as a likely process from the electronic point of view [6–7]. The migrating ethanamine chain is cationoid, m is joined to l by the electrons of the link k, l; the electrons of m, n go to n, o and fulfil the demands of aromaticity of the nucleus; electrons o, p are then taken by the oxygen atom, which thereby acquires a negative charge, and the phenyl anion brings an electron pair to k to replace those lost to the migrating group. This connected series of changes was first thought of as starting at either end, namely attack by $\phi^{\ominus}$ at k or assumption of a negative charge by the oxygen atom following attack by $MgBr^{\oplus}$ at p, but in view of the reaction between thebaine and anhydrous magnesium iodide (see below) the latter now appears the most likely. In any case the driving force of the reaction as in the majority of other migrations in this group is doubtless the tendency of the near-aromatic nucleus to become fully aromatic. The formation of two isomers results from the configuration of the —CHϕ— group in each of the two possible ways, the diphenyl nucleus being configured in one sense only.

The structure [XI] is perfectly satisfactory; examination of models shows that the nine-membered ring allows the phenyl nuclei to be disposed at right angles or any other angle without strain, ready interconversion of the two extremes being hindered by the hydrogen atoms and the phenyl group; there is only one asymmetric carbon atom, and all the peculiar properties and chemical transformations receive natural explanations. However, as pointed out by Small, the ultra-violet absorption spectra of phenyldihydrothebaine and its derivatives give no indication of the appearance of a new aromatic nucleus in conjugation with that already present in thebaine. But non-coplanar diphenyls do

NOT exhibit diphenyl-absorption, and the specific case of the formation of a ring of eighteen members by a bridge across the meta-positions affords a compound showing no diphenyl band and only end-absorption [11–12].

OXIDATION

Proof of the structure [XI] was sought and found by the oxidation of phenyldihydrothebaine with alkaline potassium permanganate, which resulted in the production of benzaldehyde, benzoic acid, and 4-methoxyphthalic acid. By exhaustive methylation of the methyl ether the optically active (+)-3:4-dimethoxy-2-(5-methoxy-2-vinylphenyl)-stilbene [XII] (prepared by Freund [1], but stated to be optically inactive) was obtained, and permanganate oxidation of this afforded 5:6:5′-trimethoxydiphenaldehyde [XIII] (also obtained by the ozonolysis of [XII]) and 5:6:5′-trimethoxydiphenic acid [XIV] (also obtained by oxidation of [XIII]). This acid was identified with an authentic specimen prepared in stages from 4-acetoxy-3:6-dimethoxyphenanthrene quinone (acetylthebaolquinone [XV]) [6–7, 9–10].

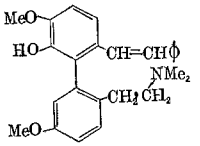


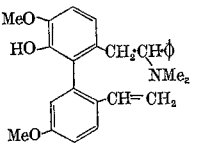
DEGRADATION

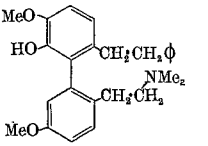
Elucidation of the degradations of phenyldihydrothebaine on the basis of [XI] is simple. Small, Sargent, and Bralley [4] studied the degradations of the four enantiomorphs, though some of the degradation products had previously been prepared by Freund [1], who worked with the mixture of (+)-α and (+)-δ forms obtained directly from the Grignard reaction.

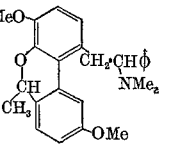
Although they are fairly resistant to degradation all the phenyldihydrothebaines, with the exception of the rare (−)-α-isomer, have been converted to nitrogen-free substances. In the first stage of exhaustive methylation they undergo degradation in two ways, giving methines [XVI] and *iso*methines [XVII], the latter predominating in each case; in fact the normal methine was only isolated during the degradation of the (+)-α-isomer.

The normal methine, which can be hydrogenated to the dihydromethine [XVIII], is unaffected by boiling with concentrated hydrochloric acid, whilst the vinyl group of the *iso*methine [XVII] can be cyclized


[XVI]


[XVII]

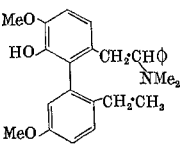

[XVIII]

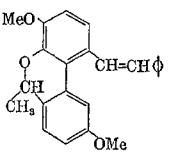

[XIX]

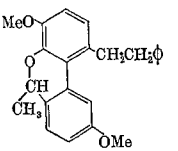
under these conditions with the phenolic hydroxyl, giving 'phenyl-9-dimethylamino-6-methoxythebendiene' [XIX]. (The names allotted to the degradation products by Small [4] are adhered to in this account to avoid further confusion, although many are obviously misnomers.) This is no longer phenolic and is indifferent to catalytic hydrogenation. The dihydro*iso*methine [XX] having an ethyl group in place of the vinyl group is unaffected by hot acid. In all the *iso*methine derivatives the $\alpha:\delta$ isomerism persists, but it no longer exists in the methine and its derivatives [4]. These reactions suffice to fix the structures of the methine and *iso*methine as [XVI] and [XVII] respectively.

Fieser and Fieser [13] are unable to see why the nitrogen-containing ring is not broken preferentially so as to give the methine in which the double bond is in conjugation with the new phenyl group as well as the aromatic nucleus of thebaine. However, Hofmann degradation involves loss of a proton from the carbon atom in the β-position to the nitrogen, and this is not under the influence of the new phenyl group. In any case the environment on both sides of the nitrogen atom is not the same, one side terminating in a catechol and the other in a phenol nucleus [10].

The phenyl group of the *iso*methine can be reduced with the double bond giving hexahydrophenyldihydrothebaine dihydro*iso*methine.


[XX]


[XXI]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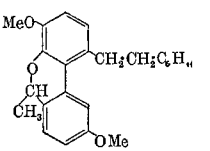
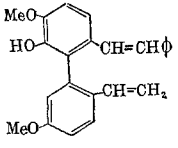

[XXIII]

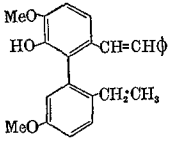
Further degradation of the cyclized *iso*methine [XIX] affords a non-phenolic, optically inactive nitrogen-free substance [XXI] called by Small '*rac*-phenyl-6-methoxythebentriene' as its optical inactivity was assumed to be due to racemization during the degradation. This substance takes up one mole of hydrogen (at the double bond) in neutral solution giving [XXII] and, it is claimed, two additional moles in acid solution over platinum oxide to give 'phonyl-6-methoxythebenane' [4]. The analytical data for the latter, however, are more consistent with an

octahydro-derivative, which would be formed by reduction of the double bond and phenyl group [10, 13] giving [XXIII].

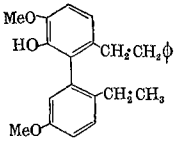
Further degradation of the methine [XVI] and *iso*methine [XVII] leads to the phenolic optically active nitrogen-free product [XXIV] discussed above. That this contains the free phenolic and vinyl groups is demonstrated by the formation of an acetyl ester and by cyclization to [XXI] by hydrochloric acid [4]. [XXIV] was originally obtained by Freund [1], who was unable to detect the two $-OCH_3$ groups, but Zeisel determination in acetic anhydride verified the presence of these [4]. The methyl ether of [XXIV], which is optically active, results from the exhaustive methylation of phenyldihydrothebaine methyl ether [10]. On heating above its melting-point it is converted into the racemate [10] together with a polymer of molecular weight above 5,000, presumably formed by polymerization of the styrene system [10].



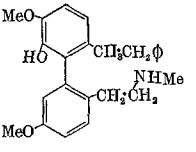
[XXIV]



[XXV]



[XXVI]



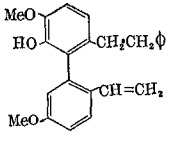
[XXVII]

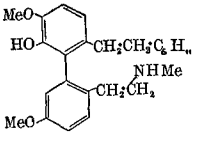
In neutral solution [XXIV] adds one mole of hydrogen at the vinyl group to give 'ethylphenyldihydrothebaol' [XXV], identical with the product of degradation of the dihydro*iso*methine [XX]. In acid solution [XXIV] is reported to add three and [XXV] two moles of hydrogen to give a compound that Small identified as a hexahydro-derivative ('ethylphenylhexahydrothebaol') [4], but that in reality is the tetrahydro-derivative [XXVI], as the analytical data show [10, 13]. The methyl ether of [XXIV] can also be reduced to a tetrahydro-derivative, (+)-2-(2-ethyl-5-methoxyphenyl)-3:4-dimethoxydibenzyl [10],

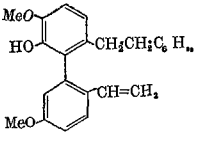
Reduction

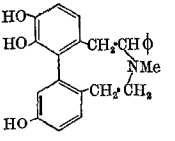
Being a benzylamine, phenyldihydrothebaine can be reduced catalytically [3–4], but not with sodium and liquid ammonia [18], to the secondary amine phenyltetrahydrothebaimine [XXVII], which on treatment with nitrous acid gives an N-nitroso-compound and on treatment with phosgene yields bis-[phenyltetrahydrothebaimine]-urea [3]. Phenyltetrahydrothebaimine-N-methomethiodide is identical with phenyldihydrothebaine dihydromethine methiodide, showing that fission of the ring has occurred between the nitrogen atom and the carbon atom carrying the phenyl group. This is confirmed by the fact that both (+)-α and (+)-δ-phenyldihydrothebaine give the same (+)-phenyltetrahydrothebaimine [4]. Phenyltetrahydrothebaimine-

N-methomethiodide can be degraded to 'vinylphenyltetrahydrothebaol' [XXVIII]. The parent base may be reduced over platinum oxide to give hexahydrophenyltetrahydrothebaimine [XXIX], presumably with reduction of the phenyl group; the same base can be obtained directly from phenyldihydrothebaine and can be degraded to a nitrogen-free substance [XXX] [4]. An attempt to verify the reduction of the phenyl group by the preparation of *cyclo*hexyldihydrothebaine failed, as, though a reaction occurred between thebaine and *cyclo*hexylmagnesium bromide, no definite compound could be isolated [4]. Cyclization of [XXX] should give [XXIII].


[XXVIII]


[XXIX]


[XXX]


[XXXI]

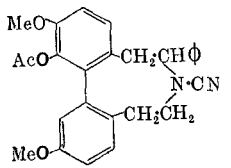
Acetylphenyldihydrothebaine is formed by acetylation of the phenol [1, 14]. Methyl and ethyl ethers of phenyldihydrothebaine were prepared by Freund, who degraded both to nitrogen-free substances [1]. Demethylation of phenyldihydrothebaine affords norphenyldihydrothebaine [XXXI] which can be methylated to phenyldihydrothebaine methyl ether [1, 4, 8]. The latter is stable to ozonolysis [15].

HALOGENATION

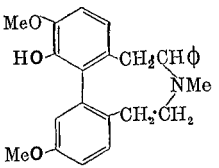
Phenyldihydrothebaine on treatment with hydrochloric acid and hydrogen peroxide is converted into a dichloro-compound that has been degraded to a methine base and nitrogen-free product ('dichlorophenyldihydrothebenol') [3]. Freund and Speyer regarded this as involving addition of chlorine to a double bond [3], but the analytical data of all the derivatives are equally compatible with formulae containing two hydrogen atoms fewer than those given and it is clear that the chlorine atoms have entered the guiacol or anisole nucleus or both nuclei [10]. The reaction with bromine presumably takes a similar course yielding dibromophenyldihydrothebaine. This is reported to undergo electrolytic reduction with the production of 'phenyltetrahydrothebaine' [3], which is very probably (+)-α-phenyldihydrothebaine; the melting-points of the methiodides differ by only one degree [10]. It is most likely that the small amount of (+)-δ-isomer originally present would be eliminated during this cycle of reactions.

Though phenyldihydrothebaine is a benzylamine its acetyl ester appears to react with cyanogen bromide without scission of the nitrogen-containing ring, possibly giving [XXXII] [3]. The reaction between phenyldihydrothebaine and 30 per cent. hydrogen peroxide in boiling

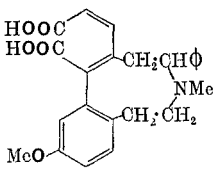
alkaline solution affords a dibasic acid, phenyldihydrothebainic acid $C_{24}H_{25}O_5N$ [3], for which the structure [XXXIII] is now suggested [10].



[XXXII]



[XI]



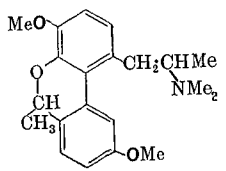
[XXXIII]

THE METHYLDIHYDROTHEBAINES

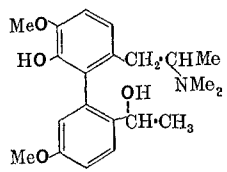
Methyldihydrothebaine, analogous to phenyldihydrothebaine, results from the interaction of thebaine and methylmagnesium iodide, and can be separated into α and δ isomers in the ratio of about 2:1. The α-compound isomerizes to the δ to the extent of about 10 per cent. on heating for twenty-four hours on the water-bath. Two other isomers, η and ω, are known, and these are the optical antipodes of the δ and α isomers respectively. In this series the α and η isomers form a molecular compound on mixing as do also the δ and ω isomers. On heating in a sealed tube α-methyldihydrothebaine gives 20 per cent. α, 75 per cent. $\alpha\eta$-molecular compound, and 4 per cent. α:ω-racemate. Under similar conditions δ-methyldihydrothebaine gives mainly $\delta\omega$-molecular compound and a small amount of α:ω-racemate. That the α and η isomers are in equilibrium is shown by the conversion of the η-isomer to the $\alpha\eta$-molecular compound on heating in a sealed tube. A small amount of the ω-isomer perchlorate is obtained by heating η-methyldihydrothebaine perchlorate. The methyldihydrothebaines form three racemates, namely $\alpha:\omega$, $\delta:\eta$, and $\alpha\eta:\delta\omega$. The molecular compounds may be separated into their constituent isomers by recrystallization of the hydrochlorides and perchlorates [5].

All four isomeric methyldihydrothebaines can be degraded to *iso*-methines [XVII, $\phi = CH_3$], but the acetyl esters of the α, δ, and η isomers split preferentially in the normal way giving methines [XVI, $\phi = CH_3$] on dry distillation of the methohydroxides. All the methines and *iso*methines degrade to the same nitrogen-free product 'vinyldihydromethylthebaol' [XXIV, $\phi = CH_3$] [5], in which the unsaturated groups are presumably too small to restrict free rotation of the phenyl nuclei, as no convincing evidence has been produced to show that this compound has ever been obtained in an optically active form. (The low rotatory power of the liquid product of degradation of δ-methyldihydrothebaine methyl ether methine [5] can be explained by assuming regeneration of a quantity of methine base by loss of methanol from the methohydroxide.)

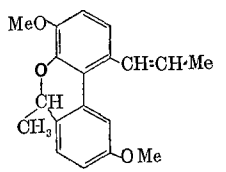
The vinyl group of the *iso*methine may be cyclized with the phenolic hydroxyl group by boiling in hydrochloric acid, the product being 'methyl-9-dimethylamino-6-methoxythebendiene' [XXXIV], which, unlike the *iso*methine, is non-phenolic and indifferent to catalytic hydrogenation. With the δ and η *iso*methines intermediate δ and η-dihydrohydroxymethyldihydrothebaine *iso*methines [XXXV] may be isolated if the cyclization is attempted with partially hydrolysed acetyl chloride; more vigorous treatment with acetylchloride completes the cyclization to [XXXIV]. Degradation of the cyclized *iso*methines [XXXIV] affords two isomeric '6-methoxymethylthebentrienes' [XXXVI] [5].



[XXXIV]



[XXXV]



[XXXVI]

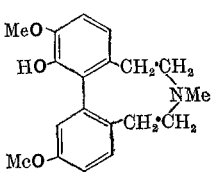
These cyclized compounds present an interesting problem. Cyclization of the phenolic hydroxyl and vinyl groups results in the formation of a new six-membered ring that locks the two phenyl nuclei in practically the same plane, thus destroying all isomerism due to restricted rotation of these two nuclei. In the phenyldihydrothebaine series the only compounds of this type shown to be optically active are those still containing the original asymmetric carbon atom; the nitrogen-free substances, whether prepared by the degradation of the cyclized *iso*methine [XIX] or by the cyclization of the optically active, nitrogen-free compound, containing the vinyl group [XXIV], are optically inactive. In the methyldihydrothebaine series, however, two optically active isomers of the cyclized nitrogen-free substance [XXXVI] are known, and the explanation of this phenomenon is doubtless as follows. The optically active forms of [XXXVI] were obtained by degradation of [XXXIV], which in turn was prepared by the cyclization of the *iso*methine [XVII, $\phi = CH_3$], and the presence of the asymmetric carbon atom in the latter would be expected to cause the production of unequal amounts of the two diastereoisomers of [XXXIV] when the new asymmetric carbon atom was brought into being as a result of the cyclization. The effect of a slight excess of one diastereoisomer of [XXXIV] when degradation was pursued to the nitrogen-free substance [XXXVI] would be to cause a slight but noticeable activity in the latter [10].

Oxidation of the methyl ether of 'vinyldihydromethylthebaol' [XXIV, $\phi = CH_3$] with potassium dichromate affords an ether-insoluble, yellow, optically inactive substance that may be a quinone [5]. A very small amount of phenanthrene together with a small quantity of an

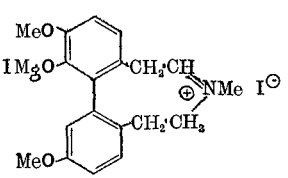
unidentified substance is obtained by the distillation of α-methyldihydrothebaine with zinc-dust [5].

Benzyldihydrothebaine results from the interaction of thebaine and benzylmagnesium bromide [2].

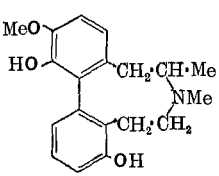
Attempts have been made to prepare the parent dihydrothebaine of this series [XXXVII] but without success [9–10, 16]. In the belief that the sequence of changes leading to phenyldihydrothebaine is initiated by the attack of the ether oxygen atom by $MgBr^{\oplus}$, the reaction between thebaine and anhydrous magnesium iodide was investigated. This yields an exceptionally sensitive substance that may have the structure [XXXVIII] [9–10]. It yields phenyldihydrothebaine when treated with phenylmagnesium bromide, but affords no detectable amount of 4-methoxyphthalic acid on oxidation. Reduction with sodium in liquid ammonia proceeds rapidly but yields no definite product. A vigorous reaction occurs when this compound is treated with lithium aluminium hydride; gas (methane ?) is evolved and a very sensitive phenolic secondary amine is formed. The latter may be the N-demethylated-[XXXVII] [10].



[XXXVII]



[XXXVIII]



[XXXIX]

Methyldihydro-ψ-codeinone also belongs to the same group as phenyldihydrothebaine. It is produced by the interaction of methylmagnesium iodide and ψ-codeinone, is very resistant to hydrogenation, shows no properties of the carbonyl group [17], and undoubtedly has the structure [XXXIX] [10, 13].

In the following table, in order to avoid confusion, the names of derivatives and designation of isomers used by Small and his co-workers are adhered to, formula numbers being added wherever possible to aid identification.

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
(+)-α-phenyldihydrothebaine [XI]	..	.	glass	..	..	..	4
—·EtOH	40–70	EtOH	prisms	+10·2	20	EtOH	4
—hydrochloride	..	..	..	..	..	..	..
—perchlorate	248d.	EtOH	..	+8·2 +35·0	20 26	acetone EtOH	4
—methiodide	216·5–218	MeOH	..	+42·7	26	EtOH	4
(−)-α-phenyldihydrothebaine [XI]	..	..	glass	−10·0	20	EtOH	4
methiodide	216	MeOH	..	−43·6	26	EtOH	4
(+)-δ-phenyldihydrothebaine [XI]	143·5	EtOH	needles	−131·0 −110·0	20 20	acetone $CHCl_3$	4
—perchlorate	200–213	EtOH	..	−44·5	24	EtOH	4
—methiodide·MeOH	200–208	MeOH	..	−43·0	23	EtOH	4

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
(−)-δ-phenyldihydrothebaine [XI]	143·5	EtOH	needles	{+131·0 +110·0	20 20	acetone $CHCl_3$	4 4
— perchlorate	209–213	EtOH	..	+42·8	24	EtOH	4
— methiodide·MeOH	206–208	MeOH	..	+44·0	20	EtOH	4
(+)-phenyldihydrothebaine methine [XVI]	126–127	75% MeOH	..	−46 5	20	EtOH	4
— perchlorate·EtOH	106–120	EtOH	..	{−34·0 −60·3	20 20	acetone EtOH	4
— methiodide	244	MeOH	..	−51·5	20	EtOH	4
(+)-phenyldihydrothebaine dihydromethine [XVIII]	..	..	oil	..	..	..	4
— methiodide (two forms)	{235 250–254}	..	..	{−5·4 −3 9	25 25	MeOH EtOH	4
(+)-α-phenyldihydrothebaine *iso*methine [XVII]	101	75% EtOH	..	−280 0	20	EtOH	4
— perchlorate·EtOH	111–117	EtOH	needles	−197·0	25	EtOH	4
— methiodide·$2H_2O$	100–110	25% EtOH	needles	−207·0	25	EtOH	4
— methiodide (anhyd.)	159–160	..	..	..	..	..	4
(−)-α-phenyldihydrothebaine *iso*methine [XVII]	101	75% EtOH	..	+281·0	20	EtOH	4
— perchlorate·EtOH	111–116	EtOH	..	+197·0	20	EtOH	4
(+)-δ-phenyldihydrothebaine *iso*methine [XVII]	117–119	70% EtOH	..	+153·0	25	EtOH	4
— perchlorate·2EtOH	114–116	EtOH	..	+89·6	23	EtOH	4
— methiodide	202–203	Et_2O+ EtOH	..	+108·0	24	EtOH	4
(−)-δ-phenyldihydrothebaine *iso*methine [XVII]	117–119	60% EtOH	..	−154·0	20	EtOH	4
— perchlorate·2EtOH	114–116	EtOH	..	−90·0	20	EtOH	4
— methiodide	202–203	Et_2O+ EtOH	..	−105·0	25	EtOH	4
(+)-α-phenyldihydrothebaine dihydro*iso*methine [XX]	70–72	70% EtOH	..	−175·0	20	EtOH	4
— perchlorate·$2H_2O$	85–87	25% EtOH	..	−104·0	25	EtOH	4
— perchlorate (anhyd.)	111–117	..	..	..	..	..	4
— methiodide	212–213	H_2O+ MeOH	..	−121·0	25	EtOH	4
(+)-δ-phenyldihydrothebaine dihydro*iso*methine	..	..	oil	..	..	..	4
— methiodide	217–219	Et_2O+ EtOH	..	+145·0	23	EtOH	4
(+)-α-hexahydrophenyldihydrothebaine dihydro*iso*methine	108–108·5	75% EtOH	needles	−24·2	20	EtOH	4
— methiodide	207–208	MeOH	..	−14·7	20	EtOH	4
'(+)-α-phenyl-9-dimethylamino-6-methoxythebendiene' [XIX]	..	..	oil	..	..	..	4
— perchlorate	168	EtOH	..	+26·5	22	EtOH	4
— methiodide	212–213	..	prisms	+0·6	20	EtOH	4
'(+)-δ-phenyl-9-dimethylamino-6-methoxythebendiene' [XIX]	..	..	oil	..	..	..	4
— methiodide	170–173	..	..	−3·8	26	EtOH	4
'*rac.*-phenyl-6-methoxythebentriene' [XXI]	162–163	EtOAc	..	0·0	20	acetone	4
'*rac.*-phenyl-6-methoxythebendiene' [XXII]	119–120·5	MeOH	plates	0 0	20	EtOAc	4
'*rac.*-phenyl-6-methoxythebenane [XXIII]	80–83·5	acetone	prisms	0 0	20	EtOAc	4
'(+)-vinylphenyldihydrothebaol' [XXIV]	149	EtOH	..	+47·1	25	EtOAc	4
— acetyl ester	145·5–147	EtOH	plates	+24·7	23	EtOAc	4
'(−)-vinylphenyldihydrothebaol' [XXIV]	149·5–150	EtOH	..	−47·7	22	EtOAc	4
— racemate with (+) isomer	146–147	..	..	0·0	20	EtOAc	4
'(+)-ethylphenyldihydrothebaol' [XXV]	118	EtOH	..	−74·4	25	EtOAc	4
— acetyl ester	122·5–123	EtOH	plates	−77·0	25	EtOAc	4
'(+)-ethylphenylhexahydrothebaol' [XXVI]	..	..	oil	..	..	..	4
— acetyl ester	82·5–83	70% EtOH	..	−23·4	21	EtOAc	4

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
(+)-phenyltetrahydrothebaimine [XXVII]	120–121	75% EtOH	plates	−35·0 −4·2	20 20	acetone 10% HOAc	4
— hydrochloride	..	..	..	..	..	..	18
— perchlorate	..	..	..	..	..	..	18
— N-methomethiodide	235 250–254	..	..	−5·2 −3·3	24 24	MeOH EtOH	4
— N-nitroso compound	193d.	..	..	..	..	..	3
(−)-phenyltetrahydrothebaimine [XXVII]	121	70% EtOH	plates	+35·5	20	acetone	4
— N-methomethiodide	235	..	..	+5·3	20	MeOH	4
(+)-bis-[phenyltetrahydrothebaimine]-urea	138–139	..	needles	..	..	..	3
Racemic phenyltetrahydrothebaimine	134	..	prisms	0·0	20	acetone	4
(+)-hexahydrophenyltetrahydrothebaimine [XXIX]	129–130·5	EtOAc	prisms	−8·5	28	EtOH	4
— hydrochloride	253–255	Et_2O+ EtOH	prisms	−17·6	28	EtOH	4
— N-methomethiodide	231–232·5	..	..	−4·8	29	EtOH	4
(−)-hexahydrophenyltetrahydrothebaimine [XXIX]	128–129·5	EtOAc	..	+10·0	25	EtOH	4
— N-methomethiodide	231–232	..	..	+6·6	25	EtOH	4
(+)-vinylphenyltetrahydrothebaol [XXVIII]	85·5–87	75% EtOH	..	−58·7	29	EtOH	4
— acetyl ester	102–104	MeOH	prisms	−48·5	28	EtOAc	4
(+)-vinylhexahydrophenyltetrahydrothebaol [XXX]	75·5–77	75% EtOH	needles	−22·7	29	EtOAc	4
— acetyl ester	79–80·5	..	..	−26·6	28	EtOAc	4
(−)-vinylhexahydrophenyltetrahydrothebaol [XXX]	70–75	..	..	+35·4	26	..	4
(+)-α-norphenyldihydrothebaine [XXXI]	130–136	50% EtOH	..	+12·3	29	EtOH	4
— hydrobromide	200–201	Et_2O+ EtOH	..	+31·4	29	EtOH	4
(+)-α-phenyldihydrothebaine methyl ether	..	..	oil	..	..	..	4
— hydrobromide	86–88	..	..	+21·9	28	EtOH	4
— perchlorate	205	EtOH	plates	+9·3	21	EtOH	10
— methiodide	205 196–197·5	..	..	..	..	..	10
(+)-α-phenyldihydrothebaine ethyl ether methiodide	209–210	..	..	+20·7	28	EtOH	4
(+)-α-phenyldihydrothebaine methyl ether methine	..	..	oil	..	..	..	1
— platinichloride	125–135	..	amorph.	..	..	..	1, 10
(+)-α-phenyldihydrothebaine ethyl ether methine	..	..	oil	..	..	..	1
— methiodide	247–248	EtOH	plates	..	..	..	1
(+)-3:4-dimethoxy-2-(5-methoxy-2-vinylphenyl)stilbene [XII]	115	EtOH	prisms	+59·0	21	acetone	10
— racemate	124	EtOH	plates	0·0	20	acetone	10
— polymer	indefinite	..	..	..	..	..	10
(+)-2-(2-ethyl-5-methoxyphenyl)-3:4-dimethoxydibenzyl	..	..	oil	+3·5	20	EtOH	10
(+)-3-ethoxy-4-methoxy-2-(5-methoxy-2-vinylphenyl)stilbene	97–98	..	rods	..	..	..	1
5:6:5′-trimethoxydiphenaldehyde [XIII]	..	..	oil	..	..	..	10
— bis-2:4-dinitrophenylhydrazone	277	dioxane	plates	..	..	..	10
5:6:5′-trimethoxydiphenic acid [XIV]	215	EtOH+ H_2O	prisms	..	..	..	10
1:5:6-trimethoxyfluorenone-4-carboxylic acid (from [XIV])	256	50% HOAc	needles	..	..	..	10
— 2:4-dinitrophenylhydrazone	286	..	amorph.	..	..	..	10
Dichlorophenyldihydrothebaine	135–140	EtOH	..	..	..	..	3
— hydriodide	203d.	..	..	..	..	..	3
— methiodide	230	HOAc	..	..	..	..	3
Dichlorophenyldihydrothebaine methine	..	..	oil	..	..	..	3
— hydriodide	c. 205	..	..	..	..	..	3
— N-free product	160–162	..	..	..	..	..	3
Dibromophenyldihydrothebaine	165–168	EtOH	..	..	..	..	3

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Dibromophenyldihydrothebaine hydrobromide	198d.	..	..	..	..	..	3
— perbromide	195–196	HOAc	..	..	..	..	3
— hydriodide	205–208d.	..	..	..	..	..	3
'Phenyltetrahydrothebaine'	..	..	oil	..	..	..	3
— hydrobromide	175–176	..	..	..	..	..	3
— methiodide	215	..	..	..	..	..	3
? Acetylphenyldihydrothebaine	92	..	..	..	..	..	3
— methiodide	202–203	EtOH	rods	..	..	..	3
Phenyldihydrothebainic acid	D.243–245	..	prisms	..	..	..	3
— barium salt	D. 280	..	needles	..	..	..	3
α-methyldihydrothebaine	87·5–89·5	EtOH + H_2O	..	+140·0	25	EtOH	5
— perchlorate	..	EtOH	..	+84·0	25	EtOH	5
— methiodide	219–221	EtOH	..	+76·0	20	EtOH	5
α-methyldihydrothebaine methyl ether methiodide	177–178	EtOAc + EtOH	..	+43·3	21	EtOH	5
δ-methyldihydrothebaine	..	..	oil	..	..	..	5
— perchlorate	..	EtOH	..	+50·0	25	EtOH	5
— methiodide	..	..	amorph.	..	..	..	5
δ-methyldihydrothebaine methyl ether methiodide	..	..	amorph.	..	..	..	5
Acetyl-δ-methyldihydrothebaine							
— perchlorate	..	EtOH	..	+67·5	25	EtOH	5
— methiodide·H_2O	109	EtOAc + EtOH	..	+56·0	25	EtOH	5
— methiodide (anhyd.)	198	..	..	..	..	..	5
η-methyldihydrothebaine	..	..	oil	..	..	..	5
— perchlorate	..	EtOH	..	−49·0	25	EtOH	5
ω-methyldihydrothebaine	86·5–89·5	EtOH	..	−140·0	25	EtOH	5
— perchlorate	..	EtOH	..	−81·0	25	EtOH	5
α:η-methyldihydrothebaine	123–124·5	EtOH	..	+48·0	25	EtOH	5
δ:ω-methyldihydrothebaine	123–124·5	EtOH	..	−48·0	25	EtOH	5
α:ω-racemic methyldihydrothebaine	179–182	..	..	0·0	25	EtOH	5
δ:η-racemic methyldihydrothebaine	79–83	H_2O + EtOH	..	0·0	25	EtOH	5
— perchlorate	..	EtOH	..	0·0	25	EtOH	5
(−)-methyldihydrothebaine methine	106–108	EtOH	..	−21·3	25	EtOH	5
— tartrate	135–140	EtOH	..	−7·0	25	EtOH	5
Racemic methyldihydrothebaine methine	139·5–141·5	EtOH	..	0·0	25	EtOH	5
(−)-methyldihydrothebaine methyl ether methine	..	..	..	..	..	..	5
— tartrate·H_2O	135–137	H_2O	..	+23·0	29	EtOH	5
— methiodide	190–192	EtOH + EtOAc	..	+20·0	23	EtOH	5
— racemate methiodide	207–209	EtOH	..	0·0	..	..	5
(−)-methyldihydrothebaine methyl ether dihydromethine	..	..	oil	..	..	..	5
— tartrate	106–110	H_2O	..	+32·3	23	EtOH	5
— methiodide	182–183	H_2O	..	+29·1	29	EtOH	5
α-methyldihydrothebaine *iso*methine	..	..	oil	..	..	..	5
— salicylate	163–164·5	EtOH	..	−90·0	20	EtOH	5
— methiodide	227–230	EtOH + EtOAc	..	−80·0	25	EtOH	5
δ-methyldihydrothebaine *iso*methine	209–211	EtOH	..	−16·0	20	EtOH	5
— methiodide·H_2O	176·5–178·5, 233	H_2O	..	−30·0	22	EtOH	5
δ-methyldihydrothebaine methyl ether *iso*methine	..	..	..	..	..	..	5
— picrate	125–128	EtOH	..	..	..	..	5
— methiodide	172·5–174	EtOH + EtOAc	..	−25·0	22	EtOH	5
η-methyldihydrothebaine *iso*methine	..	..	..	..	..	..	5
— salicylate	209–211	..	..	+14·0	20	EtOH	5
η-methyldihydrothebaine methyl ether *iso*methine methiodide	172–174	..	..	+26·4	25	EtOH	5
ω-methyldihydrothebaine *iso*methine	..	..	..	..	..	..	5
— salicylate	161–165	EtOH	..	+85·0	25	EtOH	5
α:ω-racemic methyldihydrothebaine methine salicylate	201–204	EtOH	..	0·0	25	EtOH	5

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
δ:η-racemic methyldihydrothebaine methine salicylate	190–195	..	..	0·0	25	EtOH	5
Dihydrohydroxy-δ-methyldihydrothebaine *iso*methine [XXXV]	163–165	EtOAc	..	+25·0	20	EtOH	5
Dihydrohydroxy-η-methyldihydrothebaine *iso*methine [XXXV]	..	..	..	..	..	..	5
— racemate with δ-isomer	167–168·5	..	..	0·0	25	EtOH	5
α-methyldihydrothebaine dihydro*iso*methine	..	..	oil	..	..	..	5
— salicylate	165–167	..	..	−47·7	25	EtOH	5
δ-methyldihydrothebaine dihydro*iso*methine	..	..	oil	..	..	..	5
— salicylate	182·5–184·5	..	..	+12·8	20	EtOH	5
α-methyl-9-dimethylamino-6-methoxythebendiene [XXXIV]	76·5–78	H_2O+EtOH	..	−82·0	22	EtOH	5
— methiodide·EtOH	115–117	EtOH	..	−51·0	25	EtOH	5
— methiodide (anhyd.)	207	EtOAc+EtOH	..	..	..	..	5
δ-methyl-9-dimethylamino-6-methoxythebendiene [XXXIV]	101·5–103	EtOH+H_2O	..	+33·0	23	EtOH	5
— methiodide·$\frac{1}{2}H_2O$	c. 155 and 207–208	EtOH	..	−13·0	25	EtOH	5
— racemate with η-isomer	110–112	EtOH	..	0·0	25	EtOH	5
Vinyldihydromethylthebaol [XXIV, $\phi = CH_3$]	103–105·5	EtOH	..	0·0	25	EtOH	5
(+)-6-methoxymethylthebentriene [XXXVI]	99–101	H_2O+EtOH	..	+9·0	22	EtOH	5
(−)-6-methoxymethylthebentriene [XXXVI]	56–59·5	EtOH	..	−5·0	29	EtOH	5
— racemate of (+) (−) isomers	91·5–93·5	H_2O+EtOH	..	0·0	..	..	5
Product of oxidation of vinyldihydromethylthebaol methyl ether	191–193	..	..	0·0	..	..	5
Benzyldihydrothebaine	..	..	amorph. powder	..	..	..	2
Methyldihydro-ψ-codeinone	213–214·5	*iso* PrOH	..	..	..	..	17

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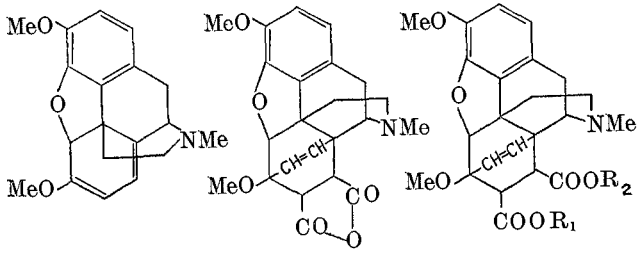
XXI

THE DIELS–ALDER REACTIONS OF THEBAINE; FLAVOTHEBAONE

THE DIELS–ALDER REACTIONS OF THEBAINE

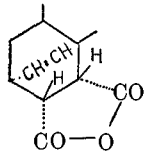
In the Diels–Alder reaction dienophiles such as benzoquinone and maleic anhydride add readily to a conjugated diene only when the two ethylenic double bonds are in an open chain or in a ring in which there is no steric hindrance. The latter condition is fulfilled in thebaine [I], which would therefore be expected to undergo facile addition of dienophiles. Such a reaction was first reported by Sandermann, who noted that addition of maleic anhydride, *p*-benzoquinone, and 1:4-naphthoquinone occurs slowly in the cold and rapidly on heating [1]. These reactions have since been more extensively studied by Schöpf, von Gottberg, and Petri [2] and by the author and his co-workers [3, 4].

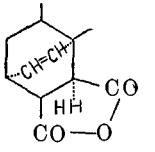
Thebaine [I] reacts with maleic anhydride in hot benzene solution to give 'thebaine-maleic anhydride' [II] [1, 2], which on heating with potassium hydroxide is converted to the dipotassium salt [III, $R_1 = R_2 = K$]. The latter on treatment with the anhydride affords the monopotassium salt [III, $R_1 = H$, $R_2 = K$?]. The diethyl ester [III, $R_1 = R_2 = Et$] is obtained by the action of ethyl alcohol and hydrogen chloride on the anhydride or of ethyl iodide on the dipotassium salt [2].

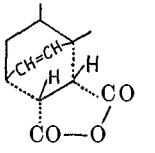


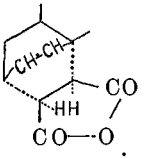
Schöpf [2] reported that neither the anhydride nor the ester could be reduced, but the latter has since been reduced catalytically to ethyl dihydro-(thebaine-maleate) [IV] and with lithium aluminium hydride to the diol [V] [3]. An attempt to prepare the isomeric ester [VI] from fumaryl chloride is in progress [3].

It is evident from the inspection of models that the addition of maleic anhydride to thebaine could give rise to four possible forms of the adduct (shown in the part-formulae [VII], [VIII], [IX], and [X]) according as the anhydride adds across the 6:14-positions on the same side ([VII] and [VIII]) of ring C as, or on the opposite side ([IX], [X]) of ring C to, the ethanamine side-chain, each mode of addition theoretically giving two isomers according to whether the anhydride ring in the product is on the same side of the new ring as the ethylene bridge ([VII] and [X]) or on the opposite side ([VIII] and [IX]). On steric grounds Schöpf allots the structure [II], i.e. the modification represented by [VIII], to the adduct [2].

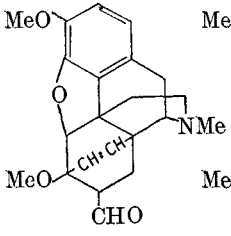

[VII]

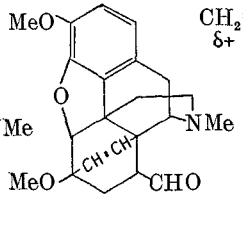

[VIII]

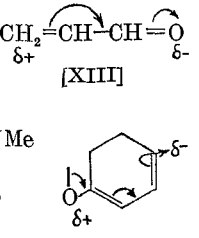

[IX]


[X]

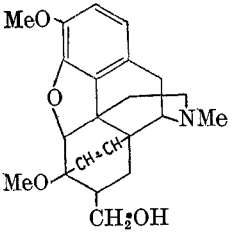
Thebaine will add acrolein in boiling benzene to give an aldehyde [5], which is most probably [XI] rather than [XII], as is shown by consideration of the forms [XIII] and [XIV], in which it is seen that the terminal carbon of acrolein is electron-deficient and that the electron density of the dienoid system in thebaine is greatest at C-14. Sodium amalgam reduction of the aldehyde affords an amorphous substance that gives benzyl and acetyl derivatives [5]. Presumably this is the alcohol [XV], which is also obtained by reduction of [XI] with lithium aluminium hydride [3].


[XI]


[XII]

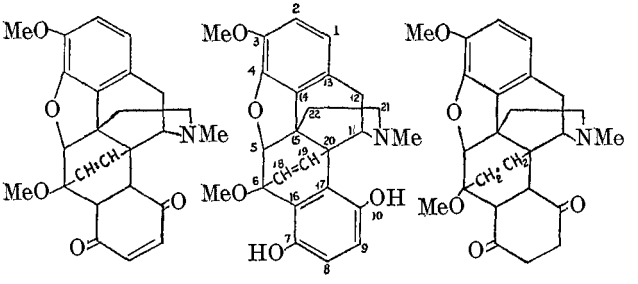

[XIII]

[XIV]


[XV]

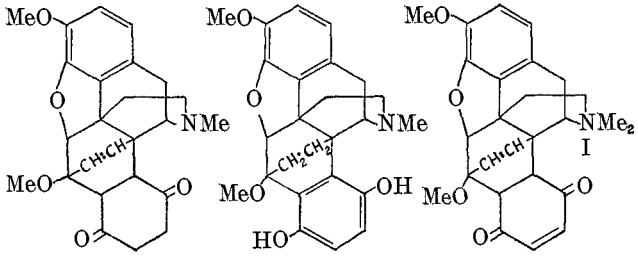
Attempts to condense thebaine with crotonaldehyde, coumarin, and ω-nitrostyrene have not so far been successful [3].

Benzoquinone may be added to thebaine in almost quantitative yield in hot benzene solution to give 'thebaine-quinone' [XVI], a bright yellow, non-phenolic substance which gives salts that are stable at room temperature [1–2]. When [XVI] is heated in high-boiling solvents, in alcoholic alkali or aqueous acid, it undergoes isomerization to 'thebaine-hydroquinone' [XVII], a change most conveniently brought about by boiling the 'quinone' [XVI] in xylene with a few drops of glacial acetic acid [2]. (The ultra-violet absorption curves of these two isomers are shown in Fig. 12.)



[XVI] [XVII] [XVIII]

Catalytic hydrogenation of 'thebaine-quinone' over platinum oxide in glacial acetic acid proceeds with the rapid absorption of one mole of hydrogen and the somewhat slower absorption of a second mole to give 'tetrahydro-thebaine-quinone' [XVIII]. If the reduction is stopped after the first mole of hydrogen has been absorbed, a product that is probably mainly [XIX] is obtained; it is believed to be mainly [XIX] as mainly non-phenolic matter is obtained after one minute's boiling with concentrated acid, under which conditions [XVI] is isomerized to [XVII] [3]. Attempted demethylation of [XVIII] with hydriodic acid affords only tars [3].



[XIX] [XX] [XXI]

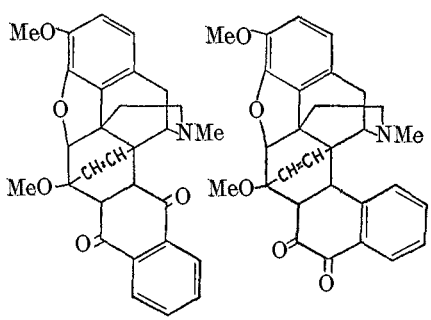
'Thebaine-hydroquinone' is a very weak base the salts of which are largely hydrolysed in solution; it is recovered as the base on recrystallization from acetic acid [2]. The two hydroxyl groups differ in

reactivity, only that at position 7 (see [XVII]) being methylated by diazomethane; the dimethyl ether can only be prepared using phenyltrimethylammonium chloride. Similarly only a monoacetyl-derivative can be prepared. The hydroxyl group at position 10 apparently forms a betaine with the nitrogen, and this has been cited as evidence in support of structure [XVII] with the hydroquinone nucleus and ethanamine side-chain on the same side of the original thebaine ring-C [2]. Catalytic hydrogenation of 'thebaine-hydroquinone' proceeds rapidly with the absorption of one mole of hydrogen and the production of dihydrothebaine-hydroquinone [XX] [2]. This can be demethylated [2].

Neither 'thebaine-quinone' nor 'thebaine-hydroquinone' form a methiodide under normal conditions, but thebaine methiodide readily reacts with benzoquinone in hot chloroform solution to give 'thebaine-quinone' methiodide [XXI], a bright orange solid soluble in hot water. Unlike [XVI], however, the methiodide is decomposed on recrystallization from high-boiling solvents such as *cyclo*hexanone, even to a small extent in hot alcohol, thebaine methiodide being recovered in good yield. Hofmann degradation of the methiodide cannot be achieved as decomposition occurs in alkaline and in acid solution [6].

The thebaine content of opium residues has been determined by treatment of the residues with benzoquinone, isolation of the adduct, and iodimetric titration of the latter in chloroform [7].

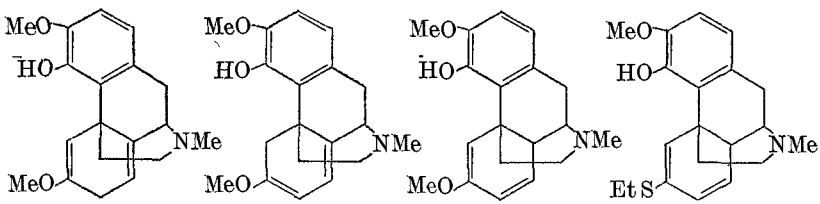
Thebaine is reported to condense with 1:4-naphthoquinone in ethanol, presumably to give [XXII] [1]; the reaction is being further investigated [3]. Thebaine methiodide readily reacts with 1:4-naphthoquinone in hot chloroform to give an orange-yellow crystalline product [3]. The reaction of thebaine with 1:2-naphthoquinone, which should yield [XXIII], is being investigated [3]. Thebaine also reacts with tetrabromo-*o*-benzoquinone to give amorphous products of unknown nature [3].



[XXII] [XXIII]

Dihydrothebaine-ϕ does not condense with benzoquinone, indicating that it has the structure [XXIV] not [XXV] [7]. Thebainone enol

methyl ether [XXVI] and β-ethylthiocodide [XXVII] should condense with benzoquinone to give compounds that are enol ethers, whilst β-dihydrothebaine [XXV] should condense with benzoquinone to give a compound analogous to [XVI], that is not an enol ether. The author intends to investigate these reactions.



FLAVOTHEBAONE

When 'thebaine-hydroquinone' is heated with glacial acetic acid and concentrated hydrochloric acid [2, 4] or with 50 per cent. sulphuric acid [4] profound rearrangement of the molecule occurs, and a new base, 'flavothebaone', is obtained.

Flavothebaone was assigned the formula $C_{24}H_{23}O_5N$ by Schöpf, von Gottberg, and Petri [2]. The base is yellow in colour and dissolves in alkali to give a deep red solution. It contains three phenolic groups, two of which are present in 'thebaine-hydroquinone', as 'thebaine-hydroquinone' dimethyl ether can be converted to flavothebaone dimethyl ether; flavothebaone methyl ether can be prepared from 'thebaine-hydroquinone' methyl ether. Flavothebaone is an α:β-unsaturated ketone, as is shown by the formation of an oxime and of an oxime containing a second molecule of hydroxylamine by addition to the double bond, and by the reduction of flavothebaone to dihydro-flavothebaone with sodium amalgam. The base was shown to contain only one reducible double bond [2].

No crystalline product is obtained when flavothebaone is oxidized with hydrogen peroxide, ozone, or other reagents. The trimethyl ether can be converted to a N-oxide on oxidation with perbenzoic acid; the N-oxide is reduced to the parent base by sulphurous acid. The trimethyl ether can be brominated to a dibromo-derivative [2].

The Beckmann transformation of flavothebaone trimethyl ether oxime yields an isoxime containing four methoxyl groups, which on treatment with methanol and hydrochloric acid yields a substance with one additional methoxyl. Both the isoxime and the methyl-derivative remain unchanged on heating with methanolic potassium hydroxide for seven hours [2].

A methine base is obtained by the alkaline degradation of flavothebaone trimethyl ether methiodide [2].

On this evidence Schöpf was unable to advance a structural formula for flavothebaone. It was, however, clear that the $\alpha:\beta$-unsaturated ketone system is in conjugation with one of the phenolic groups as, though the sodium salt of flavothebaone is red, the sodium salt of dihydroflavothebaone is colourless [2].

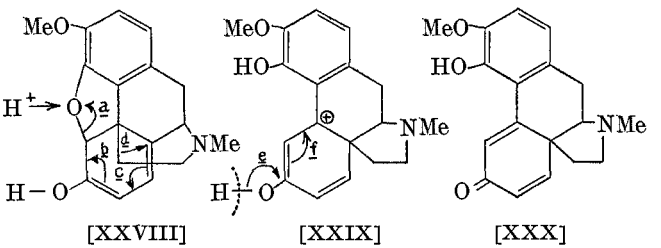
Structure

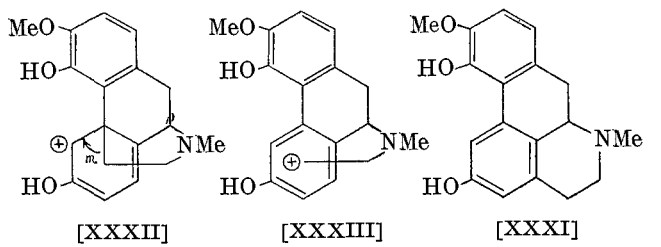
The structure of flavothebaone has been arrived at as a result of the consideration of the mechanism of the thebaine → morphothebaine rearrangement, which leads to two formulae for the rearranged substance, one of which has been shown to be untenable.

Two mechanisms have been suggested for the thebaine → morphothebaine rearrangement (see Chap. XXIII); these are briefly as follows.

(*a*) Attack of the cyclic ether oxygen by a proton and demethylation of the 6-methoxyl group, followed by the electron-shifts *a*, *b*, *c*, *d*; loss of a proton from the 6-hydroxyl group followed by the electron-shifts *e*, *f* giving the ketone [XXX] (formulae [XXVIII], [XXIX], and [XXX]), which then undergoes isomerization to morphothebaine [XXXI].

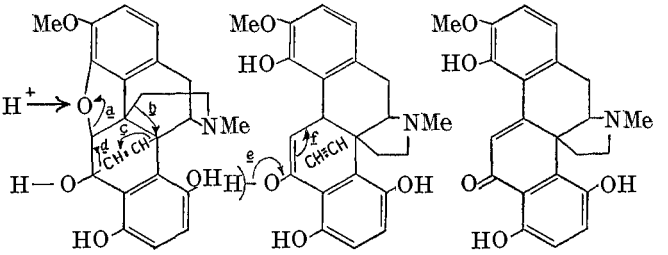
(*b*) Attack of the cyclic ether oxygen by a proton and demethylation of the 6-methoxyl group to give the carbonium ion [XXXII], isomerization of which by the electron-shift *m* gives [XXXIII]. The side-chain of [XXXIII] now moves across the π orbitals to position 8, where a proton is lost and morphothebaine is formed.



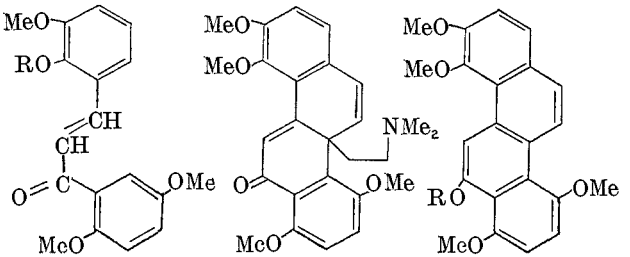


Applying mechanism (*a*) to the rearrangement of 'thebaine-hydroquinone' we have attack of the cyclic ether oxygen by a proton and demethylation of the methoxyl group, followed by the electron-shifts *a*, *b*, *c*, *d* (formula [XXXIV]), loss of a proton from the hydroxyl group

followed by the electron-shifts *e*, *f* to give [XXXVI] as the structure for flavothebaone [4]. On this view flavothebaone should have the composition $C_{22}H_{21}O_5N$ and its production should be accompanied by the production of acetylene. The structure [XXXVI] is in harmony with the known tendency of Diels–Alder adducts to suffer decomposition, and with the migration of the side-chain from C-13 to C-14 during the reduction of thebaine to metathebainone in concentrated hydrochloric acid (see Chap. XIV). Moreover, [XXXVI] is especially suited to explaining the red colour of the sodium salt of flavothebaone and the fact that the base itself is yellow.



The analytical data for flavothebaone and a large number of its derivatives were examined, but though a number of these supported the formula $C_{22}H_{21}O_5N$, an equal number supported the formula $C_{24}H_{23}O_5N$ given by Schöpf. The ultra-violet spectrum of flavothebaone trimethyl ether was compared with that of 2′:3′-dimethoxybenzylidene-2:5-dimethoxyacetophenone [XXXVII, R = Me] and that of flavothebaone dimethyl ether in neutral and alkaline solution with that of 2′-hydroxy-3′-methoxybenzylidene-2:5-dimethoxyacetophenone [XXXVII, R = H] under the same conditions, but no resemblance between the two types of compound was observed (Fig. 13), though the usefulness of this was limited by the fact that the contribution of the semi-quinone system of [XXXVI] to the absorption was not predictable [4].



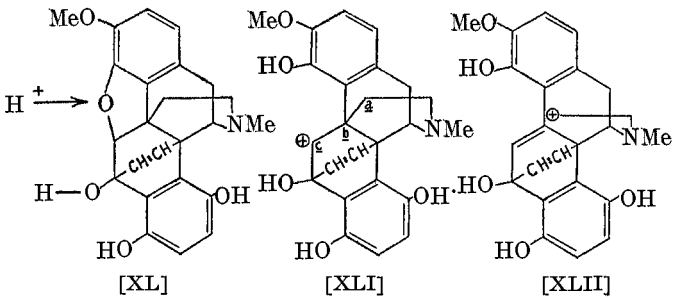
An attempt was made to degrade flavothebaone trimethyl ether

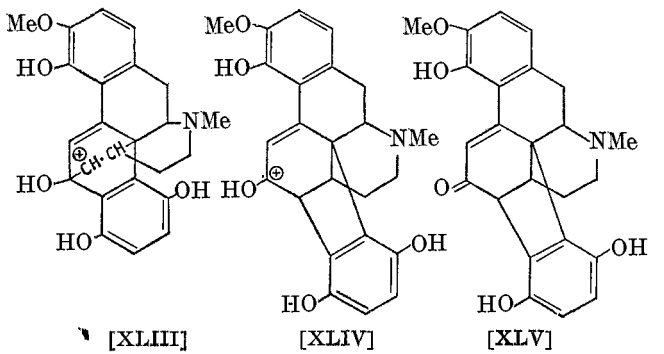
methine [XXXVIII?] to a tetramethoxyhydroxychrysene derivative [XXXIX] with loss of the nitrogen side-chain, by exhaustive methylation and by heating the methiodide with acetic anhydride. The Hofmann degradation (dry-distillation of the methohydroxide) yields some of the undegraded base, two unidentified amines and two different nitrogen-free substances apparently of composition $C_{26}H_{24}O_5$ and $C_{24}H_{22}O_5$ respectively. The acetic anhydride degradation affords an unidentified base isomeric with the methine, and a nitrogen-free substance. No chrysene derivative was obtained in either degradation [4].

A careful search for the fragment lost in going from [XXXIV] to [XXXV] met with no success [4]. In view of the negative nature of these results the molecular weights of flavothebaone trimethyl ether and flavothebaone trimethyl ether methine were determined for the author by Curzon and Hodgkin by the X-ray diffraction method. The molecular weights were found to be 448 ± 14 and 449 ± 14 respectively, and though the latter permits formulae $C_{28}H_{31}O_5N$ and $C_{26}H_{29}O_5N$, the former is consistent with $C_{27}H_{29}O_5N$ but not $C_{25}H_{27}O_5N$.

In this way the composition given by Schöpf for flavothebaone ($C_{24}H_{23}O_5N$) [2] was confirmed and the structure [XXXV] became untenable [4].

Applying the mechanism (*b*) for the thebaine → morphothebaine rearrangement to the transformation of 'thebaine-hydroquinone' to flavothebaone we have the following:





(i) Attack of the cyclic ether oxygen by a proton and demethylation [XL] leads to the carbonium ion [XLI].

(ii) The electrons of the link *a*, *b* move to *b*, *c* [XLI] to give the carbonium ion [XLII].

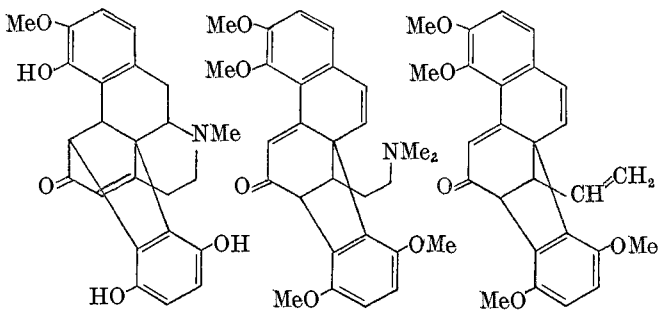
(iii) As in the morphothebaine rearrangement the positive end of the side-chain now moves to the only available position, to give the carbonium ion [XLIII].

(iv) The ion [XLIII] is of the same type as the intermediate ion in the pinacol-pinacolone rearrangement, in which aromatic groups migrate in preference to other groups, and consequently [XLIII] isomerizes to [XLIV].

(v) The ion [XLIV] finally loses a proton to give flavothebaone [XLV].

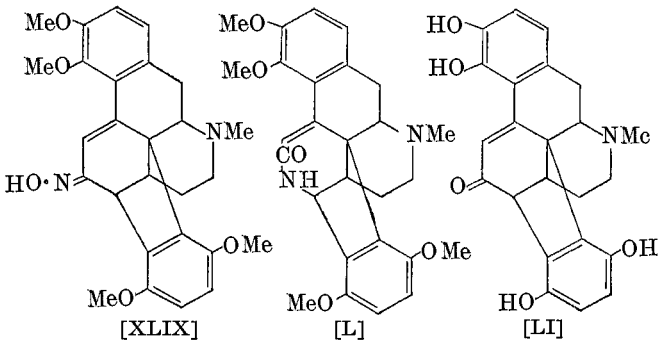
[XLV] has the composition $C_{24}H_{23}O_5N$ assigned by Schöpf to flavothebaone, contains three phenolic groups, an $\alpha:\beta$-unsaturated ketone system, and only one reducible double bond. The unsaturated ketone system is only conjugated with the guaicol nucleus, so it is surprising that the colour of flavothebaone in alkali (red) should be so much more intense than that of metathebainone under the same conditions (yellow). The ultra-violet absorption spectra of these two compounds, moreover, are not similar (Fig. 14).

One alternative formula for flavothebaone can be envisaged. The carbonium ion [XLI], like [XLIII], is of the same type as the intermediate ion in the pinacol-pinacolone rearrangement, and migration of the aromatic nucleus could occur at this stage to give [XLVI] as the structure for flavothebaone. However, [XLVI] offers no explanation of the red colour of flavothebaone in alkali as the unsaturated ketone system is not conjugated with either phenolic nucleus. Moreover, a preliminary experiment appears to indicate that 'dihydro-thebaine-hydroquinone' does not undergo rearrangement in hot acid solution.



On the basis of the structure [XLV] flavothebaone trimethyl ether methine is seen to be [XLVII] and the nitrogen-free substance $C_{20}H_{24}O_5$ obtained from the Hofmann degradation to be [XLVIII]. The natures of

the nitrogen-free substance $C_{24}H_{22}O_5$, the base, and the nitrogen-free substance obtained from the acetic anhydride degradation of [XLVII] methiodide have not yet been determined. The problem is still under investigation [4].



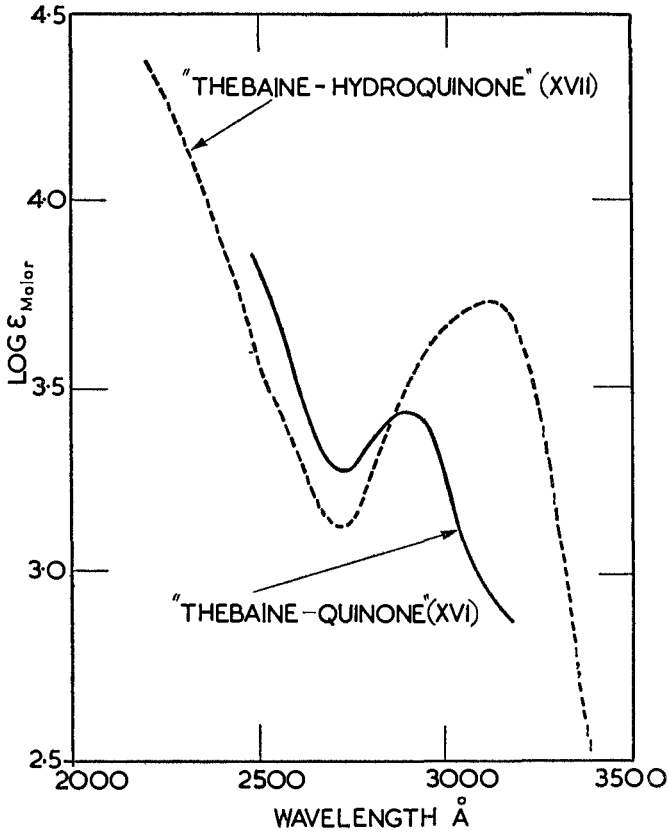


FIG. 12.

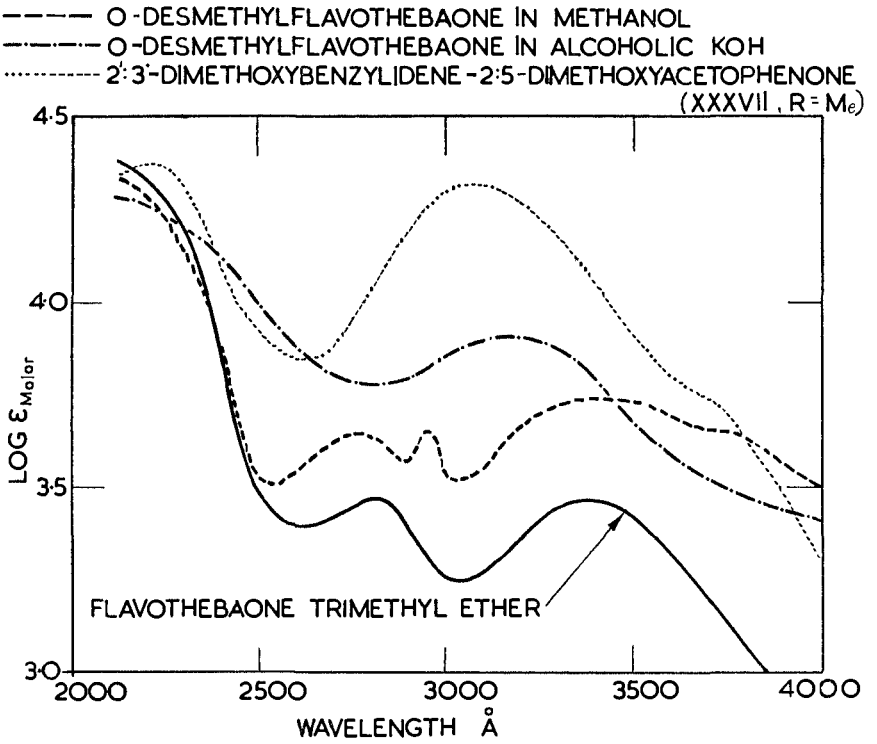

O-DESMETHYLFLAVOTHEBAONE IN METHANOL
O-DESMETHYLFLAVOTHEBAONE IN ALCOHOLIC KOH
2':3'-DIMETHOXYBENZYLIDENE-2:5-DIMETHOXYACETOPHENONE
(XXXVII, R = Me)
4·5
4·0
3·5
3·0
LOG ε Molar
FLAVOTHEBAONE TRIMETHYL ETHER
2000
2500
3000
3500
4000
WAVELENGTH Å

FIG. 13.

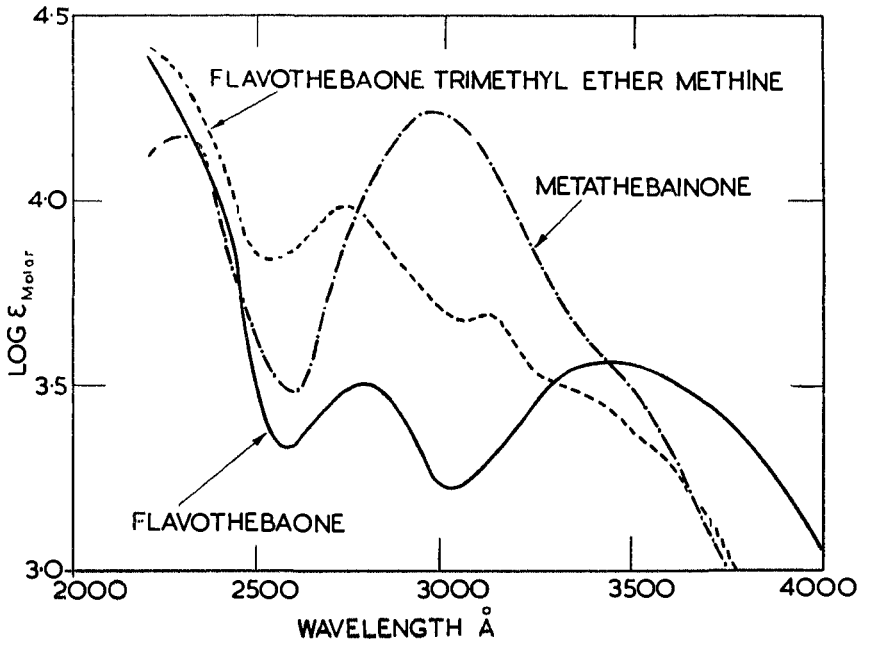

4·5
4·0
3·5
3·0
LOG ε Molar
FLAVOTHEBAONE TRIMETHYL ETHER METHINE
METATHEBAINONE
FLAVOTHEBAONE
2000
2500
3000
3500
4000
WAVELENGTH Å

FIG. 14.

The Beckmann rearrangement of flavothebaone trimethyl ether oxime [XLIX] could lead to the amide [L], which could give the corresponding amino methyl ester on heating with methanolic hydrogen chloride.

Demethylation of flavothebaone with hydrobromic acid gives O-desmethylflavothebaone [LI], also obtained by heating 'thebaine-hydroquinone' with concentrated hydrobromic acid [2].

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Thebaine-maleic anhydride	270d.	xylene	prisms	..	..	..	1–2
— monopotassium salt	..	MeOH	..	..	..	..	2
— dipotassium salt	..	MeOH	..	..	..	..	2
Ethyl thebaine-maleate	151–153	petrol	needles	..	..	..	2–3
— hydrochloride	248	..	..	..	..	..	2
Ethyl dihydro-(thebaine-maleate)	147–149	EtOH	rods	..	..	..	3
Diol [v]·H_2O	107	Et_2O	rods	..	..	..	3
Thebaine-acrolein	..	EtOH	..	..	..	..	5
— ammonia adduct?	204d.	EtOH	..	..	..	..	3
— picrate	c. 188d.	decomp.	prisms	..	..	..	3
— hydrochloride	180–182	..	..	..	..	..	5
— oxime	180	H_2O+ EtOH	..	..	..	..	5
Thebaine-acrolein Na/Hg reduction product	..	..	amorph.	..	..	..	5
— acetyl-deriv. hydrochloride	220	..	..	..	..	..	5
— benzoyl-deriv. hydrochloride	175–180	..	..	..	..	..	5
'Thebaine-quinone'	250	benzene	yellow prisms	−191·6	20	$CHCl_3$	2–4
'Thebaine-quinone' methiodide	205	decomp.	needles	..	..	..	6
'Dihydro-thebaine-quinone'?	195–200d.	β-ethoxy-ethanol	needles	..	..	..	3
'Tetrahydro-thebaine-quinone'?	222	β-ethoxy-ethanol	plates	..	..	..	3
'Thebaine-hydroquinone'	270	MeOH	prismatic needles	..	..	..	2
— hydrochloride	D. 280	..	..	..	..	..	2
— *p*-toluenesulphonate	283	H_2O	..	..	..	..	2
Monoacetyl-thebaine-hydroquinone	259	MeOH	..	..	..	..	2
Thebaine-hydroquinone monomethyl ether	238	EtOH	..	..	..	..	2
— hydriodide	261d.	H_2O	..	..	..	..	2
— acetyl-derivative	259	benzene	..	..	..	..	2
Thebaine-hydroquinone dimethyl ether·EtOH	212	EtOH	..	..	..	..	2
Dihydro-thebaine-hydroquinone	273	MeOH	..	..	..	..	2
O:O-desmethyl-dihydro-thebaine-hydroquinone hydrobromide·$2H_2O$	295	..	..	..	..	..	2
'Thebaine-1:4-naphthoquinone'	..	..	..	..	..	..	1
Flavothebaone·H_2O	255–257	..	needles	..	..	..	2
Flavothebaone·MeOH	200–206	MeOH	..	..	..	..	2
— hydrochloride·H_2O	D. 330	H_2O	..	..	..	..	2
— acid hydrochloride·$3H_2O$	312	..	..	..	..	..	2
— perchlorate	D.270–272	EtOH	prisms	..	..	..	4
— picrate	D.239–240	EtOH	prisms	..	..	..	4
— oxime	222d.	..	..	..	..	..	2
— oximo hydrochloride	> 350	..	..	..	..	..	2
— oxime triacetyl-deriv.	231	..	..	..	..	..	2
— oxime+$NH_2·OH·\frac{1}{2}H_2O$	282	..	..	..	..	..	2
— isoxime (from Beckmann transformation)	275d.	..	..	..	..	..	2
— isoxime tetraacetyl-deriv.	279	φ·CH_3	..	..	..	..	2
Triacetylflavothebaone	273	benzene	..	..	..	..	2
Flavothebaone methyl ether	276	MeOH	..	..	..	..	2
— hydrochloride	308	H_2O	needles	..	..	..	2
Flavothebaone dimethyl ether	257	MeOH	..	..	..	..	2
Flavothebaone trimethyl ether	253	MeOH	plates	+17·8	20	$CHCl_3$	2, 4
— hydrochloride	188–189	..	needles	..	..	..	2
— methiodide	251	..	plates	+38·3	20	H_2O	2, 4
— methomethylsulphate	288d.	..	..	..	..	..	2

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Flavothebaone trimethyl ether N-oxide	200–202	..	..	..	..	..	2
— N-oxide hydrochloride	312d.	..	..	..	..	..	2
— oxime	258	EtOH	..	..	..	..	2
— oxime hydrochloride·2½H_2O	271–272	H_2O	..	..	..	..	2
— isoxime·½MeOH	212–213	MeOH	..	..	..	..	2
— isoxime hydrobromide	275–276	H_2O	..	..	..	..	2
— isoxime methyl ester? hydriodide	275–276	H_2O	..	..	..	..	2
— isoxime methyl ester? hydrobromide?	252–254	H_2O	..	..	..	..	2
O-desmethylflavothebaone hydrobromide·2½H_2O	285d.	H_2O	..	..	..	..	2
Dibromoflavothebaone trimethyl ether	270–272	EtOH	..	..	..	..	2
Dihydroflavothebaone hydrochloride	350	H_2O	..	+242·0	14	MeOH	2
Dihydroflavothebaone trimethyl ether	238	MeOH	needles	+213·0	16	$CHCl_3$	2
—oxime	256–257	EtOH	..	..	..	..	2
Flavothebaone trimethyl ether methine	160–161	40% EtOH	plates	−125·6	20	$CHCl_3$	2, 4
— methiodide	295	H_2O	..	−104·7	20	H_2O	2, 4
N-free product $C_{26}H_{24}O_5$	182	MeOH	yellow plates	..	..	..	4
N-free product $C_{24}H_{22}O_5$?	247	MeOH	prisms	+764	19·5	$CHCl_3$	4
Base from acetolysis	249	MeOH	plates	+176	18	$CHCl_3$	4
N-free product from acetolysis	230–233	..	..	..	..	..	4

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XXII

APOMORPHINE

WHEN morphine [I] is heated with concentrated hydrochloric acid at 140–145° C. a deep-seated rearrangement of the molecular structure occurs and a new base, apomorphine [II], is produced [1]. Several other methods of preparation of this base have been recorded as follows: heating morphine with phosphoric acid [2] or zinc chloride [3–5]; heating chlorocodide [6] or codeine [7] with concentrated hydrochloric acid; and by passing gaseous hydrogen chloride through a solution of morphine in syrupy phosphoric acid [8–9]. The last-mentioned method gives very good yields. The substance obtained by the action of moderately concentrated sulphuric acid on morphine [10–13] is probably apomorphine sulphonic acid [14]. Apomorphine-3-methyl ether (apocodeine) can be prepared by heating codeine with phosphoric acid [15], oxalic acid [16–20], or zinc chloride [21–24], and apomorphine-3-ethyl ether by the action of zinc chloride on morphine-3-ethyl ether [24].

PROPERTIES

Though its salts were soon obtained crystalline, the free base was long thought to be amorphous and was not crystallized until 1904 [16]. Apomorphine readily undergoes aerial oxidation, and both the base and its salts turn green on exposure to the air. The oxidation is particularly rapid in alkaline solution when apomorphine, like pyrogallol, absorbs oxygen [25]. The base can only be obtained crystalline by liberation from its salts with sodium bicarbonate in the absence of air, followed by extraction with ether or chloroform and crystallization from the latter solvent in an atmosphere of nitrogen.

DETECTION

The following colour tests have been recorded for apomorphine.

Reagent	*Colour*	*References*
conc. H_2SO_4+H·CHO	violet → rose → blue-black	26
conc. H_2SO_4+hexamethylenetetramine	brown-violet	26
conc. H_2SO_4+ammonium vanadate	blue	26
conc. H_2SO_4+ammonium molybdate	blue	26
conc. H_2SO_4+sodium arsenate	dark blue	27
conc. H_2SO_4+$KReO_4$	greyish-violet → violet	28
conc. H_2SO_4+ammonium persulphate	green → blue	26
conc. H_2SO_4+selenic acid	dark violet	26
conc. H_2SO_4, 40° C., 7 min.; dilute; add conc. NH_4OH	brown, slowly develops purple fluorescence	14
PbO_2+HOAc warm, filter; add conc. H_2SO_4	dark green	29

Reagent	*Colour*	*References*
HOAc + basic magnesium hypochlorite layered on to conc. H_2SO_4	dark, opaque brown ring; dark blue underneath	30
Ammonium iodoxybenzoate	straw to garnet	31
Uranium acetate + sodium acetate + H_2O	brown ppt.	26
10% $FeCl_3$ soln.	blue	26
N/10 $KMnO_4$	green	26
Aqueous $NaNO_2$, then HCl	blood red	26
Boil + KOH	brown	26
$CuSO_4$ + trace KCN	red → rose → brown → grey → green	32
Shake base + aqueous NaOH + $CHCl_3$ in air	aqueous layer red-violet, $CHCl_3$ layer blue	26
Shake + benzene + 1% $K_3Fe(CN)_6$ in absence of acids	benzene layer violet-red turned violet by Na_2CO_3	26

The most sensitive test for apomorphine is that described by Grimbert and Leclère [33] as follows: a solution of a salt of the base is boiled for a few seconds with five drops of saturated mercuric chloride solution and five drops of 10 per cent. sodium acetate and the solution extracted with amyl alcohol, which is coloured blue (sensitive to 1 part in 800,000 [34]).

Other methods of detecting and estimating apomorphine are given in references [35–62 inc.].

Chemical Properties

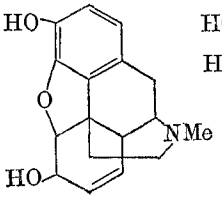
Apomorphine was shown to have the composition $C_{17}H_{17}O_2N$ by Matthiessen and Wright [1]. Mayer and Wright [25] obtained pyridine by the destructive distillation of the alkaloid, but were unable to identify any of the products of oxidation. The alkali-solubility of the base and the formation of a dibenzoyl-derivative indicates that apomorphine contains two phenolic hydroxyl groups, and the colour with ferric chloride and ease of oxidation suggest that these are present in a catechol system.

The two phenolic groups differ markedly in reactivity. Methylation of apomorphine affords apomorphine-3-methyl ether, identical with apocodeine, which on further methylation gives apomorphine-3:4-dimethyl ether [18]. A monoacetyl-derivative has also been prepared [63].

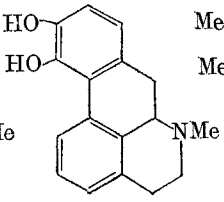
Hofmann Degradation

The nitrogen atom of apomorphine [II] carries one methyl group [64], and is apparently contained in a ring as it is not eliminated from the molecule until the second step of exhaustive methylation. Alkaline degradation of apomorphine-3:4-dimethyl ether methiodide affords two products that arise by fission of the nitrogen ring in each of the two possible ways, namely the optically inactive apomorphine dimethyl ether methine [III] and the optically active *iso*methine [IV], which still

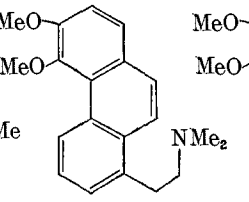
contains the nitrogen atom attached to position 9 of the phenanthrene skeleton [65]. The only alkaloids of the morphine group that degrade to *iso*methines are those that no longer contain the typical morphine skeleton.



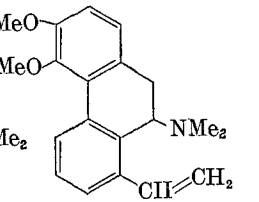
[I]



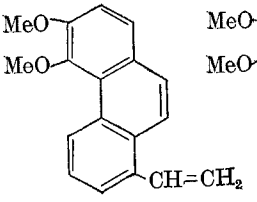
[II]



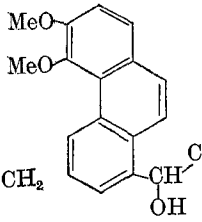
[III]



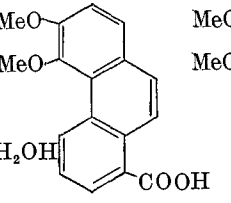
[IV]



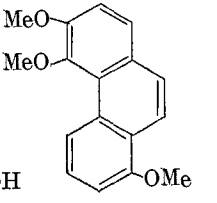
[V]



[VI]



[VII]



[VIII]

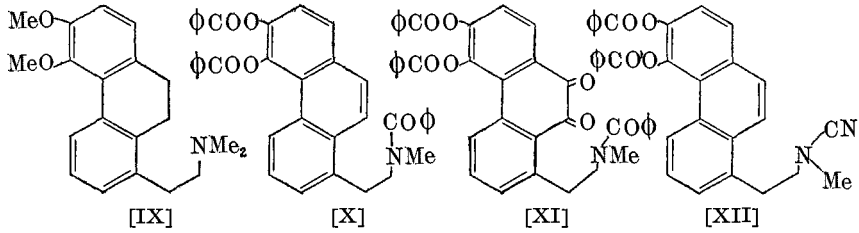
Further degradation of the methine and *iso*methine yields the same 3:4-dimethoxy-8-vinylphenanthrene [V], which can be oxidized, first to 3:4-dimethoxy-8-(α:β-dihydroxyethyl)-phenanthrene [VI] and finally to 3:4-dimethoxyphenanthrene-8-carboxylic acid [VII] [16, 66]. The latter has been converted via the 8-amino compound to 3:4:8-trimethoxyphenanthrene [VIII] [67], shown to be identical with an authentic specimen [68]. Two ethylphenanthrenes, not identical with 9-ethylphenanthrene, are obtained by distilling [V] with zinc-dust [66]. Position 8 of the phenanthrene system was thus established as the point of attachment of the carbon end of the side-chain in apomorphine. Position 9 as point attachment of the nitrogen was assumed on the basis of evidence derived from the chemistry of morphine and was finally proved by synthesis.

The Emde reduction of apomorphine dimethyl ether methochloride affords the dihydromethine [IX] [69].

Other Degradations

When apomorphine is treated with excess of benzoyl chloride scission of the nitrogen-containing ring occurs with introduction of a benzoyl group on the nitrogen, the product being tribenzoylapomorphine [X] [16]. That this is an aromatic phenanthrene derivative is revealed by its oxidation to a phenanthrene quinone [XI]; no groups are lost during this reaction, thus the 9:10 positions must be free of substituents [70].

A similar ring-fission occurs when apomorphine is heated with acetic anhydride and hydrochloric acid [71] and when the mono- and dimethyl ethers are heated with benzoyl chloride [72]. Another reaction that involves fission of the nitrogen ring is the reaction between dibenzoylapomorphine and cyanogen bromide, which results in [XII] [73]. Other tetrahydro*iso*quinoline derivatives also suffer ring-fission with this reagent [74–76].

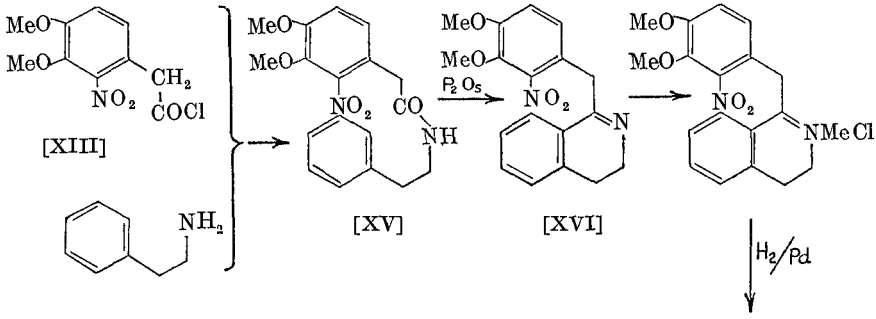


[IX] [X] [XI] [XII]

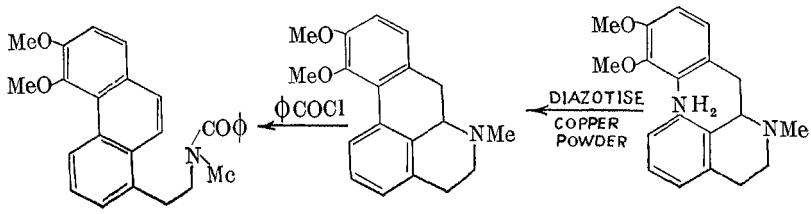
Synthesis

Two syntheses of apomorphine dimethyl ether have been recorded, as follows.

(*a*) Späth and Hromatka, making use of the Bischler–Napieralsky *iso*quinoline and Pschorr phenanthrene syntheses condensed 2-nitro-3:4-dimethoxyphenylacetyl chloride [XIII] with β-phenylethylamine [XIV] and converted the resulting amide [XV] to the benzyldihydro*iso*-quinoline [XVI] by boiling it with phosphorus pentoxide in xylene.



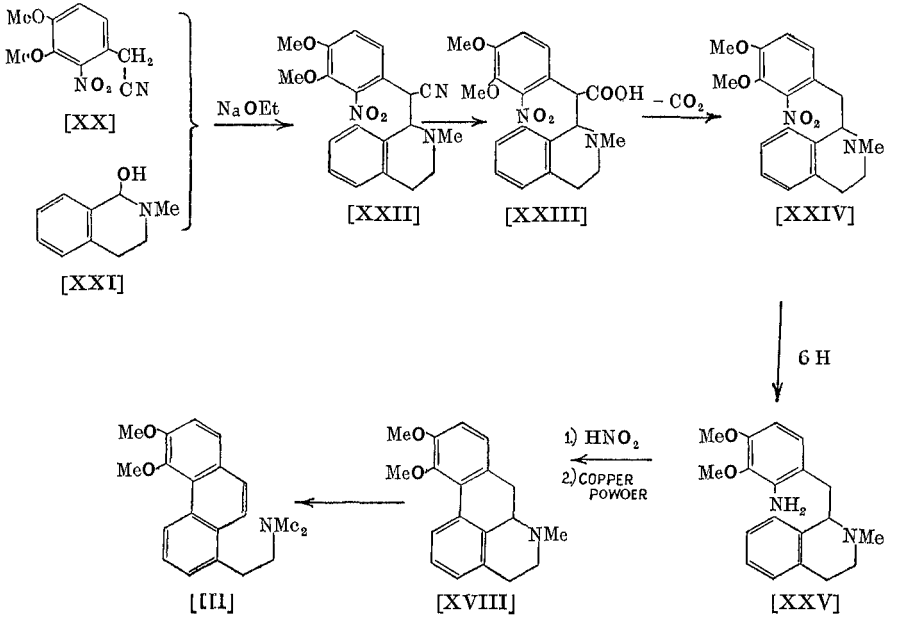
[XIII] [XIV] [XV] [XVI]



[XIX] [XVIII] [XVII]

[XVI] was then converted to the methochloride which was reduced to [XVII], the nitro group being simultaneously reduced to amino. Diazotization of [XVII] followed by treatment with copper powder afforded *dl*-apomorphine dimethyl ether [XVIII]. As the natural *l*-apomorphine could not be racemized, comparison between the natural and the synthetic material was accomplished by benzoylating both, when the same inactive [XIX] was obtained [72]. This synthesis is of interest as it had thrice previously been attempted unsuccessfully [77–79], the failure of these attempts being attributable to an insufficient time for, or an insufficiently high temperature during, closure of the *iso*quinoline ring.

(*b*) Whereas the authenticity of the Späth and Hromatka synthesis has never been questioned, considerable doubt surrounds the alternative synthesis claimed by Pschorr and Avenarius [80], the validity of which has been openly questioned by Gulland [81]. Synthesis was claimed by the following method. Condensation of 2-nitro-3:4-dimethoxyphenylacetonitrile [XX] with 1-hydroxy-2-methyl-1:2:3:4-tetrahydro*iso*quinoline [XXI] in the presence of sodium ethoxide afforded [XXII], the cyano-group of which was hydrolysed to give the acid [XXIII] and the latter decarboxylated to [XXIV]. Reduction of [XXIV] followed by Pschorr phenanthrene ring closure of the resulting [XXV] was alleged to give *dl*-apomorphine dimethyl ether, comparison with the natural *l*-isomer being made after degradation of both to the inactive methine base [III]. The experimental details accompanying this alleged synthesis are quite inadequate.



Gulland [81] has pointed out that not only did Pschorr and Avenarius fail to isolate the intermediates in their synthesis, but also this method had previously been attempted [82], not only for apomorphine dimethyl ether but for other aporphine bases as well, and that in every experiment in a large number carried out under a variety of conditions, fission of the primary condensation product occurred with regeneration of the starting materials or their derivatives. No aporphine base, not even an aminobenzylisoquinoline, was ever obtained, and in the specific case of the attempted synthesis of apomorphine dimethyl ether, in place of the 'apomorphine dimethyl ether methiodide', m.p. 195° C., reported by Pschorr and Avenarius, only N-methyl-1:2:3:4-tetrahydro*iso*quinoline, m.p. 192° C., was obtained. No successful repetition of this synthesis has ever been published. A thorough criticism of the claim and of the experimental work is given by Gulland and Virden [82].

Derivatives of Apomorphine

Apomorphine-1-sulphonic acid is obtained by the sulphonation of apomorphine with ice-cold concentrated sulphuric acid [14, 83–84]. It is probably identical with the substance obtained by the action of moderately concentrated sulphuric acid on morphine [10–13].

'2-nitrosoapomorphine', prepared by Wieland and Kappelmeier from '2-nitrosomorphine' [85], is presumably 2-nitroapomorphine [86–87]. 2-aminoapomorphine [85], 2-phenylazoapomorphine [88–89], and 2-(*p*-chlorophenylazo)-apomorphine [89] can be prepared by the rearrangement of the corresponding substituted morphines.

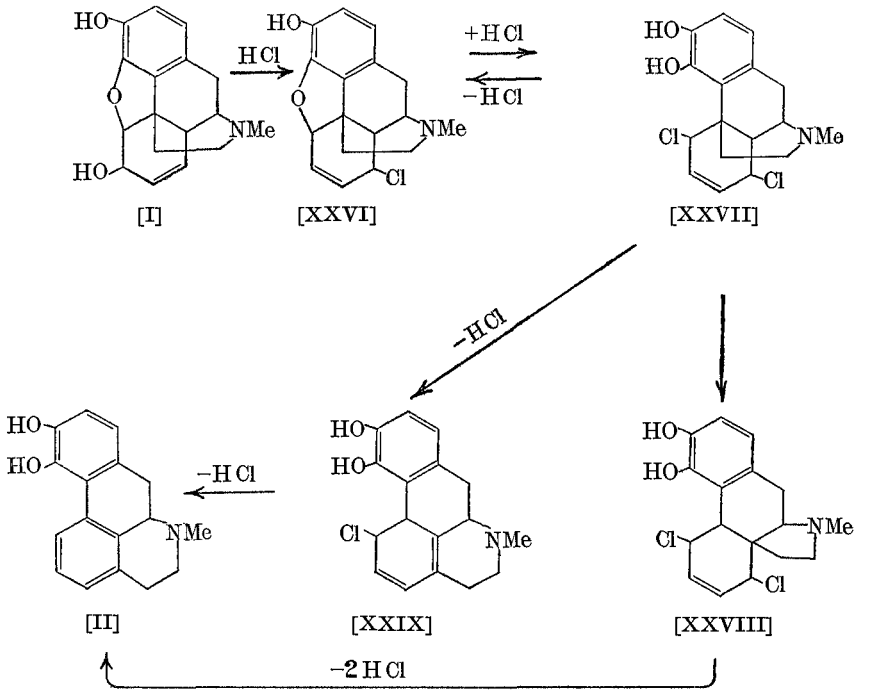
The demethylation of morphothebaine (see Chap. XXIII) affords 6-hydroxyapomorphine, which is even more sensitive in alkaline solution than apomorphine [90].

The Mechanism of the Morphine → Apomorphine Conversion

In warm concentrated hydrochloric acid morphine adds one molecule of hydrogen chloride at the 4:5-oxygen bridge and suffers replacement of the alcoholic hydroxyl group by chlorine, subsequently or simultaneously undergoing an $\alpha:\gamma$-shift of the substituent giving dichlorodihydrodesoxymorphine hydrochloride [XXVII]. The latter readily loses hydrogen chloride even in hot water, giving β-chloromorphide [XXVI], from which it may be regenerated by the action of hydrogen chloride.

That β-chloromorphide [XXVI] is an intermediate in the production of [XXVII] from morphine is shown by the fact that if the reaction is stopped when crystals of [XXVII] first appear, morphine and β-chloromorphide can be isolated from the solution in approximately equal amounts, together with [XXVII]. Under the conditions of the morphine → apomorphine conversion both β-chloromorphide and [XXVII] give yields of

apomorphine comparable to those obtained from morphine itself [15, 91]. β-chloromorphide was early believed to be an intermediate in the conversion of morphine to apomorphine [92–93].



On the basis of the above Small, Faris, and Mallonee [15] have advanced the following mechanism for the morphine → apomorphine conversion. Three stages are envisaged:

(*a*) Replacement of the alcoholic group of morphine [I] by chlorine and subsequent or simultaneous α:γ-shift of the substituent giving β-chloromorphide [XXVI].

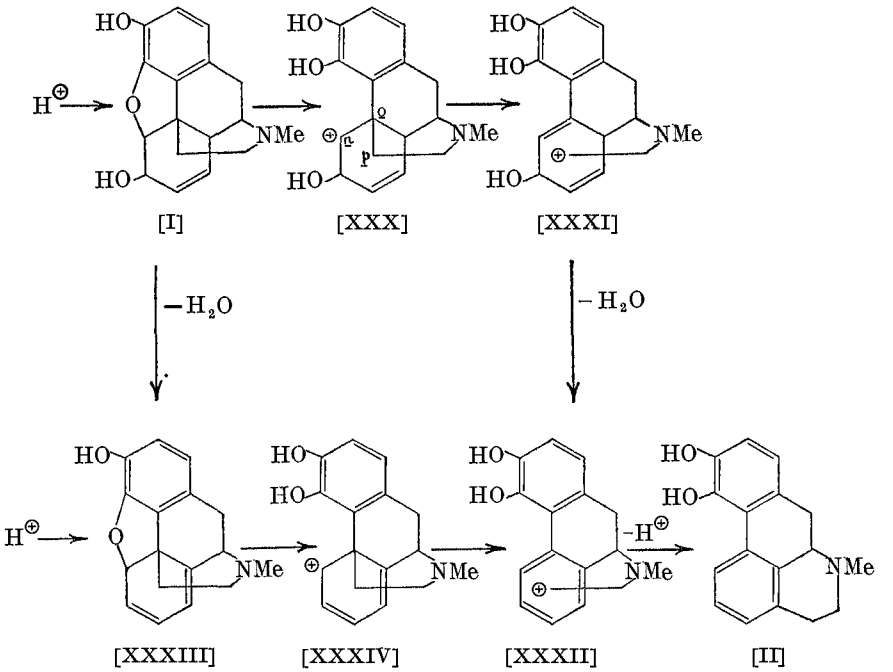
(*b*) The cyclic ether group of [XXVI], activated by the 6:7-double bond, undergoes addition of hydrogen chloride to yield [XXVII].

(*c*) Rearrangement of [XXVII] to apomorphine [II] via [XXVIII] or [XXIX] with loss of two molecules of hydrogen chloride.

It is believed that apocodeine is formed in a similar way, and support for the mechanism is cited in the fact that ψ-codeine, in which the α:γ-shift of (*a*) has already occurred, gives a somewhat better yield [15, 17].

However, though such a mechanism is possible in the specific case of the conversion of morphine to apomorphine in hydrochloric acid, it cannot be operative in phosphoric acid or in the production of apocodeine by heating codeine with oxalic acid. It is possible to give a

general mechanism applicable to all cases and also to the conversion of thebaine to morphothebaine (Chap. XXIII) and thebenine (Chap. XXV) and of 'thebaine-hydroquinone' to flavothebaone (Chap. XXI) as follows.



Attack at the cyclic ether oxygen of morphine [I] by a proton results in the migration of the electrons of the link *m*, *n* to the oxygen atom giving the carbonium ion [XXX]. The electrons of *o*, *p* now move to *n* to replace those lost to the oxygen atom giving the carbonium ion [XXXI]. Dehydration then occurs, leaving ring C fully aromatic, whereupon the side-chain becomes attached at the only possible point—position 8—with expulsion of a proton and formation of apomorphine. The movement of the chain from C-13 to C-8 is a natural migration across the π orbitals, and indeed the side-chain must be regarded as never becoming detached from ring C. The stage at which dehydration occurs is immaterial and the reaction might well follow the course

$$[\text{I}] \rightarrow [\text{XXXIII}] \rightarrow [\text{XXXIV}] \rightarrow [\text{XXXII}] \rightarrow [\text{II}]$$

without affecting the argument.

The ultra-violet absorption spectrum of apomorphine (Fig. 15, compared with morphine) has been studied by Girardet [94] and by Gompel and Henri [95].

The alkaloids of *stephania japonica* apparently contain bases of the apomorphine group. Kondo and Sanada [96–97] have shown that desoxyepistephanine methiodide is the optical antipode of apomorphine dimethyl ether methiodide.

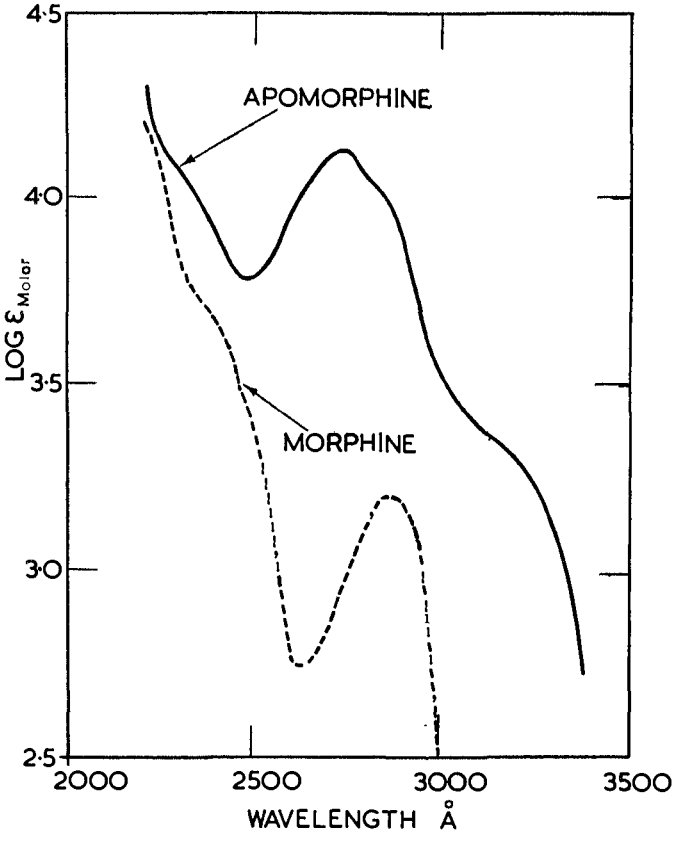


FIG. 15.

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Apomorphine	..	subl.	..	..	..	..	98
		$CHCl_3$	..	..	..	..	16
hydrochloride	..	H_2O	prisms	−30·5*	16	H_2O	16, 99
— sulphate	..	..	..	..	..	..	100
— silicotungstate	..	..	..	..	..	..	101
— methochloride	205–210	EtOH	..	..	..	..	102–103
— methobromide·MeOH	180	MeOH	..	..	..	..	102–4
— methonitrate	..	acetone	plates	..	..	..	102–103
— methomethylsulphate	..	..	..	..	..	..	102–103
Monoacetylapomorphine?	..	..	..	..	..	..	63
Diacetylapomorphine	129	..	..	−67·3	..	dil. HCl	16
— methiodido	233	..	..	−47·2	..	Ac_2O	16
Triacetylapomorphine	137	..	..	..	..	..	71
Dibenzoylapomorphine	156–158	EtOH	prisms	+43·4*	17	$CHCl_3$	16
— methiodide	220–230	..	needles	..	..	..	16

* $[\alpha]_5^{\ }$

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Dibenzoylacetylapomorphine	156–158	..	..	..	..	..	16
Tribenzoylapomorphine	217–218	$CHCl_3$	needles	..	..	..	16, 70
Tribenzoylapomorphine quinone	178–179	..	yellow needles	..	..	..	70
— phenylhydrazone	235–236	..	..	..	..	..	70
Apomorphine-3-methyl ether (Apocodeine)	..	..	..	+66·8	22	EtOH	16
	105–110	..	..	−90·0	15	EtOH	17–18
	121–121·5	MeOH	prisms	−97·0	24	EtOH	15
— hydriodide	288	..	..	..	..	..	..
— methiodide	229–230	..	..	+10·4	21	H_2O	16
	230–233	..	..	−17·0	15	MeOH	..
Monobenzoylapomorphine-3-methyl ether	85–90	EtOH	needles	..	..	..	16
Diacetylapomorphine-3-methyl ether $\cdot H_2O$	130	..	..	..	..	..	16
Monoacetylapomorphine-3-methyl ether methiodide	241–242	..	..	−39·0	15	H_2O	16
Apomorphine dimethyl ether	..	..	oil	−148·0	15	EtOH	18
— hydriodide	c. 220	..	..	−49·0	15	EtOH	18
— *d*-bitartrate	177–178	..	..	..	..	..	72
— methiodide	195	..	..	−46·0	15	EtOH	18, 16
Benzoylapomorphine dimethyl ether	166·5	..	..	..	..	..	72
2-nitroapomorphine	> 300	EtOH	red needles	..	..	..	85
— hydrochloride	D. > 200	..	..	..	..	..	85
2-aminoapomorphine	..	..	amorph.	..	..	..	85
— hydrochloride	260–265	..	..	..	..	..	85
2-phenylazoapomorphine	> 310	..	..	..	..	..	88–89
2-(*p*-chlorophenylazo)-apomorphine	..	..	..	..	..	..	89
6-hydroxyapomorphine hydrobromide	261–262	H_2O	needles	..	..	..	90
Apomorphine-1-sulphonic acid	> 300	..	needles	..	..	..	84
							14, 83
Apomorphine dimethyl ether methino	..	..	..	..	..	..	16
— hydrochloride	220–221	..	needles	..	..	..	16
— methiodide	242–244	H_2O	plates	..	..	..	16
Apomorphine dimethyl ether dihydromethine	70·5–71·5	..	leaflets	..	..	..	69
— methiodide	240	..	..	..	..	..	69
Apomorphine dimethyl ether *iso*-methine	..	..	..	+138·6	..	..	65
3:4-dimethoxy-8-vinylphenanthrene	80	EtOH	plates	..	..	..	16
— picrate	128	H_2O+EtOH	violet needles	..	..	..	16
— dibromide	145–147	HOAc	needles	..	..	..	16
— tribromide	158–159	..	leaflets	..	..	..	16
— pentabromide	153–154	petrol	rods	..	..	..	66
3:4-dimethoxy-8-(α:β-dihydroxyethyl)-phenanthrene	145	EtOH	leaflets	..	..	..	66
— diacetate	126–127	MeOH	prisms	..	..	..	66
3:4-dimethoxyphenanthrene-8-carboxylic acid	196	HOAc	needles	..	..	..	16
— ethyl ester	81–83	EtOH	rods	..	..	..	67
— hydrazide	194–195	EtOH	needles	..	..	..	67
— urethane	164–165	EtOH	needles	..	..	..	67
3:4-dimethoxy-8-aminophenanthrene hydrochloride	290d.	H_2O	needles	..	..	..	67
3:4-dimethoxy-8-hydroxyphenanthrene	182–183	EtOH	prisms	..	..	..	67
3:4:8-trimethoxyphenanthrene	138	EtOH	..	..	..	..	67
— picrate	129	..	needles	..	..	..	67
— dibromide	139–140	..	..	..	..	..	67
α-Ethylphenanthrene from zinc-dust distn. of 3:4-dimethoxy-8-vinylphenanthrene	109–110	MeOH	leaflets	..	..	..	66
— picrate	138–140	..	..	..	..	..	66
— quinone	187–188	..	..	..	..	..	66
β-Ethylphenanthrene from same source	..	..	..	..	..	..	66

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XXIII

MORPHOTHEBAINE

WHEN thebaine [I] is dissolved in concentrated hydrochloric or hydrobromic acid an orange-red solution, from which no recognizable substance can be isolated, is obtained, but if this solution is heated in closed vessels for one hour at 80–90° C. a crystalline 'acid hydrochloride' of morphothebaine [II] separates [1–2]. Methyl iodide has been shown to be evolved when the reaction is carried out in hydriodic acid [3]. Morphothebaine may also be prepared by the action of concentrated hydrochloric acid on codeinone [III] at 100° C. [4].

Morphothebaine shows the following colour reactions.

Reagent	*Colour*	*References*
conc. H_2SO_4	colourless	5
conc. H_2SO_4+sodium molybdate	steel blue (violet tinge) → green-yellow	5
conc. H_2SO_4+ammonium vanadate (small amount)	dirty violet	5
conc. H_2SO_4+ammonium vanadate (large amount)	brown	5
conc. H_2SO_4+conc. HNO_3	pale yellow	5
conc. HNO_3	blood red	5
diazosulphanilic acid in NaOH	intense red	6

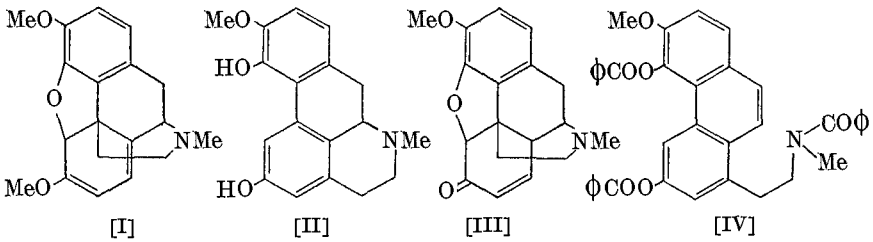
It is precipitated by potassium chromate, ferricyanide, bismuthi-iodide, and mercuri-iodide, ammonium molybdate, platinic chloride, and auric chloride [1].

Morphothebaine was first believed to be simply a demethylated thebaine and to have the composition $C_{17}H_{15}OH(OH)_2$ [3], but later was correctly shown to have the formula $C_{18}H_{19}O_3N$, and to contain one methoxyl group [7]. It contains two phenolic hydroxyl groups and cannot be converted back to thebaine [7].

DEGRADATION

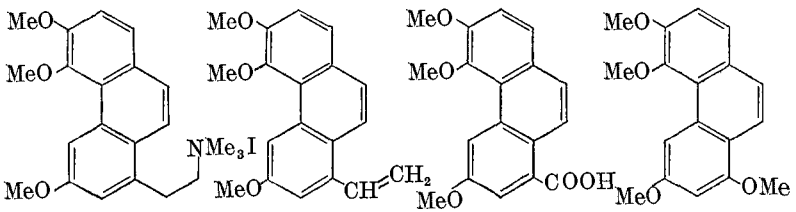
Howard prepared what he believed was monoacetylmorphothebaine [1], but this was subsequently proved to be a triacetyl-derivative [7], and its formation involves scission of the nitrogen-containing ring [8], though this was not at first recognized. Similarly the base on heating with benzoyl chloride gives a tribenzoylmorphothebaine [IV] [9], which is a fully aromatic phenanthrene derivative, and can be oxidized with chromic acid to tribenzoylmorphothebainequinone. The latter is not crystalline but gives a crystalline phenylhydrazone $C_{45}H_{35}O_7N_3$ and, with *o*-phenylenediamine, a crystalline azine $C_{45}H_{33}O_6N_3$, and may be hydrolysed to N-benzoylmorphothebaine quinone, which gives a

phenylhydrazone $C_{31}H_{27}O_5N_3$ and an azine $C_{31}H_{25}O_4N_3$. These reactions show that no groups are lost during the oxidation to a quinone, so that in [IV] no substituents are located at the 9 or 10 positions [10]. In these reactions morphothebaine behaves like apomorphine (see Chap. XXII).



Exhaustive Methylation

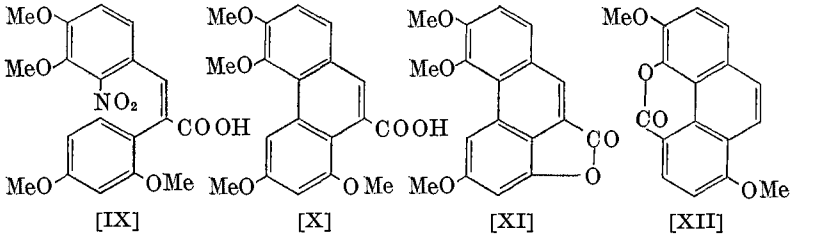
Morphothebaine affords with difficulty a dimethyl ether on methylation in *iso*amyl ether with nascent diazomethane [5]. When the phenolic base is heated with sodium methoxide and methyl iodide, and when the methiodide is heated with methyl sulphate and alkali, methylation and Hofmann degradation occurs, the product being morphothebaine dimethyl ether methine methiodide [V], further degradation of which yields 3:4:6-trimethoxy-8-vinylphenanthrene [VI], trimethylamine, and a grey, sandy powder, sintering between 200° C. and 300° C., having the composition $(C_{19}H_{18}O_3)_n$, which is probably a polymer of [VI] [9].



The trimethoxyvinylphenanthrene obtained in this way is isomeric with that obtained by the degradation of thebenine (see Chap. XXV), but unlike that isomer it is stable in hot acetic acid. On oxidation with potassium permanganate it affords 3:4:6-trimethoxyphenanthrene-8-carboxylic acid [VII], which on prolonged boiling under reflux is decarboxylated to 3:4:6-trimethoxyphenanthrene [9], also obtained by heating the silver salt of the acid at 250–280° C. under pressure [11].

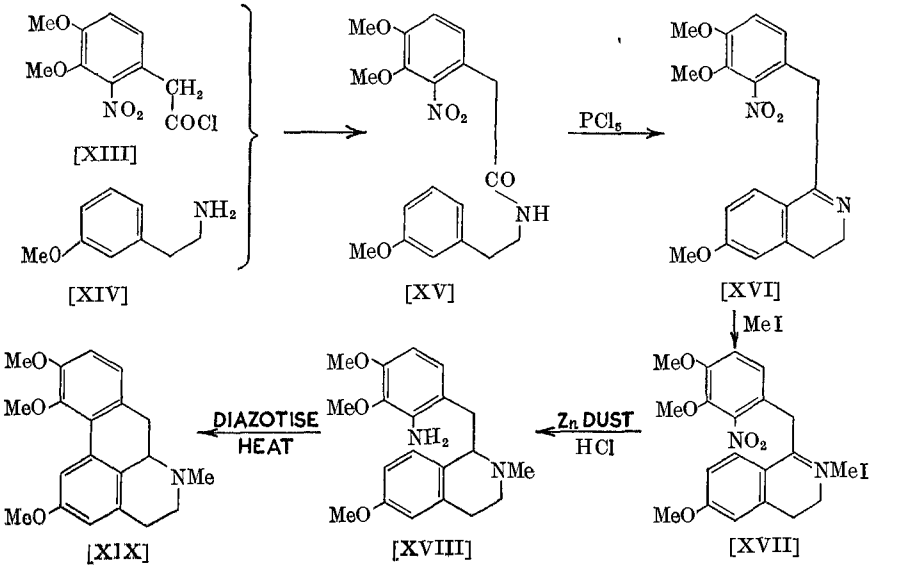
The azide of [VII] on treatment with alcohol yields the urethane, which with alcoholic ammonia affords 3:4:6-trimethoxy-8-aminophenanthrene, and this can be converted through the 8-hydroxy-compound to 3:4:6:8-tetramethoxyphenanthrene [VIII] [11]. The latter

has been synthesized from [IX] by reduction, ring closure, and decarboxylation of the resulting [X]. When [X] is heated in glacial acetic acid demethylation of the 8-methoxyl group occurs, the product being the lactone [XI] [12]. This recalls the behaviour of the azide and nitrile of 3:4:8-trimethoxyphenanthrene-5-carboxylic acid, which can readily be converted to the lactone [XII] (see Chap. XXV) [13].



By the degradation of morphothebaine to 3:4:6:8-tetramethoxyphenanthrene the position of all the substituents in the phenanthrene skeleton was revealed, and the structure of the base [II] was finally confirmed by the following synthesis of the dimethyl ether.

2-nitro-3:4-dimethoxyphenylacetyl chloride [XIII] was condensed with β-(3-methoxyphenyl)-ethylamine [XIV], giving the amide [XV], which was cyclized to the benzyl*iso*quinoline [XVI], and the product converted to the methiodide [XVII] and reduced with zinc and hydrochloric acid to [XVIII]. The *dl*-morphothebaine dimethyl ether [XIX] was obtained from the latter by diazotization and Pschorr phenanthrene ring-closure, the racemate resolved by *d*-tartaric acid, and the *l*-isomer

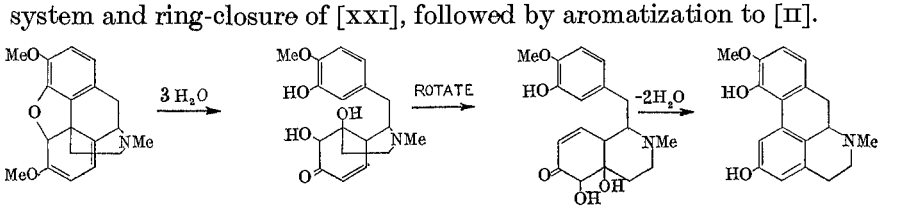


proved to be identical with morphothebaine dimethyl ether [14]. The *d*-isomer is identical with methyl-ψ-epistephanine [15].

Demethylation of morphothebaine can be effected by heating with dilute hydrobromic acid at 170° C., the product being 6-hydroxyapomorphine, which reduces silver nitrate very rapidly and is oxidized by atmospheric oxygen even more readily than apomorphine [16]. Morphothebaine and its dimethyl ether give dark green amorphous substances on oxidation with alcoholic iodine [5].

The Mechanism of the Thebaine → Morphothebaine Transformation

Several mechanisms have been postulated for the transformation of thebaine to morphothebaine; of these those of Freund [17], Faltis [18], and Freund and Speyer [19], which are based on erroneous concepts of the structure of thebaine, need not be considered. Gulland and Robinson [20] postulated hydrolytic fission of the 4:5-ether bridge and C-12:13 bond of thebaine [I] to give [XX], followed by rotation of the *iso*quinoline system and ring-closure of [XXI], followed by aromatization to [II].



[I] [XX] [XXI] [II]

Schöpf and Borkowsky have carefully studied the transformation and noted the following [2]: Neither thebaine nor morphothebaine can be recovered from the orange-red halochromic solution of the former in concentrated hydrochloric acid, but as this solution is obtained from the former and gives the latter in good yield on heating to 80–90° C., it is reasonable to suppose that it contains an intermediate in the transformation. The ultra-violet absorption spectra of thebaine and metathebainone [XXV], both in concentrated hydrochloric acid, are similar (Fig. 16) and, since metathebainone may be obtained from the halochromic solution by reduction [21], it is reasonable to suppose that the intermediate bears some relationship to [XXV]. The colour of the orange-red solution is due to halochromism and is discharged on dilution with water, but reappears if more hydrochloric acid is added.

Schöpf and Borkowsky postulate the following series of changes: Hydrolysis of the enol ether group and addition of hydrogen chloride to the 8:14-double bond of thebaine [I], giving [XXIII], which undergoes rearrangement with the side-chain and chlorine atom exchanging places, and the resulting β-chloroketone [XXII] undergoes further rearrangement with migration of the chlorine to C-5 and opening of the cyclic

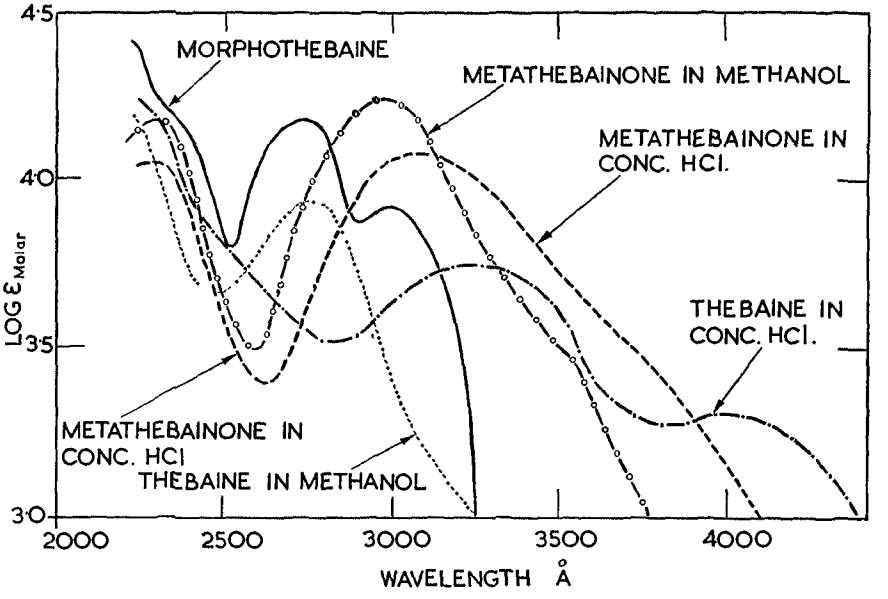
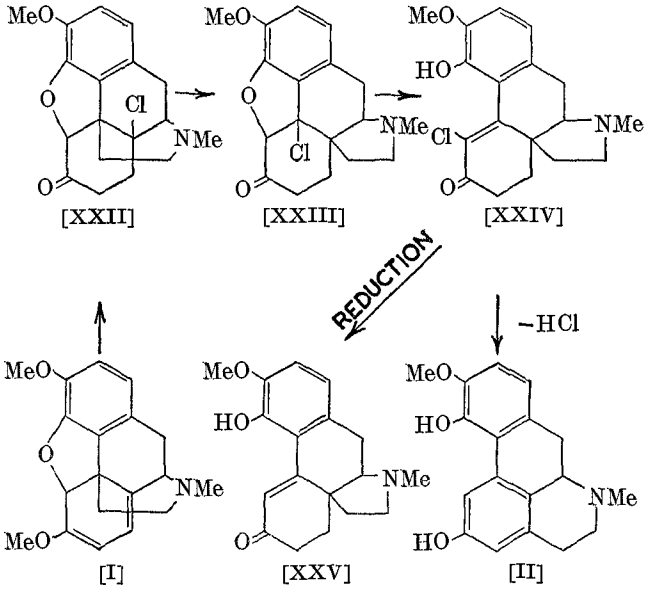
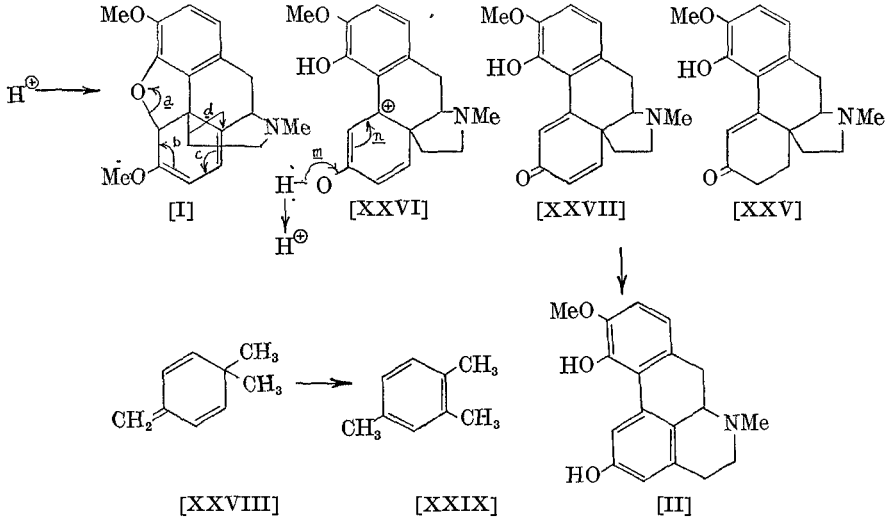


FIG. 16.



ether link to give a metathebainone-like intermediate [XXIV]. The latter is then supposed to give metathebainone [XXV] on reduction or morphothebaine on elimination of hydrogen chloride with migration of the side-chain from C-14 to C-8 [2].

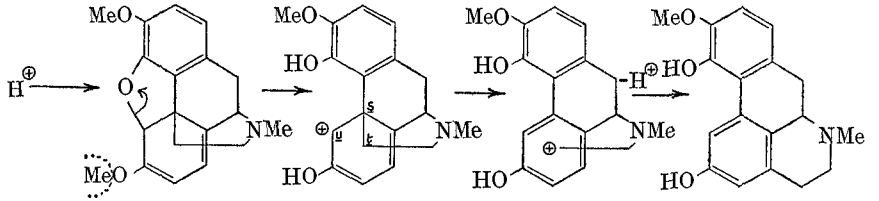
This mechanism involves several forced assumptions and is very improbable. The initial reaction when thebaine [I] is treated with concentrated hydrochloric acid is undoubtedly addition of a proton at the cyclic ether link; the subsequent processes may be regarded in either of two ways. Demethylation is assumed in both cases.



(*a*) Addition of the proton initiates the electron-shifts *a*, *b*, *c*, and *d* involving migration of the side-chain from C-13 to C-14, giving [XXVI]. This then loses a proton as shown causing the further electronic shifts *m* and *n* to give [XXVII], which is assumed to be the intermediate responsible for the red colour of thebaine in concentrated hydrochloric acid [22–23]. [XXVII] can be reduced to metathebainone [XXV] and on heating in acid solution migration of the side-chain to C-8 occurs, giving morphothebaine [II] in a manner analogous to the isomerization of [XXVIII] to [XXIX] under acid conditions [24]. This mechanism has the advantage that it explains the similarity in absorption spectra of the halochromic solutions of thebaine and metathebainone in concentrated acid and the fact that the intermediate halochromic solution contains neither thebaine nor morphothebaine. Also an analogy for the conversion of [XXVII] to [II] is known [24–25]. A rigid application of this mechanism, however, leads to an untenable formula for flavothebaone (see Chap. XXI).

(*b*) Addition of the proton affords the carbonium ion [XXX]. The electrons of the link *s*, *t* move to *u* to replace those lost to the oxygen, and ring C becomes aromatic, giving the carbonium ion [XXXI]. The positive end of the side-chain now migrates across the π orbitals to the only accessible position, C-8, with loss of a proton and production of [II]. It is not clear, however, why such an intermediate as [XXX] or [XXXI]

should reduce to metathebainone or should have an absorption spectrum similar to this base in acid solution. This mechanism, however, also results in an unsatisfactory formula for flavothebaone.



[I] [XXX] [XXXI] [II]

The ultra-violet spectrum of morphothebaine has been determined by Girardet [26]. It is shown in comparison with that of thebaine in Fig. 16.

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Morphothebaine	197d.	MeOH	rhombs	−130·0	15	EtOH	2, 5
— hydrochloride	256–260	H_2O	needles	..	..	..	1, 7
— acid hydrochloride (M_2·3HCl)	254–255	..	needles	..	..	..	2
— hydrobromide	270–275	H_2O	..	..	..	..	7
— acid hydrobromide (M_2·3HBr)	..	..	granules	..	..	..	7
— sulphate·7H_2O	..	..	prisms	..	..	..	1
— nitrate·2H_2O	..	..	cryst.	..	..	..	1
— oxalate	..	..	amorph.	..	..	..	1
— picrate	..	..	amorph.	..	..	..	1
— methiodide	221–223	HOAc	..	..	..	..	3, 7
— ethiodide	..	..	rhombs	..	..	..	3
— benzylchloride	..	..	needles	..	..	..	3
Triacetylmorphothebaine	193–194	H_2O+ EtOH	..	..	..	..	7
Tribenzoylmorphothebaine·Et_2O	120 and 181	Et_2O	..	..	..	..	9
Tribenzoylmorphothebaine	184	EtOH	..	..	..	..	10
Tribenzoylmorphothebainequinone	..	..	oil	..	..	..	10
— phenylhydrazone	227	..	..	..	..	..	10
— azine	201	..	..	..	..	..	10
N-benzoylmorphothebainequinone	267	..	..	..	..	..	10
— phenylhydrazone	..	..	..	..	..	..	10
— axino	..	..	..	..	..	..	10
Morphothebaine dimethyl ether	..	..	oil	−184·8	15	EtOH	5
— from synthesis	..	..	oil	+174·2* / −173·5	..	$CHCl_3$ / $CHCl_3$	14
— *d*-bitartrate	208–209	EtOH	needles	+75·5* / −75·0	15 / 15	H_2O / H_2O	5 / 14
— methiodide	266–268 / 190–195	..	..	..	..	..	9
dl-morphothebaine dimethyl ether	..	..	oil	−88·2	..	H_2O	14
— hydriodide	227	..	..	..	..	..	14
Morphothebaine dimethyl ether methine methiodide	266–268	HOAc	..	..	..	..	14
3:4:6:-trimethoxy-8-vinyl-phenanthrene	60–61	..	prisms	..	..	..	9, 11
— picrate	125–126	..	violet needles	..	..	..	9
3:4:6-trimethoxyphenanthrene-8-carboxylic acid	201	HOAc	needles	..	..	..	9, 11
— methyl ester	101–102	MeOH	needles	..	..	..	11
— ethyl ester	83–84	MeOH	leaflets	..	..	..	11
— hydrazide	176–177	EtOH	needles	..	..	..	11
— urethane	137–138	EtOH	needles	..	..	..	11

* Optical antipode.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
3:4:6-trimethoxy-8-aminophenanthrene hydrochloride	250	H_2O	needles	..	..	..	11
3:4:6-trimethoxy-8-hydroxyphenanthrene	..	..	..	..	..	..	11
3:4:6:8-tetramethoxyphenanthrene	108–109	MeOH	needles	..	..	..	11
— picrate	147–148	..	..	..	..	..	11

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XXIV

ISOTHEBAINE

DURING the period of growth of the oriental poppy, *Papaver orientale*, the plant contains appreciable amounts of thebaine, but during late fall, after ripening and dying of the aerial plant, little, if any, of this alkaloid is to be found, but at this time an optically active base, isomeric with thebaine, may be isolated from the root of the poppy. This base, called isothebaine, was first isolated by Gadamer [1–2] as an unidentified phenolic alkaloid and subsequently examined by Klee [3]. It has also been shown to be present in *Papaver bracteatum* [4].

DETECTION

Klee [3] recorded the following colour tests for the alkaloid:

Reagent	*Colour*
conc. H_2SO_4	colourless
conc. H_2SO_4 + conc. HNO_3 . .	pale yellow
conc. H_2SO_4 + sodium molybdate .	blue → olive green
conc. H_2SO_4 + ammonium vanadate .	bright olive green
conc. HNO_3	dark violet

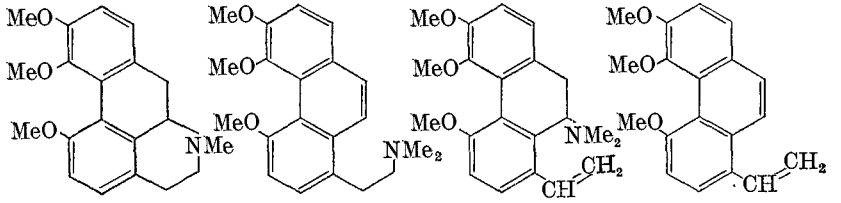
COMPOSITION

Isothebaine has the composition $C_{19}H_{21}O_3N$, contains one phenolic hydroxyl group, one N·Me group, and two ·OMe groups [3]. Acetylation of the base in pyridine affords a monoacetyl-derivative [4], but boiling the base in acetic anhydride results in scission of the nitrogen-containing ring and production of a diacetyl-derivative, which is optically inactive [3–4]. In this reaction isothebaine resembles apomorphine and morphothebaine.

HOFMANN DEGRADATION

Methylation of isothebaine with nascent diazomethane affords the methyl ether for which the structure [I] was suggested by Klee [3]. The Hofmann degradation of the methyl ether methiodide yields two methine bases, isothebaine methyl ether methine [II ?], which is optically inactive, and isothebaine methyl ether *iso*methine [III ?], which is optically active [3, 5]. Kiselev and Konovalova [5] have also noted the production during the reaction of trimethylamine and the same nitrogen-free product as is obtained by the further degradation of either the methine or the *iso*methine [3–6]. This nitrogen-free product is a trimethoxyvinylphenanthrene, possibly [IV] [3, 6], and can be oxidized by

potassium permanganate to a trimethoxyphenanthrene-carboxylic acid that can be decarboxylated to a trimethoxyphenanthrene, m.p. 78·5° C. [6], picrate m.p. 159° C. [3, 5–6]. Klee believed this to be 3:4:5-trimethoxyphenanthrene (picrate m.p. 166° C.), obtained by Vongerichten and Dittmer from morphenol [7] and subsequently synthesized (picrate m.p. 167° C.) by Pschorr and Koch [8]. This identity, and the 3:4:5-placing of the oxygen substituents in the isothebaine formula, has, however, been challenged by Kiselev and Konovalova [6].



The trimethoxyphenanthrene obtained by the degradation of isothebaine methyl ether is oxidized by nitric acid to benzene-1:2:3:4-tetracarboxylic acid [5]. (Compare the production of the same acid as final product of oxidation of 3:4:6-trimethoxyphenanthrene [9–10].)

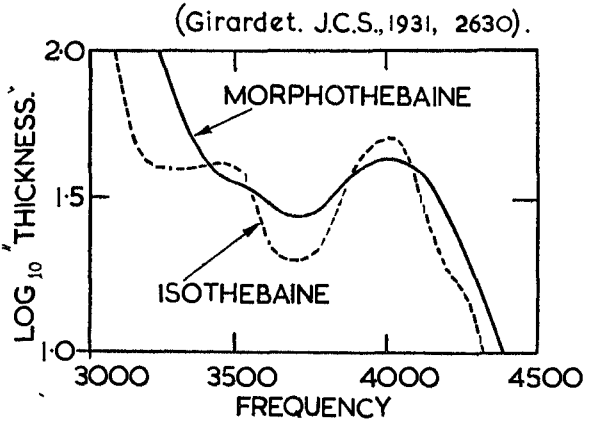


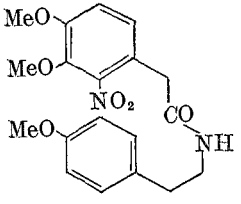
FIG. 17.

Hofmann degradation of isothebaine methiodide gives a resinous methine base degradation of which involves loss of trimethylamine and production tars [6]. The oxidation of isothebaine and its methyl ether with iodine gives only green, amorphous substances [3].

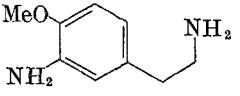
The ultra-violet absorption spectrum of isothebaine has been studied by Girardet [11]. It is shown with that of morphothebaine in Fig. 17.

Attempts to confirm the structure [I] for isothebaine methyl ether have so far met with no success. The amide [V] could not be cyclized

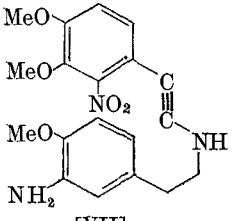
to a benzyl*iso*quinoline derivative; [VI] could not be acylated on the aliphatic amino group alone, and the diacyl-derivative could not be cyclized to an *iso*quinoline derivative in spite of the presence of an acylamino group in a position expected to facilitate ring-closure, the only product isolated from the attempted cyclization being the acetylene [VII] [12].



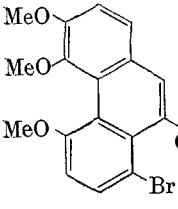
[V]



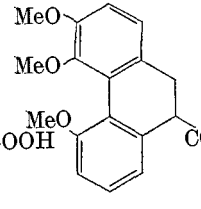
[VI]



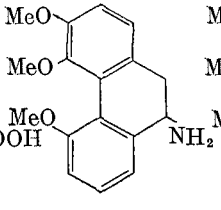
[VII]



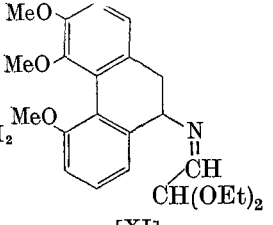
[VIII]



[IX]



[X]



[XI]

Failure to prepare the required benzyl*iso*quinoline derivative either by Bischler–Napieralsky ring closure or through condensation of the pseudo-base from 7-methoxy*iso*quinoline with 3:4-dimethoxy-2:6-dinitrotoluene has more recently been reported by Schlittler and Müller [6]. These workers, finding that the condensation of substituted desoxybenzoins with amino-acetals according to the method of Pommeranz and Fritsch also failed to give the required *iso*quinoline, attempted the synthesis of isothebaine methyl ether in the following way.

The condensation of 2-bromo-5-methoxyphenylacetic acid with 2-nitro-3:4-dimethoxybenzaldehyde followed by reduction and cyclization by Pschorr's method affords 3:4:5-trimethoxy-8-bromophenanthrene-9-carboxylic acid [VIII] in 10 per cent. overall yield. Debromination of this followed by sodium amalgam reduction resulted in the 9:10-dihydro-derivative [IX], which was converted by the Curtius degradation to 3:4:5-trimethoxy-9-amino-9:10-dihydrophenanthrene [X]. The latter, on condensation with glyoxal diethylacetal, afforded [XI], which was cyclized by concentrated sulphuric acid yielding two bases; one, m.p. 228° C., was non-phenolic and gave an ultra-violet absorption spectrum that differs profoundly from that of isothebaine; the other, m.p. 176° C., was phenolic, but the analytical data show that it cannot be a derivative of isothebaine [6].

The constitution of isothebaine is therefore still in doubt and must remain so until the synthesis of the base or one of its derivatives is achieved or the trimethoxyphenanthrene obtained by degradation is positively identified.

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
Isothebaine	203–204	Et_2O+ EtOH	..	+285·1	18	EtOH	3–4
— hydrochloride	213–214d.	..	..	..	..	..	4
— perchlorate	255d.	EtOH	..	..	..	..	4
— sulphate	120–121	..	needles	..	..	..	3
— nitrate	..	..	..	..	..	..	3
— *l*-bitartrate	..	..	needles	..	..	..	3
— methiodide	237d.	EtOH	..	..	..	..	4
Acetylisothebaine	143–145	petrol	..	+197·3	..	$CHCl_3$	4
Diacetylisothebaine	80–85	30% EtOH	..	..	..	..	3
	60–70	..	..	..	..	..	4
Isothebaine methyl ether	..	..	..	+234·5	15	$CHCl_3$	3
— *l*-bitartrate	226–227	90% EtOH	needles	+143·0	15	H_2O	3
— methomethylsulphate	237–238	..	needles	+158·1	15	H_2O	3
Isothebaine methyl ether methine	196–197	..	..	..	..	..	5
Isothebaine methyl ether *iso*methine	105	Et_2O	needles	−283·9	15	Et_2O	3, 5
— methomethylsulphate	195–196	H_2O+ MeOH	needles	..	..	..	3
?-trimethoxy-8-vinylphenanthrene	215–219	..	..	..	..	..	3, 5
?-trimethoxyphenanthrene-8-carboxylic acid	170–171	HOAc	needles	..	..	..	3, 5–6
— methyl ester	116–117	..	..	..	..	..	6
?-trimethoxyphenanthrene	78·5	..	..	..	..	..	6
— picrate	159	..	needles	..	..	..	3, 5–6

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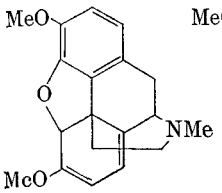
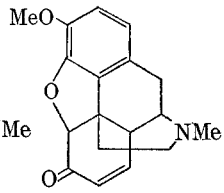
XXV

THEBENINE

PROFOUND modification of the structure, with migration of the basic side-chain and reversion to a fully aromatic phenanthrene derivative, occurs when thebaine [I] [1] or codeinone [II] [2] is heated with dilute hydrochloric acid, the product being the phenolic secondary amine thebenine [III]. Triacetylthebenine is produced when ψ-codeinone [IV] is heated with acetic anhydride [3], and thebenine-8-methyl ether (methebenine), 8-ethyl ether (ethebenine), and 8-propyl ether (prothebenine) can be prepared by heating thebaine or codeinone with hydrochloric acid and methyl, ethyl, and propyl alcohol respectively [2, 4]. Methebenine, which can be hydrolysed to thebenine by hot 20 per cent. hydrochloric acid [4], is also obtained by the action of stannous chloride and acetic anhydride on thebaine [5].



[I]



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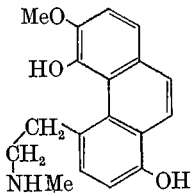
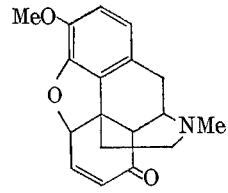


[III]



[IV]

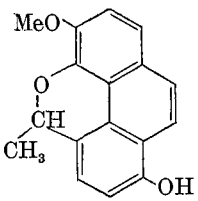
Thebenine was originally thought to be isomeric with thebaine [1], but its composition was later established as $C_{18}H_{19}O_3N$. The base with methyl iodide gives N-methylthebenine methiodide, which on alkaline degradation affords trimethylamine and a nitrogen-free substance, thebenol, indicating that the nitrogen atom in thebenine is not bound in a ring. Treatment of the base with ethyl iodide, followed by degradation, gives thebenol and methyldiethylamine, proving that thebenine must be a secondary amine [6–7].

Methebenine was shown by Pschorr and Massaciu [8] to be phenolic, thus disproving Freund's view [4] that thebenine is a cyclic ether. The phenolic group of methebenine is unreactive, however, and can only be methylated when the nitrogen atom is quaternary. Methebenine, ethebenine, and prothebenine can be converted into O:N-diacetyl-derivatives [4, 8], whereas thebenine yields a triacetyl-derivative [3–4, 7]. These facts clearly point to the presence of two phenolic groups in thebenine.

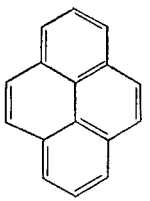
Thebenol contains one phenolic hydroxyl group, but methebenol,

ethebenol, and prothebenol (produced by the degradation of methebenine, ethebenine, and prothebenine [4]) are non-phenolic, so that thebenol must contain a cyclic ether system produced by cyclization of one of the thebenine hydroxyl groups with the vinyl group resulting from degradation. That the hydroxyl group involved in the cyclization is the one at C-4 is revealed by the fact that ethebenine, which can be degraded to ethebenol, can be degraded also to 3:4-dimethoxy-8-ethoxyphenanthrene and so must be thebenine-8-ethyl ether [9–10] (see below). Accordingly thebenol is allotted the structure [V]; a six-membered ether ring is preferred on steric grounds [11] to the seven-membered ring originally proposed [9].

Thebenol can be methylated to methebenol and acetylated; on evaporation with 30 per cent. potassium hydroxide [7] or fusion with aniline hydrochloride [12] it is demethylated to northebenol, which, like thebenol itself, gives an 'iodhydrin' on heating with concentrated hydriodic acid [7]. Thebenol contains an asymmetric carbon atom, but attempts to resolve it by condensing it with glucose residues yielded only decomposition products [12]. The hydrocarbon pyrene [VI] is formed when thebenol is distilled with zinc-dust or reduced with hydriodic acid [7]; pyrene is also obtained from thebaine under the same conditions [13].



[V]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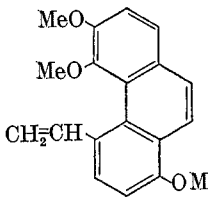
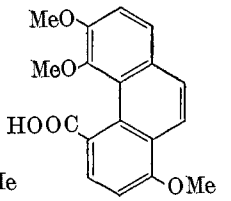


[VII]



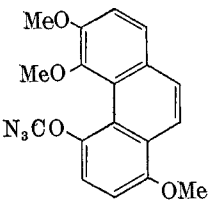
[VIII]

Hofmann degradation of N-methylthebenine dimethyl ether methiodide or methomethylsulphate, which result from the complete methylation of thebenine, affords 3:4:8-trimethoxy-5-vinylphenanthrene [VII], the 4-methoxyl group of which is so readily hydrolysed that boiling with acetic acid or alcoholic hydrogen chloride results in formation of methebenol and bromination in formation of bromomethebenol [8]. 3:4:8-Trimethoxy-5-vinylphenanthrene can be reduced to 3:4:8-trimethoxy-5-ethylphenanthrene, identical with a specimen prepared from 2-nitroveratric aldehyde and 2-methoxy-5-ethylphenylacetic acid by the Pschorr phenanthrene synthesis [11].

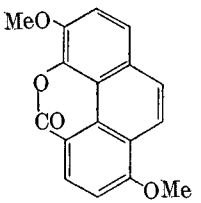
3:4:8-Trimethoxyphenanthrene-5-carboxylic acid [VIII] and a neutral substance 'oxymethebenol' are obtained by the oxidation of 3:4:8-trimethoxy-5-vinylphenanthrene [VII] [8, 9, 11], and the acid on decarboxylation affords 3:4:8-trimethoxyphenanthrene [9], identical

with the compound synthesized by Pschorr and Busch [14]. In the same way ethebenine can be degraded through 3:4-dimethoxy-8-ethoxy-5-vinylphenanthrene and 3:4-dimethoxy-8-ethoxyphenanthrene-5-carboxylic acid to 3:4-dimethoxy-8-ethoxyphenanthrene [9–10], the latter being identical with an authentic specimen prepared by synthesis [10].

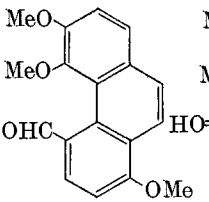
3:4:8-Trimethoxyphenanthrene-5-carboxylic acid [VIII] can be converted through the ester to the azide [IX], but attempts to degrade the latter to the 5-amino compound failed; nitrogen was lost and the product was identified as the lactone [X] of 4-hydroxy-3:8-dimethoxyphenanthrene-5-carboxylic acid [11].



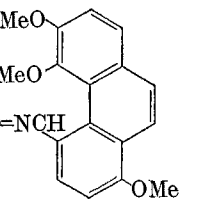
[IX]



[X]



[XI]



[XII]

The chief product of oxidation of 3:4:8-trimethoxy-5-vinylphenanthrene is a neutral substance that Pschorr called 'oxymethebenol' [8]; this is in reality the 5-aldehyde [XI]. It cannot be oxidized to the acid, but the oxime [XII] gives the nitrile on dehydration; the nitrile, though stable in hot alkali, is converted to the lactone [X] by hot acids [11]. 'Oxyethebenol' [9] is doubtless the 8-ethoxy-analogue of [XI].

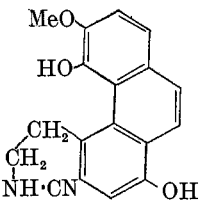
Reduction

Thebenine cannot be reduced electrolytically or with sodium and alcohol, but catalytic hydrogenation [15] or reduction with sodium hydrosulphite [16] converts it to 9:10-dihydrothebenine [XIII], which is too unstable to survive degradation. The dimethyl ether, however, can be degraded to 9:10-dihydromethebenol, the 4-methoxyl group being demethylated during the degradation [16]. (9:10-Dihydromethebenol was originally given the inaccurate name 'methoxydihydrothebenol' [16].) An oil, possibly dihydropyrene, results from the reduction of 9:10-dihydromethebenol with hydriodic acid and red phosphorus under pressure [16].

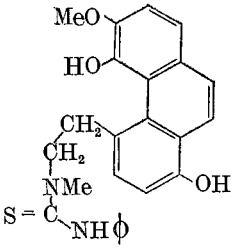
Being a secondary amine, thebenine reacts with phenyl*iso*thiocyanate to give thebenylphenylthiourea [XIV] [7].

During investigations of the reaction between cyanogen bromide and cyclic bases von Braun [17] discovered that thebaine reacts with this compound to give a substance subsequently identified as cyanonorthebenine [XV] [18]. This cannot be prepared from thebenine, nor can it be hydrolysed to northebenine. On catalytic reduction it absorbs eight

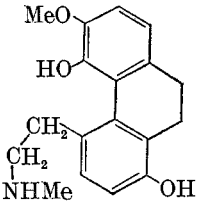
atoms of hydrogen and gives an oily base isolated as methiodide, $C_{20}H_{26}O_2NI$, which has been assigned the structure [XVI] [18].



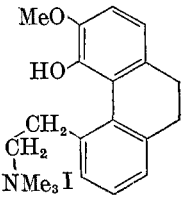
[XV]



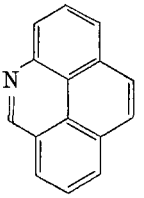
[XIV]



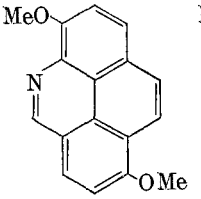
[XIII]



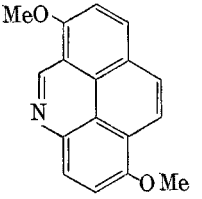
[XVI]



[XVII]



[XVIII]



[XIX]

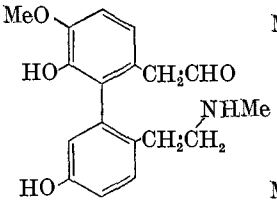
When thebenine is distilled with zinc-dust, in addition to pyrene a phenanthridine-like base, stable to chromic acid, is obtained. This substance, thebenidine, has the structure [XVII] [19] and has recently been synthesized by the action of phosphorus pentoxide on 4-formamidophenanthrene [20]. During the dehydration of the oxime [XII] a quantity of a basic substance was obtained. It is believed to be [XVIII] or the isomeric [XIX] [11] (cf. the rearrangement of C and N during the preparation of *iso*quinoline by the dehydration of cinnamaldoxime [21]).

The Mechanism of the Thebaine → Thebenine Transformation

Several mechanisms have been proposed for the conversion of thebaine to thebenine. Those of Freund and Speyer [22] and of Gulland and Robinson [23] are based on bridge formulae for thebaine that are now abandoned. However, Gulland and Robinson [23] suggested that the aldehyde [XX] is a precursor of thebenine [III] to which it may be converted by dehydration, a view still believed to be substantially correct. The mechanism suggested by Faltis [24] is based on an impossible formula for thebaine and need not be considered.

Schöpf and Borkowsky [25] postulated the 1:4-addition of water to the dienoid system of thebaine [I] to give [XXI], which could then undergo hydrolysis and ψ-codeine transformation to [XXII]. The ether bridge was then believed to break with introduction of a C-5:14 double bond, necessitating migration of the side-chain from C-14 to C-5,

resulting in fission of the C-9:N link for steric reasons, followed by aromatizing dehydration. Gulland and Virden [11], however, pointed out that [XXI] in its hydrolysed form is 14-hydroxycodeine, which is unaffected by hot dilute hydrochloric acid, and does not give triacetylthebenine on heating with acetic anhydride. (This may not be a valid objection as it is very doubtful whether 14-hydroxycodeine has in fact a structure analogous to [XXI]—see Chap. XVIII.)



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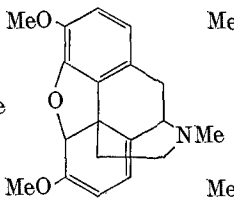
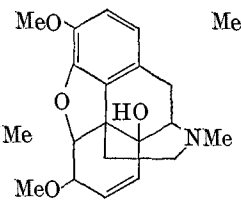
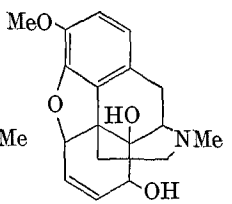


[I]

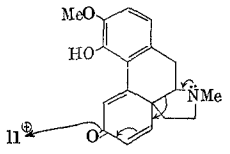


[XXI]

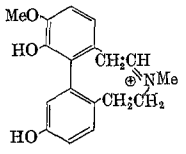


[XXII]

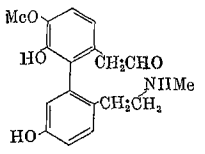
The reaction is best explained by reference to the intermediate [XXIII] already postulated in the thebaine → morphothebaine transformation. Addition of a proton to [XXIII] can proceed as shown, to give [XXIV], which is the ion of the internal Schiff's base of [XX] and can be hydrolysed to the latter in acid solution with great ease. [XX] then cyclizes as postulated above to give thebenine.



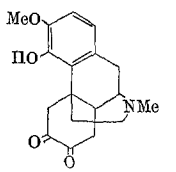
[XXIII]



[XXIV]



[XX]



[XXV]

Attempts to convert oripavine (the 3-demethylated analogue of thebaine) to an analogue of thebenine failed to give clearly-defined products [26].

The prolonged action of hydrochloric acid on thebaine or thebenine affords an amorphous substance, thebaicine, of unknown nature [1].

*iso*THEBENINE

Sinomeninone [XXV] (see Chap. XXVI) on heating with acetic anhydride and sodium acetate is converted to 3-methoxy-4:6-diacetoxyphenanthrene (20 per cent.) and triacetyl*iso*thebenine (10 per cent.); 1-bromosinomeninone under the same conditions gives 20 per cent. 1-bromotriacetyl*iso*thebenine. Catalytic reduction of these two bases yields triacetyl-9:10-dihydro*iso*thebenine [15], identical with the 'triacetyl*iso*thebenine' prepared by Schöpf, Pfeiffer, and Hirsch [27] from (—) 1-bromosinomeninone (see Chap. XXVI).

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Refs.
Thebenine	..	..	amorph.	1, 7
— hydrochloride·$3H_2O$	235	H_2O	yellow cryst.	1, 7
— sulphate·H_2O	209–210	H_2O	yellow leaflets	1, 7
— thiocyanate	..	..	cryst.	1
— platinichloride	..	..	amorph.	1
— mercurichloride	..	..	prisms	1
— oxalate·H_2O	275–276	H_2O	needles	1
N-methylthebenine methiodide	206–208	H_2O	..	7
Triacetylthebenine	160–161	EtOH	..	4, 3, 2
Methebenine	165–167	EtOH	..	4, 2
— hydrochloride	250	..	..	4
— hydriodide	195–198	..	..	4
— sulphate	238·5	..	..	4
N-methylmethebenine methiodide	215	H_2O+ EtOH	..	4
N-methylbenzoylmethebenine methiodide	271	..	..	8
Diacetylmethebenine	176	..	..	4
Dibenzoylmethebenine	159	..	..	8
N-methylthebenine dimethyl ether				
— methiodide	247	..	..	8
— methomethylsulphate	283–285	..	..	11
Ethebenine	..	..	amorph.	4
— hydrochloride	248	H_2O+ EtOH	..	4
— hydriodide·H_2O	206–207	..	..	4
N-methylethebenine methiodide	215	..	..	4
N-methylethebenine-4-methyl ether				
— methomethylsulphate	241	..	..	9
— methiodide	252	..	..	9
Diacetylethebenine	168	..	..	4
Prothebenine	172–173	EtOH	..	4
— hydrochloride	220–221	..	..	4
— hydriodide	212–213	..	..	4
N-methylprothebenine methiodide	202	..	..	4
9:10-dihydrothebenine	D. 147–148	..	rods	16
— hydrochloride	237–238	..	leaflets	16
— thiosulphate	194–195	..	..	16
N-methyl-9:10-dihydrothebenine hydriodide	130–131	H_2O	leaflets	16
N-methyl-9:10-dihydrothebenine dimethyl ether				
— methiodide	D. 245	..	..	16
— methomethylsulphate	D.270–271	..	..	16
Thebenylphenylthiourea	85	..	..	7
Thebenol	186–188	acetone	..	6–7
— sodium salt	210–212	..	..	6
Acetylthebenol	102–103	..	..	7
Methebenol	133–134	HOAc	plates	4, 7–8
— picrate	106	..	..	8
Monobromomethebenol	148–149	..	..	8
Ethebenol	103–104	HOAc	..	4
Prothebenol	103–105	HOAc	..	4
Dihydromethebenol	133–134	..	..	16
Northebenol	202–203	..	..	7
— 'iodhydrin'	D. 270	..	..	7
3:4:8-trimethoxy-5-vinylphenanthrene	122·5	EtOH	plates	8
— picrate	110	..	..	8
3:4-dimethoxy-8-ethoxy-5-vinylphenanthrene	78	petrol	plates	9
3:4:8-trimethoxyphenanthrene-5-carboxylic acid	219–221 230–237	.. HOAc	.. needles	9 11

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Refs.
3:4:8-trimethoxyphenanthrene-5-carboxylic acid methyl ester	149–151	MeOH	..	11
— hydrazide	177	EtOH	needles	11
— azide	D. 65	..	..	11
3:4-dimethoxy-8-ethoxyphenanthrene-5-carboxylic acid	191	HOAc	needles	9
3:4:8-trimethoxyphenanthrene	137–138	..	..	9
— picrate	129	..	..	9
3:4-dimethoxy-8-ethoxyphenanthrene	100	..	..	9
— picrate	119	..	..	9
3:4:8-trimethoxy-5-ethylphenanthrene	112–113	EtOH	needles	11
3:4:8-trimethoxy-5-aldehydophenanthrene ('oxymethebenol')	151	benzene +petrol	plates	11
— oxime·½C_6H_6	140–153	benzene	leaflets	11
— semicarbazone	243–246	ϕNO_2	needles	11
3:4:8-trimethoxy-5-cyanophenanthrene	145–146	MeOH	needles	11
Lactone of 3:8-dimethoxy-4-hydroxyphenanthrene-5-carboxylic acid	246–247	HOAc	needles	11
'Oxyethebenol'	129	..	..	9
Cyanonorthebonine	146–147	EtOH	leaflets	18
Methiodide of product of reduction of cyanonorthebenine	298–299	EtOH	leaflets	18
Thebenidine	144–148	benzene	..	19
— methiodide	240	..	..	19
3:8-dimethoxythebenidine ? [XVIII] or [XIX]	229–230	..	orange leaflets	11
— picrate	D. 255	MeOH	..	11
Thebaicine	..	..	amorph.	1
Triacetyl*iso*thebenine	167	..	..	15
1-bromotriacetyl*iso*thebenine	191	..	..	15
	168–170	96% EtOH	..	27
Triacetyl-9:10-dihydro*iso*thebenine	182–183	..	..	15, 27

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XXVI

SINOMENINE

THE alkaloid sinomenine was first isolated from the stem and roots of the Japanese plant *Sinomenium diversifolius* by Ishiwari in 1920 [1]. It also occurs in *Sinomenium acutum* and probably in han-fangchi [2–4]. Goto [5] first called the alkaloid cucoline, but subsequently adopted the name sinomenine.

STRUCTURE

Sinomenine was initially believed to have the composition $C_{16}H_{19}O_3N$ [1], but was subsequently shown to be $C_{19}H_{23}O_4N$ [5–7]. The base is soluble in alkali, gives a colour with ferric chloride, and affords alkali-insoluble monobenzoyl- and monomethyl-derivatives [6], and is thus recognized as a phenol. In addition the molecule contains a tertiary nitrogen atom, two methoxyl groups [5], one double bond [5, 7], and one carbonyl group [5, 7]. The presence of a carbonyl group in dihydrosinomenine has also been demonstrated [5, 7].

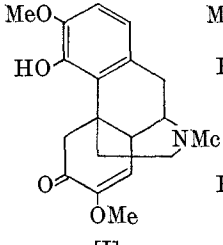
Phenanthrene and trimethylamine are obtained, together with an unidentified quinoline-like oil when the base is distilled with zinc-dust [5, 7], and the ease with which the alkaloid can be converted to non-basic phenanthrene derivatives led Ochiai [7] to suspect the presence of an easily ruptured tetrahydro*iso*quinoline system in the sinomenine molecule. This was confirmed by the method of Gadamer (treatment with ethyl chloroformate, when derivatives of tetrahydro*iso*quinoline, but not of tetrahydroquinoline or tetrahydropyridine or piperidine, suffer ring fission [8]) when sinomenine [I] was converted into a compound $C_{25}H_{32}O_8NCl$, in which the nitrogen-containing ring has been ruptured, —COOEt becoming attached to the nitrogen and —Cl to a carbon atom [7].

Sinomenine, like thebaine, is readily degraded to derivatives of phenanthrene on heating with acid anhydrides. The reaction with benzoic anhydride affords dibenzoylsinomenol [II, R = $\phi \cdot CO$] [7, 9]. The parent sinomenol [II, R = H] may be prepared by heating sinomenine with 66 per cent. potassium hydroxide, ethylmethylamine also being produced [9]; it can be methylated to dimethylsinomenol [II, R = Me], which is also accessible, indirectly, from sinomenine methyl ether (methylsinomenine) [10]. Initially two series of sinomenol derivatives were thought to exist [9], but the higher-melting of these were subsequently shown by molecular weight determination to be dimolecular, and to be derived from 1:1′-disinomenol [11]. The simple sinomenol

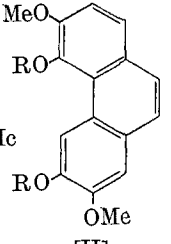
derivatives are obtained in yields of over 50 per cent. in the degradations, while the yield of dimolecular compounds is always under 15 per cent. [11].

The distillation of sinomenol with zinc-dust affords phenanthrene, and the former was soon recognized as a dimethoxydihydroxy-derivative of the latter [9]. Diacetyl- and dibenzoylsinomenol give the corresponding quinones, [III, R = Ac] and [III, R = $\phi \cdot$CO] respectively, on oxidation with chromic acid, indicating that the 9:10-positions in sinomenol are substituent-free. Hydrolysis of these quinones yields sinomenolquinone [III, R = H], methylation and ethylation of which affords dimethyl- [III, R = Me] and diethylsinomenolquinone [III, R = Et] respectively [9, 12].

Three of the four methoxyl groups in dimethylsinomenol were believed to be located in the 3:4:6-positions of phenanthrene, owing to the degradation of sinomenine to derivatives of the optical antipode of dihydrothebainone (see below), and dimethylsinomenol was finally identified as 3:4:6:7-tetramethoxyphenanthrene by the following synthesis [12–14].



[I]



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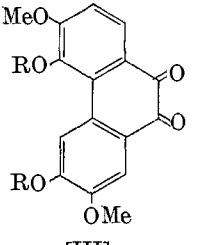

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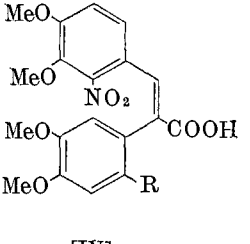

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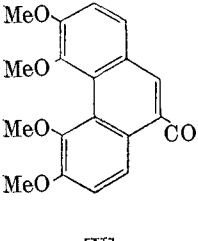

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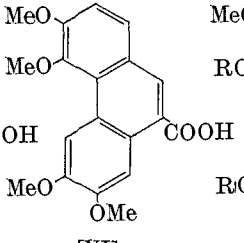

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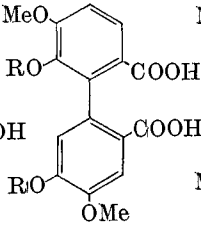
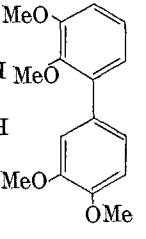


[VII]



[VIII]

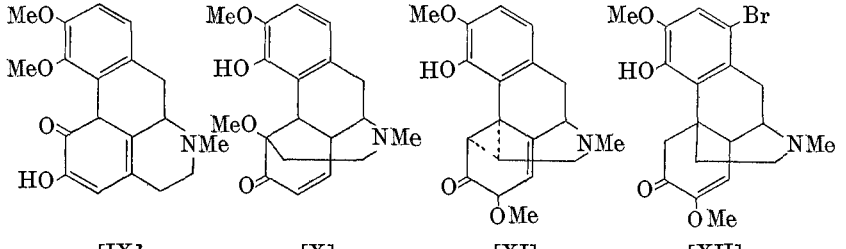
2-Nitroveratric aldehyde and 3:4-dimethoxyphenylacetic acid were condensed to give the acid [IV, R = H]. Reduction and Pschorr phenanthrene ring-closure of this gave two tetramethoxyphenanthrene carboxylic acids; one of these, also accessible from the bromo-acid [IV, R = Br], must be the 3:4:5:6-isomer [V] and the other the 3:4:6:7-isomer [VI]. The latter on decarboxylation afforded dimethylsinomenol [II, R = Me].

Dibenzoylsinomenolquinone [III, R = $\phi \cdot CO$] can be oxidized by 30 per cent. hydrogen peroxide in hot glacial acetic acid to 4:5′-dimethoxy-5:6′-di(benzoyloxy)diphenic acid [VII, R = $\phi \cdot CO$], hydrolysis and methylation of which yields 4:5:5′:6′-tetramethoxydiphenic acid [VII, R = Me], and decarboxylation of the latter can be effected by boiling with copper powder in quinoline, giving 2:3:3′:4′-tetramethoxydiphenyl [VIII] [15]. 4:5:5′:6′-Tetramethoxydiphenic acid, like 5:6:5′-trimethoxydiphenic acid [16], could not be resolved into optical isomers [15].

Following the establishment of positions of the groups in dimethylsinomenol the structures [IX] [17] and [X] [18] having an oxygen function at position 5 became untenable, and the structure [XI] was proposed [19–20]. This was subsequently modified to the generally accepted structure [I] by Goto and Sudzuki [12], when it was discovered that sinomenine contains a hydrolysable enol ether group.

Bromination

The bromination of sinomenine gives 1-bromosinomenine [5, 9, 21] [XII], the structure of which is revealed by the reduction of the compound to 1-bromodihydrosinomenine, dihydrosinomenine, and sinomenine, and by the fact that the diazo-reaction with 1-bromosinomenine is much less intense than with sinomenine [21]. A second substance is also produced by the bromination of sinomenine, but this is non-phenolic and is discussed later under 1-bromosinomeneine.



[IX] [X] [XI] [XII]

Reduction

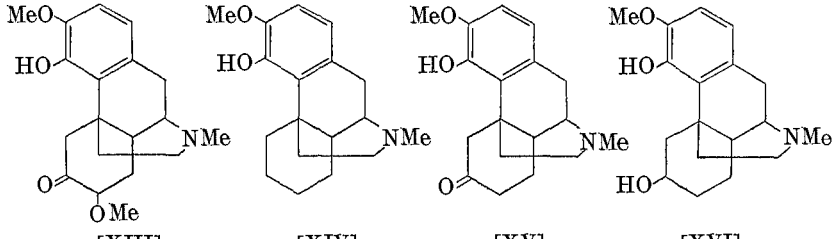
The reduction of sinomenine yields a variety of products according to the conditions.

(*a*) Catalytic hydrogenation yields dihydrosinomenine [XIII] [5, 7, 9, 22]. Dihydrosinomenine, like sinomenine, reduces potassium permanganate in the cold [5].

(*b*) Zinc-dust or amalgamated zinc and cold hydrochloric acid also reduces sinomenine to dihydrosinomenine [23].

(*c*) The Clemmensen reduction of sinomenine with amalgamated zinc

and hot concentrated hydrochloric acid affords desmethoxydesoxydihydrosinomenine [23] (also called desoxytetrahydrosinomenine by Ochiai [14, 18, 24], but the former name will be used here as it is more indicative of the structure of the base), which is the optical antipode of tetrahydrodesoxycodeine [XIV], obtained by the Clemmensen reduction of dihydrothebainone [XV]. This reduction also results in the production of desmethoxydihydrosinomeninol [24], which is the optical antipode of the dihydrothebainol [XVI] obtained by the sodium amalgam reduction of dihydrothebainone [XV] [18, 24–26].



[XIII] [XIV] [XV] [XVI]

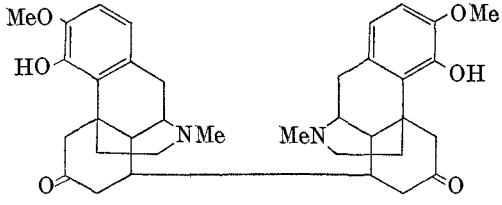
(*d*) Electrolytic reduction of sinomenine gives desmethoxydesoxydihydrosinomenine [XIV] [24].

(*e*) Sinomenine is converted by reduction with sodium amalgam in alkaline solution to a dimolecular substance, bis-8:8′-desmethoxydihydrosinomenine [23–24]. This contains two methoxyl groups and two carbonyl groups and is assigned the structure [XVII], as it is most probable that the link between the two units is in the β-position relative to the carbonyl group [23]. Thebainone-A [XVIII] is reduced under the same conditions to bis-8:8′-dihydrothebainone, which is the antipode of [XVII] [27]. The 7:8 double bond must be present for this type of reduction to occur, as dihydrosinomenine [XIII] can be reduced by sodium amalgam in alkaline solution only to desmethoxydihydrosinomenine [XIV] with no trace of [XVII] [23].

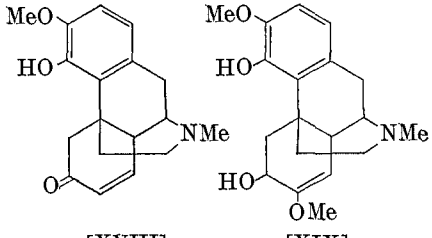
The reduction of sinomenine in alkaline solution with sodium amalgam affords, in addition to [XVII], desmethoxydihydro*iso*sinomeninol, the properties of which are ill defined and of the structure of which nothing is known beyond the fact that it is dimolecular [18, 23, 14], and two isomeric desmethoxydihydrosinomeninols, one of which is also obtained in the Clemmensen reduction of sinomenine [24]. These desmethoxydihydrosinomeninols correspond to the two dihydrothebainols [XVI] [14, 25–26], of which they are the antipodes [24].

(*f*) The 7-methoxyl group of sinomenine is not lost during reduction of the alkaloid with sodium amalgam in acetic acid, the product of this reaction being sinomeninol [XIX]. The easy loss of the methoxyl group in other reductions is attributable to the loosening effect of the vicinal carbonyl group, and when this is first reduced to —CH·OH—, by

sodium amalgam in acetic acid, elimination of the methoxyl does not occur [22]. Catalytic reduction of sinomeninol yields dihydrosinomeninol [22].



[XVII]



[XVIII] [XIX]

The reduction of sinomenine with glacial acetic acid and sodium amalgam gives a dimolecular phenol $(C_{18}H_{24}O_3N)_2 \cdot H_2O$ about which nothing further is known [24].

The reduction of dihydrosinomenine [XIII] also follows a complicated course, the nature of the products varying markedly with the mode of reduction as follows.

1. Clemmensen reduction yields desmethoxydesoxydihydrosinomenine [XIV] [18].

2. Sodium amalgam reduction gives the following according to the conditions:

(*a*) desmethoxydihydrosinomenine, which is the optical antipode of dihydrothebainone [XV] [23–24];

(*b*) desmethoxydihydrosinomeninol, m.p. 138° C., the optical antipode of the dihydrothebainol [XVI] that results from the sodium amalgam reduction of dihydrothebainone [XV] [14, 25, 24]. This compound is also obtained by the sodium amalgam reduction of desmethoxydihydrosinomenine [24];

(*c*) desmethoxydihydrosinomeninol, m.p. 158° C., presumably the optical antipode of the dihydrothebainol [XVI], m.p. 165° C., that results from the catalytic reduction of dihydrothebainone [28], [20].

3. Goto and Mitsui [22] showed that mixed crystals of desmethoxydihydrosinomenine and desmethoxydihydrosinomeninol separate from

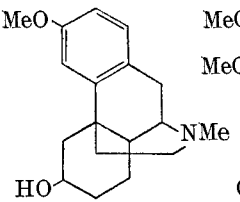
the sodium amalgam reduction of dihydrosinomenine, and that further reduction of these under the same conditions gives pure desmethoxydihydrosinomeninol, m.p. 138° C. The mixed crystals may be separated into their constituent compounds through the hydrobromides [29].

4. The mother liquors from the isolation of the mixed crystals give about 5 per cent. of the dihydrosinomeninol that is obtained by the catalytic reduction of sinomeninol [XIX] [22].

5. The reduction of dihydrosinomenine with 5 per cent. sodium amalgam in 6 per cent. acetic acid give 50 per cent. of dihydrosinomeninol [22]. This base is the only product of the reduction of dihydrosinomenine in which the methoxyl group at C-7 is retained.

Desmethoxydesoxydihydrosinomenine. The identification of this base as the optical antipode of tetrahydrodesoxycodeine [XIV] was of considerable importance in the elucidation of the structure of sinomenine. Goto and Mitsui [30] showed by direct comparison of the bases and their degradation products that desmethoxydesoxydihydrosinomenine and the desoxytetrahydrosinomenine of Ochiai [14, 18, 24, 31] are in fact identical. The latter was originally believed to be the antipode of 'dihydrothebacodine', prepared by Speyer and Siebert [26] by the Clemmensen reduction of dihydrothebainone and allotted by them the structure [XX], and the base prepared in this way was found to give a racemate with the sinomenine derivative [18].

However, desmethoxydesoxydihydrosinomenine on treatment with methyl sulphate and potassium iodide in alkali yields a methiodide identical with that given by the product of Clemmensen reduction of methylsinomenine [XXI], and this methiodide must therefore have the structure [XXII], and furthermore desmethoxydesoxydihydrosinomenine and the 'dihydrothebacodine' prepared according to the directions of Speyer and Siebert must have a hydroxyl group at C-4 and be in fact enantiomorphic forms of tetrahydrodesoxycodeine [XIV] [31].



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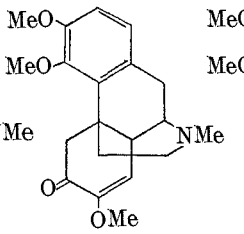
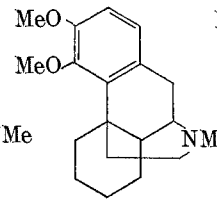
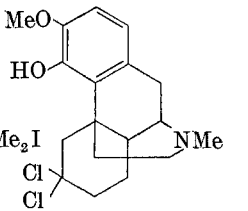


[XXI]



[XXII]



[XXIII]

This conclusion was also reached by Goto and Mitsui [30], who converted desmethoxydihydrosinomenine, established as the optical antipode of dihydrothebainone [XV], to a ketodichloride [XXIII] by treatment with phosphorus pentachloride, and this on catalytic reduction afforded desmethoxydesoxydihydrosinomenine [XIV]. In this

sequence of reactions the hydroxyl group at C-4 must be retained and the carbonyl group converted to methylene, and the product must be the optical antipode of tetrahydrodesoxycodeine.

Goto and Mitsui then made an examination of the electrolytic reduction of numerous sinomenine derivatives, but in no case was the removal of the hydroxyl group at C-4 observed. The compounds reduced in this way were sinomenine, dihydrosinomenine, desmethoxydihydrosinomenine, desmethoxydihydrosinomeninol, sinomeninol, dihydrosinomeninol, sinomenine hydrate, and α- and β-desmethoxysinomenine hydrate [30].

Further attempts to prepare Speyer and Siebert's 'dihydrothebacodine' have all resulted in tetrahydrodesoxycodeine [32] (see Chap. XV). Kondo and Ochiai [24, 31] suggested the name dihydrothebainan for [XIV], but this has not been generally adopted.

The reduction of 1-bromosinomenine proceeds parallel to the reduction of sinomenine and gives:

(*a*) 1-bromodihydrosinomenine, dihydrosinomenine, and sinomenine on catalytic hydrogenation [21];

(*b*) 1-bromodihydrosinomenine on reduction with zinc and cold hydrochloric acid [33];

(*c*) 1-bromodesmethoxydesoxydihydrosinomenine, the optical antipode of 1-bromotetrahydrodesoxycodeine, identical with the product of bromination of desmethoxydesoxydihydrosinomenine, on Clemmensen reduction [33–34];

(*d*) 1:1′-dibromo-bis-8:8′-desmethoxydihydrosinomenine, by sodium amalgam reduction in alkaline solution. This compound may also be prepared by the bromination of bis-8:8'-desmethoxydihydrosinomenine [33–34].

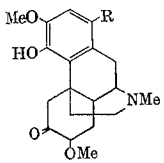
(*e*) The reduction of 1-bromodihydrosinomenine with sodium amalgam affords a 35 per cent. yield of 1-bromodesmethoxydihydrosinomenine, the optical antipode of 1-bromodihydrothebainone, also obtained by the bromination of desmethoxydihydrosinomenine [33–35].

Condensation with Diazonium Salts and with Formaldehyde

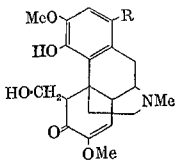
Sinomenine and dihydrosinomenine on condensation with benzenediazonium chloride in alkaline solution give 1-benzeneazosinomenine and 1-benzeneazodihydrosinomenine [XXIV, $R = \phi \cdot N = N$] respectively, and these can be converted by reduction into 1-aminodihydrosinomenine [XXIV, $R = NH_2$] [36].

The presence of a reactive methylene group in the sinomenine molecule is demonstrated by the condensation of the alkaloid with

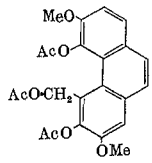
formaldehyde. This reaction results in the production of 5-(hydroxymethyl)-sinomenine [XXV, R = H] and 1:5-di-(hydroxymethyl)-sinomenine [XXV, R = CH_2OH]; of these the former gives an intense diazo-reaction but the latter only gives a weak diazo-reaction and is therefore believed to have the second substituent in position 1. Reduction of 5-(hydroxymethyl)-sinomenine affords 5-(hydroxymethyl)-dihydrosinomenine, which cannot be prepared from dihydrosinomenine; acetolysis of the same compound yields ethylmethylamine and 4:6-diacetyl-5-(acetoxymethyl)-sinomenol [XXVI]. 1:5-Di-(hydroxymethyl)-sinomenine, however, yields no crystalline products on reduction or acetolysis [37].



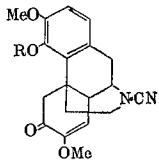
[XXIV]



[XXV]



[XXVI]



[XXVII]

Reaction with Cyanogen Bromide

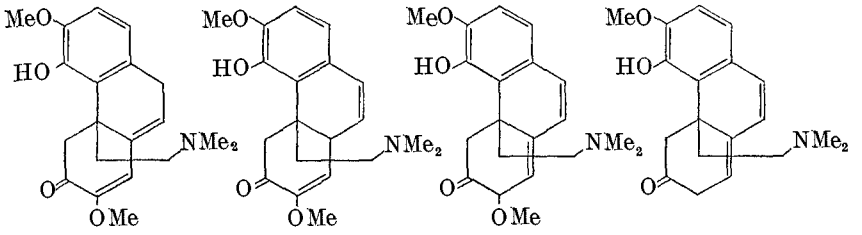
No scission of the nitrogen-containing ring occurs when benzoyl- and methylsinomenine are treated with cyanogen bromide; the ·NMe group is replaced by ·NCN, the products being cyanonorbenzoyl- and cyanonormethyl-sinomenine, [XXVII, R = ϕ·CO] and [XXVII, R = Me] respectively [24].

Exhaustive Methylation

A. **The alkaline degradation of sinomenine methiodide** has been found to yield three different products, namely, sinomenine *achro*methine, *roseo*methine, and *violeo*methine.

Sinomenine *achro*methine [XXVIII] (initially called N-methylanhydrosinomenine [17]) is obtained when sinomenine methiodide is heated for one minute with two equivalents of 2 per cent. aqueous sodium hydroxide. It cannot be recrystallized, even from alcohol, and is best purified through the sodium salt. The name is assigned as a result of the faint yellow halochromism of a solution of the base in concentrated sulphuric acid. Like sinomenine it gives sinomenol and dibenzoylsinomenol on heating with 66 per cent. potassium hydroxide and benzoic anhydride respectively [38].

Sinomenine *roseo*methine [XXIX] (initially called β-sinomenine methine [17]), which is obtained by the slow isomerization of the *achro*methine on standing for several years, also results from the degradation of sinomenine methiodide with five equivalents of 5 per cent. sodium hydroxide. The base is yellow in colour and gives an intense maroon halochromic solution in concentrated sulphuric acid [17, 38].



[XXVIII] [XXIX] [XXX] [XXXI]

Sinomenine *violeo*methine [XXX] (initially called sinomenine α-methine [17]) is obtained in 20 per cent. yield when sinomenine *achro*methine is heated with 10 per cent. sodium hydroxide [38] and also, in low yield, when sinomenine methiodide is degraded [17]. Its methiodide, formed in almost quantitative yield by the action of cold 10 per cent. sodium hydroxide on sinomenine *achro*methine methiodide, is degraded by hot alkali to sinomenol. Sinomenine *violeo*methine gives an intensely blue halochromic solution in concentrated acid solution [38]. The thebainone analogue, thebainone-B methine [XXXI], has also been prepared [39].

B. **The combined methylation and degradation of sinomenine** has been found to give the following:

1. With methyl sulphate only, sinomenine methomethylsulphate is formed [40].

2. With methyl sulphate and cold alkali the product is methylsinomenine methomethylsulphate [40].

3. With methyl sulphate and hot alkali the product is methylsinomenine *violeo*methine methomethylsulphate, which can also be prepared by the low-temperature methylation of a solution of sinomenine *achro*methine in 10 per cent. sodium hydroxide that has been allowed to stand for fifteen hours [40].

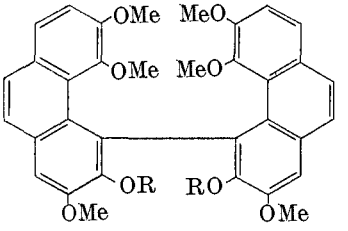
4. Methylation with methyl sulphate and cold alkali, followed by neutralization and boiling with saturated sodium carbonate solution, affords methylsinomenine *roseo*methine methomethylsulphate [40].

5. Methylsinomenine *violeo*methine methomethylsulphate on further degradation with 2 per cent. alkali gives 4:4′-dimethyl-bis-5:5′-sinomenol [XXXII, R = H] (initially believed to be trimethoxyketovinyltetrahydrophenanthrene [17]) [40].

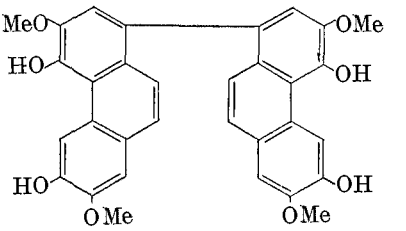
6. If the alkaline degradation and methylation of sinomenine is allowed to proceed for several weeks tetramethyl-bis-5:5′-sinomenol [XXXII, R = Me] (first thought to be α-tetramethoxyvinyldihydrophenanthrene [17]) is obtained) and from the mother liquors, after oxidation, dimethylsinomenolquinone can be isolated [40].

7. Those two dimolecular substances, which are different from the derivatives of 1:1′-disinomenol [XXXIII], are obtained in varying

amounts together with dimethylsinomenol (which is identical with the β-tetramethoxyvinyldihydrophenanthrene of Goto [17]) when sinomenine is boiled with alkali and excess of methyl sulphate [40].



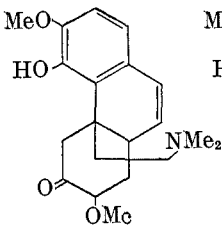
[XXXII]



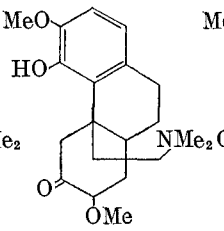
[XXXIII]

C. **Sinomenine can be degraded** with ethyl sulphate and alkali to 5:5′-diphenanthrene derivatives, but such derivatives are not obtained in this way from 1-bromosinomenine [41]. 1-Bromosinomenine methiodide can readily be degraded to 1-bromosinomenine methine [35] (presumably the stable *violeo*-isomer), but methylation and degradation with methyl sulphate and alkali gives 1-bromo-4-methylsinomenol (1-bromo-3:4:7-trimethoxy-6-hydroxyphenanthrene) [35, 42]. Similarly degradation of 1-bromosinomenine with ethyl sulphate and alkali leads to 1-bromo-4-ethylsinomenol [43]. 1-Bromomethylsinomenine can be prepared by the methylation of 1-bromosinomenine with diazomethane and can be degraded successively to 1-bromomethylsinomenine methine and 1-bromo-4-methylsinomenol [44]. Catalytic reduction of derivatives of 1-bromosinomenol results in removal of the halogen [43].

D. **Hofmann degradation of dihydrosinomenine** [XIII] **methiodide** affords dihydrosinomenine methine [XXXIV], which can be reduced to dihydrosinomenine dihydromethine [XXXV] and degraded further to 7-methoxydehydro-(—)-thebenone [XXXVI]. The latter can be reduced to 7-methoxy-(—)-thebenone [XXXVII]. The sign of optical rotation is inverted at each stage of the degradation sinomenine → dihydrosinomenine → dihydrosinomenine methine → dihydrosinomenine dihydromethine → 7-methoxy-(—)-thebenone, a phenomenon also observed in the degradations ending with (—)-thebenone and (—)-thebenane [45].



[XXXIV]



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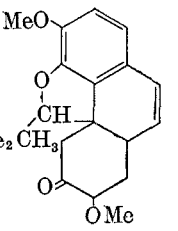
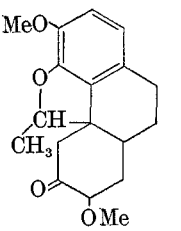
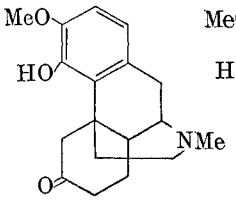


[XXXVI]

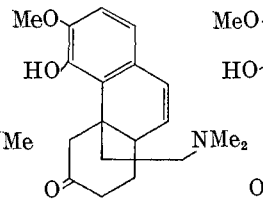


[XXXVII]

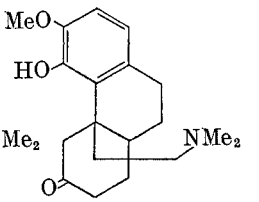
E. **Exhaustive methylation of desmethoxydihydrosinomenine** [XV], which is the antipode of dihydrothebainone, gives desmethoxydihydrosinomenine methine [XXXVIII], which can be reduced to the dihydromethine [XXXIX]. These two bases on further degradation yield 9:10-dehydro-(—)-thebenone [XL] and (—)-thebenone [XLI], respectively [46]. The bromination of [XXXIX] gives the 1-bromo-derivative, which can be degraded to 1-bromo-(—)-thebenone. 1-Bromodesmethoxydihydrosinomenine can be degraded to 1-bromodesmethoxydihydrosinomenine methine and 1-bromo-9:10-dehydro-(—)-thebenone. An isomer of the latter, 9 ?-bromo-9:10-dehydro-(—)-thebenone, is obtained by the bromination of 9:10-dehydro-(—)-thebenone. All these derivatives give racemates on mixing with the corresponding compounds from the dihydrothebainone series [47]. Oxidation of (—)-thebenone with chromic acid gives (—)-thebenone ketone [XLII] [48].



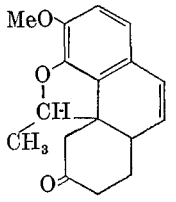
[XV]



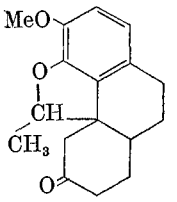
[XXXVIII]



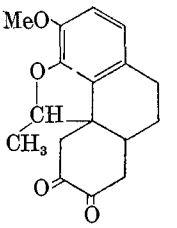
[XXXIX]



[XL]



[XLI]

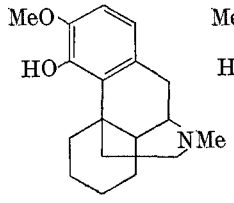


[XLII]

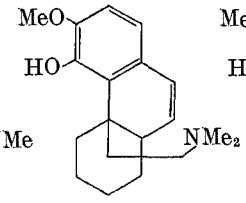
Oxidation of desmethoxydihydrosinomenine with silver nitrate results in linking of two molecules in the 1:1'-position to give bis-1:1'-desmethoxydihydrosinomenine, which can be degraded to bis-1:1'-desmethoxydihydrosinomenine methine, bis-1:1'-desmethoxydihydrosinomenine dihydromethine, bis-1:1'-9:10-dehydro-(—)-thebenone, and bis-1:1'-(—)-thebenone, all of which can be racemized with the corresponding compound prepared from the thebaine series [49].

F. **Exhaustive methylation of desmethoxydesoxydihydrosinomenine** [XIV], the optical antipode of tetrahydrodesoxycodeine, leads to the methine [XLIII], dihydromethine [XLIV], 9:10-dehydro-(—)-thebenane [XLV], and (—)-thebenane [XLVI] [18, 30, 48], which form racemates with the compounds prepared from tetrahydrodesoxycodeine [50]. Desmethoxydesoxydihydrosinomenine dihydromethine

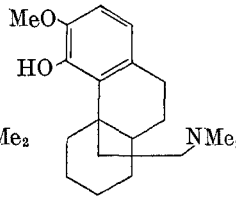
[XLIV] on bromination with three equivalents of bromine gives a perbromide that decomposes to the 1:9?-dibromoderivative [XLVII] [51–52]. Both desmethoxydesoxydihydrosinomenine and tetrahydrodesoxycodeine can be oxidized to bis-1:1′-derivatives by silver nitrate [50].



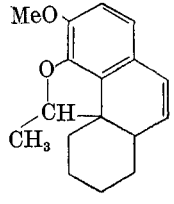
[XIV]



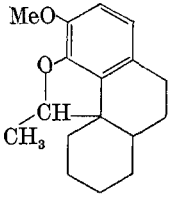
[XLIII]



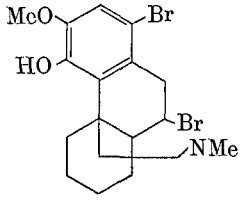
[XLIV]



[XLV]



[XLVI]



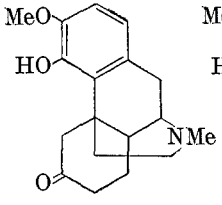
[XLVII]

1-BROMOSINOMENEINE

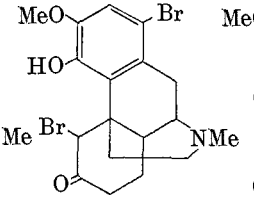
As already stated, the bromination of sinomenine gives two substances, 1-bromosinomenine and a compound first called 1-bromo*iso*-sinomenine [5, 9, 21], which was found to be non-phenolic [9] and to have undergone some change in ring C [21]. This was subsequently shown to be an oxidized substance, and was renamed 1-bromosinomeneine [53]. It is always obtained in 2–20 per cent. yield in the bromination of sinomenine with one equivalent of bromine, the highest yield being obtained by a rapid addition of the bromine, when a perbromide is precipitated; the oxidation to 1-bromosinomeneine occurs during the decomposition of the perbromide. The yield of 1-bromosinomeneine is increased to 40 per cent. by the use of two equivalents of bromine [53].

The nature of this substance was first elucidated by Schöpf and Pfeiffer [54], who, following the conversion of dihydrothebainone [XLVIII], through 1:5-dibromodihydrothebainone [XLIX] to 1-bromodihydrocodeinone [L] by bromination and treatment with alkali, and the similar conversion of 14-hydroxydihydrothebainone [LI] to 1-bromo-14-hydroxydihydrocodeinone [LII], showed that 1-bromosinomeneine results in 80 per cent. yield from treating sinomenine with bromine and then with alkali [54]. The intermediate 1:5-dibromosinomenine [LIII] has been isolated and converted to 1-bromosinomeneine by warming

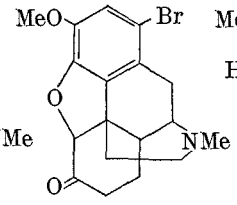
in alcohol [55]. In view of the known relationship of sinomenine to thebainone-A it is clear that 1-bromosinomeneine is in fact the optical antipode of 1-bromo-7-methoxycodeinone and has the structure [LIV] [54]. Treatment of dihydrosinomenine with three equivalents of bromine followed by digestion of the resulting uncrystallizable oil with alkali also gives [LIV] [35].



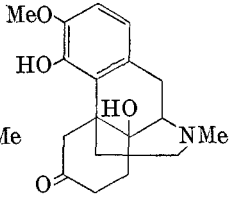
[XLVIII]



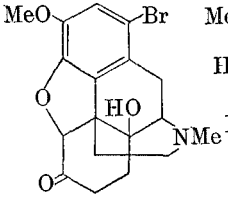
[XLIX]



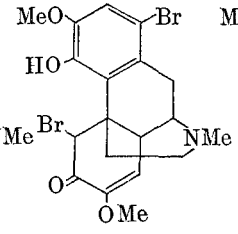
[L]



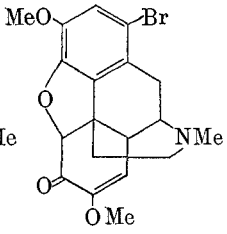
[LI]



[LII]



[LIII]

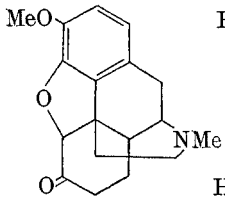


[LIV]

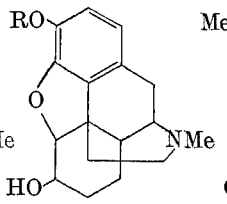
1-Bromodesmethoxydihydrosinomeneine can be prepared by brominating desmethoxydihydrosinomenine and treating the product with alkali; it is the optical antipode of 1-bromodihydrocodeinone [L] with which it forms a racemate [35]. On catalytic reduction it yields (+)-dihydrocodeinone [LV] [35], which can be further reduced by hydrogenation in pyridine over platinum oxide to (+)-dihydrocodeine [LVI, R = Me] and the latter can be demethylated to (+)-dihydromorphine [LVI, R = H] [56, 57]. With phosphorus pentachloride (+)-dihydrocodeine gives (+)-6-chlorodihydrocodide [LVII] which affords (+)-desoxycodeine-C [LVIII] on heating with sodium methoxide in an autoclave [57]. All these compounds give racemates when mixed with their antipodes derived from the morphine series. (+)-7-hydroxydihydrocodeine [LIX] is formed by the mild oxidation of (+)-desoxycodeine-C with 1 per cent. potassium permanganate [58].

1-Bromodiacetylsinomeneine, given the structure [LX] by Goto and Shishido [59], together with traces of 1-bromodiacetylsinomenol, results from the action of acetic anhydride and sodium acetate on 1-bromosinomeneine. [LX] gives no identifiable product on acid or alkaline hydrolysis, catalytic reduction or acetylation at 180° C., but gives an amine C_9H_7N or $C_{14}H_{12}N_2$ on alkali fusion. 1-Bromodiacetylsinomenol, which

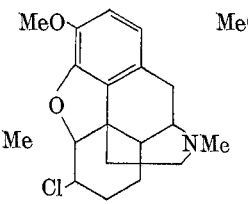
gives diacetylsinomenol on reduction, may also be obtained by the acetolysis of 1-bromosinomenine methiodide, 1-bromosinomenine methine, and 1-bromosinomeneine methine.



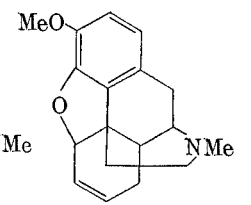
[LV]



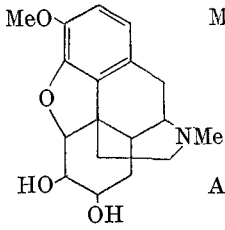
[LVI]



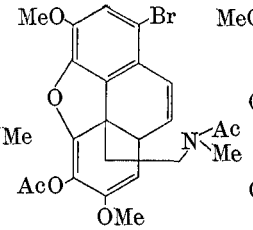
[LVII]



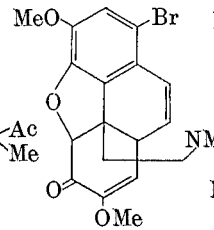
[LVIII]



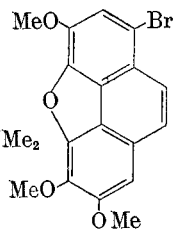
[LIX]



[LX]



[LXI]



[LXII]

Hofmann Degradation

The Hofmann degradation of 1-bromosinomeneine methiodide yields 1-bromosinomeneine methine [35] which has not been related to the sinomenine methines and is here arbitrarily assigned the structure [LXI]. This degradation is in marked contrast to the degradation of codeinone and thebaine methiodides, which leads directly to fully aromatic phenanthrene derivatives. 1-Bromosinomeneine methiodide on boiling with methyl sulphate and alkali suffers complete degradation to 1-bromo-3-methyl-6:7-dimethoxymorphenol [LXII] [35].

An entirely different methine base is obtained when 1-bromosinomeneine methiodide is mixed with an equimolecular quantity of 10 per cent. alkali at 20° C. and the mixture extracted with chloroform. This base is 1-bromodehydrometasinomenine methine and it is allotted the structure [LXIII] for the following reasons [60].

(*a*) It is soluble in alkali and gives a green colour with ferric chloride.

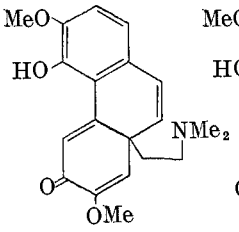
(*b*) One new methyl group, only, appears on methylation.

(*c*) It dissolves in concentrated sulphuric acid to give a deep blue solution, and it gives 1-bromodiacetylsinomenol quantitatively on acetolysis and is therefore a methine base.

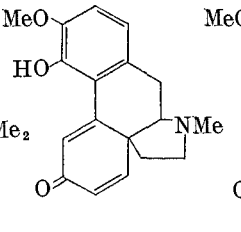
(*d*) The side-chain must be attached to C-13 or C-14, otherwise it would not be eliminated during acetolysis.

(*e*) The base is yellow and gives a deep-red sodium salt.

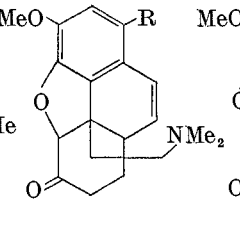
The production of this compound is of great interest as it is a derivative of [LXIV], the intermediate postulated in the complex changes that thebaine undergoes in acid solution (see Chaps. XXIII and XXV).



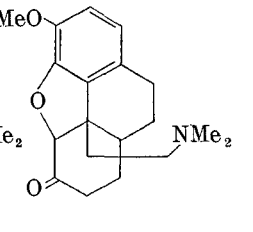
[LXIII]



[LXIV]



[LXV]



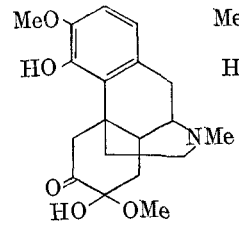
[LXVI]

1-Bromodesmethoxydihydrosinomeneine and desmethoxydihydrosinomeneine may both be converted into methine bases, [LXV, R = Br] and [LXV, R = H], which can be reduced to desmethoxydihydrosinomeneine dihydromethine [LXVI]. These compounds are the antipodes of those derived from the dihydrocodeinone series [29].

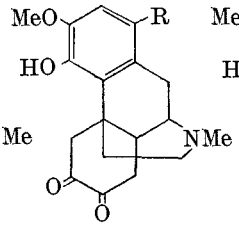
SINOMENININONE AND ITS DERIVATIVES

Sinomenine is an $\alpha:\beta$-unsaturated-α-methoxyketone and thus contains a hydrolysable enol ether system and can be hydrolysed to an α-diketone. Indeed sinomenine itself possesses some of the properties of an α-diketone; e.g. it can reduce cold potassium permanganate solution, Fehling's solution, and ammoniacal silver nitrate [6].

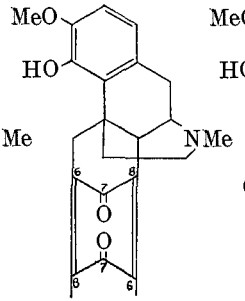
Hydrolysis of the enol ether may be achieved by 2N hydrochloric acid at 100° C., and if the solution is neutralized with sodium carbonate sinomenine hydrate [LXVII] is precipitated. This apparently exists in the hemiacetal form, but the 7-methoxyl group is readily lost and for all practical purposes sinomenine hydrate behaves as the α-diketone sinomeninone [LXVIII, R = H], and gives a dioxime and disemicarbazone [61].



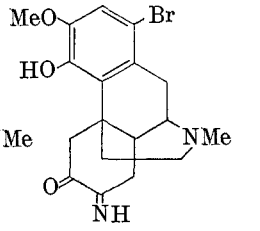
[LXVII]



[LXVIII]



[LXIX]

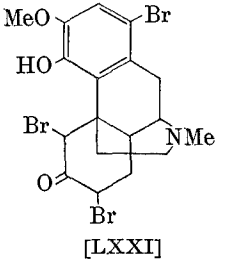


[LXX]

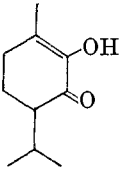
When the base is liberated from the solution after hydrolysis with ammonia instead of sodium carbonate a dimolecular base bis-desmethylsinomenylidine is obtained instead of sinomenine hydrate [23], and this base is also obtained by the action of ammonia on the latter [61]. It is believed to arise from the self-condensation of the diketone, the carbonyl group at C-6 in each molecule condensing with the active methylene group at C-8 in the other, and the product is in fact a quinone. The structure of the product is shown in essence in [LXIX]. The condensation of sinomeninone to bis-desmethylsinomenylidene is analogous to the self-condensation of diacetyl to *p*-xylene quinone [62].

1-Bromosinomenine may be hydrolysed to 1-bromosinomeninone [LXVIII, R = Br], which exists in the α-diketone form [63]. The hydrogen bromide produced during the bromination of sinomenine will cause hydrolysis of the product to 1-bromosinomeninone if the reaction mixture is allowed to stand for several weeks [53]. 1-Bromosinomeninone, in marked contrast to sinomenine hydrate, gives a monomolecular imide [LXX] on treatment with concentrated ammonia; the imide is readily hydrolysed to the original diketone. The oxime hydrochloride of [LXX] is believed to give 1-bromosinomeninone dioxime when precipitated with sodium carbonate in the presence of hydroxylamine [63].

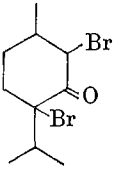
The optical antipode of 1-bromosinomeninone, viz. (—)-1-bromosinomeninone, is produced in small amounts during the conversion of dihydrothebainone to 1-bromodihydrocodeinone [L] by bromination and subsequent treatment with alkali. That it arises from the 7-bromo-derivative is confirmed by its production when dihydrothebainone is brominated with three equivalents of bromine and the resulting 1:5:7-tribromodihydrothebainone [LXXI] treated with alkali, and when 1-bromodihydrocodeinone [L] is treated with one equivalent of bromine in the presence of potassium carbonate and methanol [64]. The formation of (—)-1-bromosinomeninone [LXVIII, R = Br] from 1:5:7-tribromodihydrothebainone [LXXI] is analogous to the production of buchucamphor [LXXII] from dibromomenthone [LXXIII] and from dibromocarvomenthone [LXXIV] on treatment with alkali [65].



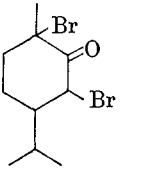
[LXXI]



[LXXII]



[LXXIII]

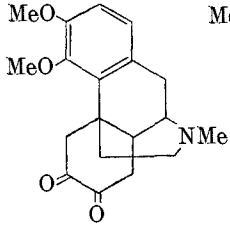


[LXXIV]

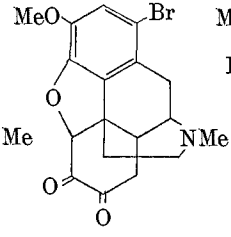
Methylsinomeninone [LXXV], which exists in the α-diketone form, is

prepared by the hydrolysis of methylsinomenine; it gives only amorphous, intractable products when treated with concentrated ammonia solution [66]. The hydrolysis of 1-bromomethylsinomenine affords 1-bromomethylsinomeninone [44].

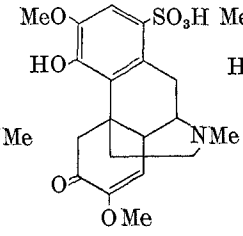
1-Bromosinomeneine [LIV] also contains an enol ether group, and it too can be hydrolysed to an α-diketone, 1-bromosinomeneine ketone [LXXVI] [53].



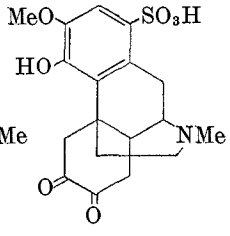
[LXXV]



[LXXVI]



[LXXVII]



[LXXVIII]

Hydrolysis of the enol ether group of sinomenine is apparently not effected by concentrated sulphuric acid below 10° C., as sinomenine under these conditions gives sinomenine-1-sulphonic acid [LXXVII]. Sinomenine hydrate on treating in this way loses the 7-methoxyl group, the product being sinomeninone-1-sulphonic acid [LXXVIII]. Sinomenine derivatives with position 1 (i.e. *para* to the phenolic group) substituted, e.g. 1-bromosinomenine and disinomenine (see below) cannot be sulphonated in this way [67–68].

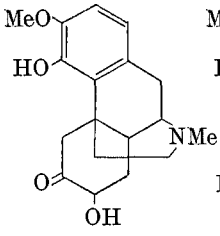
Bromination

The bromination of sinomenine hydrate with three equivalents of bromine and of 1-bromosinomeninone with two equivalents of bromine yields 1:5:8-tribromosinomeninone, which is converted into 1-bromosinomeninone by catalytic reduction, and to 1-bromodesmethoxydesoxydihydrosinomenine on reduction by Clemmensen's method [69].

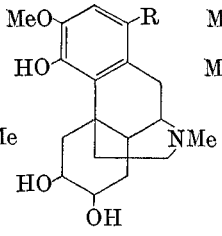
Reduction

Catalytic or sodium amalgam reduction of sinomenine hydrate results in the loss of the 7-methoxyl group and production of two diastereoisomeric substances, α- and β-dihydrosinomeninone [LXXIX] [70], initially called α- and β-desmethoxysinomenine hydrate [61]. These compounds also result from the partial demethylation of dihydrosinomenine [XIII], and so must have the structure [LXXIX] and be diastereoisomeric about C-7, and not the alternative 6-hydroxy-7-keto form. The α-isomer can be converted into the β by 25 per cent. hydrobromic acid, 5 per cent. alkali, or by heating over 200° C.; on warming with thionyl chloride it undergoes dehydration to desmethoxysinomenine,

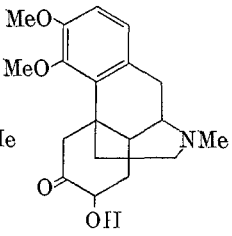
the antipode of thebainone-A [XVIII] [70]. The bromination of α-dihydrosinomeninone affords 1-bromodihydrosinomeninone, identical with one of the products of catalytic reduction of 1-bromosinomeninone [66]. The catalytic reduction of (—)-1-bromosinomeninone gives the antipodes of α- and β-dihydrosinomeninone [70]. The catalytic hydrogenation of 1-bromosinomeninone in pyridine over platinum oxide gives rise to 1-bromotetrahydrosinomeninone [LXXX, R = Br], (+)-tetrahydrosinomeninone, and (+)-7-hydroxydihydrothebainol, the last two named being diastereoisomers of structure [LXXX, R = H]; both give triacetyl-derivatives and so must contain three hydroxyl groups [58]. All these derivatives are racemized when mixed with their antipodes prepared in the thebaine series [58, 70].



[LXXIX]



[LXXX]



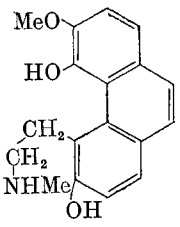
[LXXXI]

Catalytic hydrogenation of methylsinomeninone in slightly alkaline solution gives 80 per cent. dihydromethylsinomeninone [LXXXI] [66].

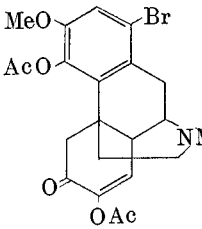
ACETOLYSIS

4:6-Diacetoxy-3-methoxyphenanthrene and triacetyl*iso*thebenine are obtained by the acetolysis of sinomenine hydrate and the 1-bromo-derivatives of these can be prepared in the same way from 1-bromosinomeninone. Catalytic reduction of both triacetyl*iso*thebenine and its 1-bromo-derivative affords triacetyl-9:10-dihydro*iso*thebenine [55], believed by Schöpf, Pfeiffer, and Hirsch [64] to be triacetyl*iso*thebenine when the same sequence of reactions was carried out on (—)-1-bromosinomeninone. *Iso*thebenine is probably 4:6-dihydroxy-3-methoxy-5-(β-methylaminoethyl)-phenanthrene [LXXXII], or the 4:7-dihydroxy-isomer [64]. On heating with sodium hydroxide and methyl alcohol at 80° C., 1-bromotriacetyl*iso*thebenine yields a compound $C_{20}H_{20}O_4NBr$ in 7 per cent. yield; this is probably 1-bromo-N-acetyl*iso*thebenine [55] (see also Chap. XXV).

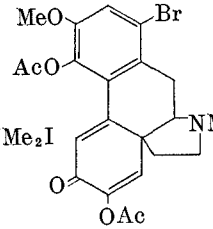
The acetolysis of 1-bromosinomeneine ketone [LXXVI] and of 1-bromosinomenine methiodide gives 1-bromo-3:4:6-triacetoxyphenanthrene [59] (cf. the production of 3:4:6-triacetoxyphenanthrene in the acetolysis of thebainone-A [XVIII] [71]). Catalytic reduction of this affords 3:4:6-triacetoxyphenanthrene [59].



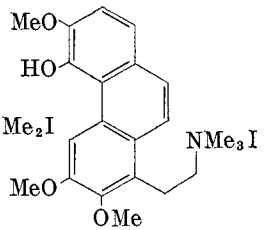
[LXXXII]



[LXXXIII]



[LXXXIV]



[LXXXV]

The acetolysis of 1-bromosinomeneine ketone [LXXVI] gives, in addition to the above, 'diacetyl-1-bromodehydrosinomenine', the methiodide of which was assigned the composition $C_{25}H_{25}O_6NBrI$, and this on heating with methyl sulphate and alkali suffers replacement of two acetyl groups by methyl and Hofmann degradation, to give 'dimethyl-1-bromodehydrosinomenine methine' methiodide, $C_{22}H_{29}O_4NBrI$. Acetolysis of 1:5-dibromosinomenine also yields 'diacetyl-1-bromodehydrosinomenine', so the 4:5-ether bridge must be opened during acetolysis [72].

It is difficult to fit structural formulae to these degradation products; [LXXXIII] has the composition $C_{23}H_{27}O_6NBrI$; [LXXXIV] has the composition $C_{23}H_{25}O_6NBrI$ and on hydrolysis, morphothebaine rearrangement, degradation and methylation could give [LXXXV], $C_{22}H_{28}O_4NBrI$.

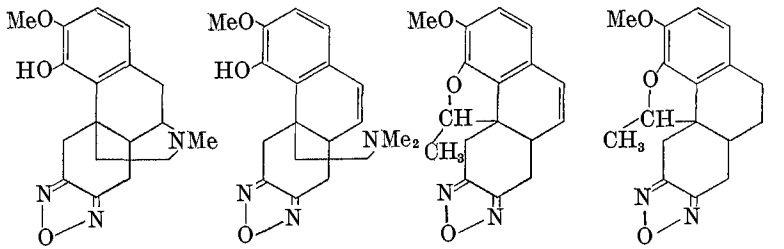
Hofmann Degradation

The exhaustive methylation of the free diketones has not been studied, but sinomenine hydrate on heating with ethyl sulphate and alkali gives 5:5′-diphenanthrene derivatives as does sinomenine under the same conditions [41].

Sinomeninone dioxime on boiling with potassium hydroxide is dehydrated to sinomeninone furazan [LXXXVI], and sinomeninone dioxime methiodide is degraded by hot alkali to sinomeninone furazan methine [LXXXVII] which on further degradation gives trimethylamine and 9:10-dehydro-(—)-thebenone ketone furazan [LXXXVIII]. The latter is too sparingly soluble to permit reduction, but (—)-thebenone ketone furazan [LXXXIX] is obtained by the degradation of sinomeninone furazan dihydromethine [48].

In an exactly analogous manner 1-bromosinomeninone dioxime on heating affords 1-bromosinomeninone furazan (also obtained by the bromination of [LXXXVI]) which can be degraded to 1-bromosinomeninone furazan methine. The latter results in poor yield from the bromination of sinomeninone furazan methine [LXXXVII], but the chief product of this reaction is, using two equivalents of bromine, 1:9 ?-dibromosinomeninone furazan methine, or, using three equivalents of bromine, 1:9:10-tribromosinomeninone furazan dihydromethine, which suffers

loss of hydrogen bromide to give 1:9?-dibromosinomeninone furazan methine when heated with acetone or sulphurous acid [51–52].

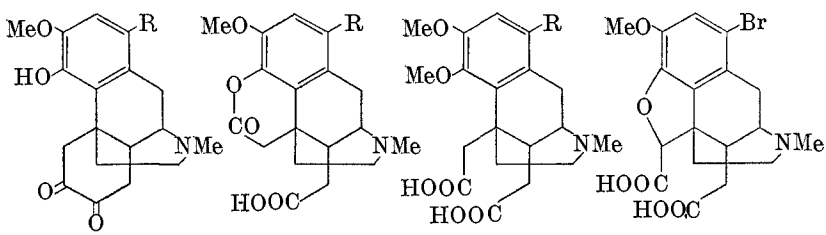


[LXXXVI] [LXXXVII] [LXXXVIII] [LXXXIX]

Further degradation of 1-bromosinomeninone furazan methine yields 1-bromo-9:10-dehydro-(—)-thebenone ketone furazan, which cannot be prepared by the bromination of [LXXXVIII] as this reaction gives the isomeric 9?-bromo-derivative. The Hofmann degradation of 1:9?-dibromosinomeninone furazan methine and the bromination of [LXXXVIII] and its 1- and 9?-bromo-derivatives all yield, finally, 1:9?-dibromo-9:10-dehydro-(—)-thebenone ketone furazan. 1-Bromo-(—)-thebenone ketone furazan may be prepared either by the bromination of [LXXXIX] or by the bromination of sinomeninone furazan dihydromethine, followed by the degradation of the resulting 1-bromo-derivative [51–52].

SINOMENINIC ACID AND ITS DERIVATIVES

Like other α-diketones and *ortho*-quinones, e.g. dibenzoylsinomenolquinone [15], sinomenine hydrate [LXVII behaving as LXVIII, R = H] on heating with 30 per cent. hydrogen peroxide in glacial acetic acid is oxidized to a dibasic acid, sinomeninic acid [XC, R = H]. This on bromination gives 1-bromosinomeninic acid [XC, R = Br], also obtainable by the oxidation of 1-bromosinomeninone [LXVIII, R = Br] [73]. (—)-1-bromosinomeninic acid can be prepared by the oxidation of (—)-1-bromosinomeninone; it can be reduced catalytically to (—)-sinomeninic acid [74]. These acids exist as lactones.



[LXVIII] [XC] [XCI] [XCII]

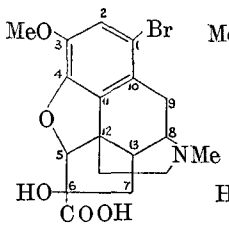
Methylsinomeninic acid [XCI, R = H] and 1-bromomethylsinomeninic acid [XCI, R = Br] are formed when methylsinomeninone [73] and 1-bromomethylsinomeninone [44] respectively are oxidized with hydrogen peroxide. Similarly the oxidation of 1-bromosinomeneine ketone [LXXVI] affords 1-bromosinomeneinic acid [XCII] [73]. The ultraviolet absorption spectra of [XC, R = H], [XC, R = Br], and [XCI, R = H] are very similar to that of sinomenine hydrate, which in turn is almost identical with that of sinomenine [73].

Methylsinomeninic acid [XCI, R = H] gives the acid chloride on treatment with thionyl chloride and this is converted into the imide by ammonia. On heating with acetic anhydride [XCI, R = H] gives not the anhydride but methyldihydrosinomenilone (see below) [75].

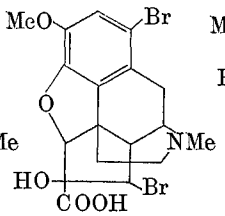
SINOMENILIC ACID AND ITS DERIVATIVES

1-Bromosinomeneine ketone [LXXVI] can be made to undergo the benzil → benzilic acid transformation in hot alkali, the product being 1-bromosinomenilic acid [XCIII]. This acid is also obtained when the amorphous product of bromination of 1-bromosinomeninone with one equivalent of bromine is treated with alkali, and from sinomenine hydrate and one equivalent of bromine [69].

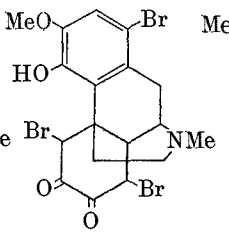
1:7-Dibromosinomenilic acid [XCIV] cannot be prepared by the bromination of [XCIII], but results from the action of aqueous methanolic alkali on 1:5:8-tribromosinomeninone [XCV] and from the action of aqueous alkali on the product of bromination of 1-bromosinomeneine ketone [LXXVI] with one equivalent of bromine. On reduction with sodium amalgam in alkaline solution it affords [XCIII].



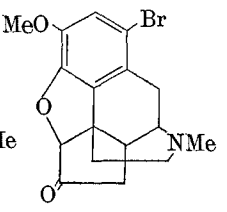
[XCIII]



[XCIV]



[XCV]



[XCVI]

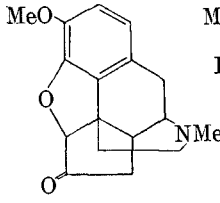
[XCIII] and [XCIV] may also be prepared by the bromination of α-dihydrosinomeninone. With one equivalent of bromine this reaction affords 1-bromodihydrosinomeninone and 1-bromosinomeninone; with two equivalents, 1-bromosinomeninone and 1-bromosinomenilic acid; with three equivalents, 1:7-dibromosinomenilic acid. β-dihydrosinomeninone behaves similarly but gives a mixture of 1-bromo- and 1:7-dibromosinomenilic acid with two equivalents of bromine [70].

When 1-bromosinomenilic acid [XCIII] is warmed above 35° C. with 20 per cent. oleum degradation to the ketone 1-bromosinomenilone [XCVI] occurs. The dibromo-acid [XCIV] loses water at 150° C. *in vacuo* over phosphorus pentoxide to give a lactide [69]. These derivatives have also been prepared in the thebaine series [74].

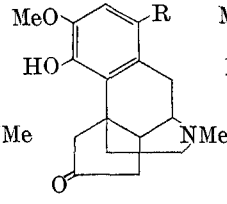
SINOMENILONE AND ITS DERIVATIVES

The catalytic reduction of 1-bromosinomenilone [XCVI] yields sinomenilone [XCVII], but sodium amalgam reduction gives 1-bromodihydrosinomenilone [XCVIII, R = Br], which affords dihydrosinomenilone [XCVIII, R = H] on hydrogenation.

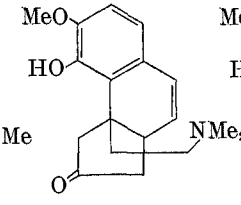
Alkaline degradation of dihydrosinomenilone methiodide leads to dihydrosinomenilone methine [XCIX], which on further degradation yields anhydrobis-sinomelone; the dihydromethine [C] likewise can be degraded to give anhydrobis-dihydrosinomelone. These two compounds arise from the unknown sinomelone [CI] and dihydrosinomelone [CII] by self-condensation [76].



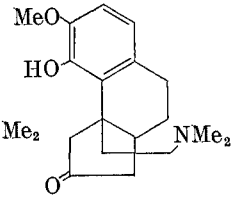
[XCVII]



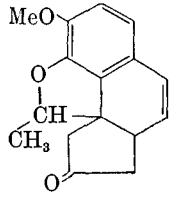
[XCVIII]



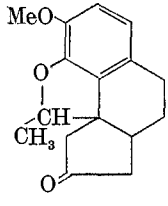
[XCIX]



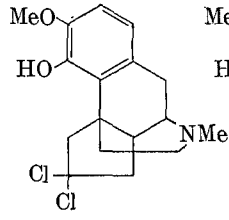
[C]



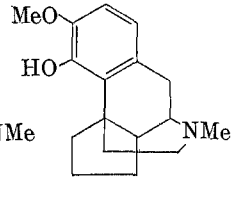
[CI]



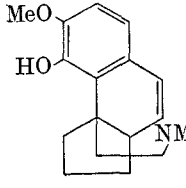
[CII]



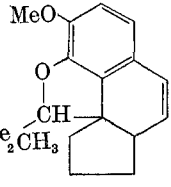
[CIII]



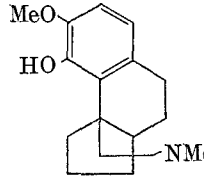
[CIV]



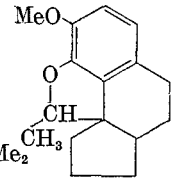
[CV]



[CVI]



[CVII]



[CVIII]

Treatment of dihydrosinomenilone [XCVIII, R = H] with phosphorus

pentachloride results in the production of 6:6-dichlorodihydrosinomenilan [CIII] which can be hydrogenated to dihydrosinomenilan [CIV]. Hofmann degradation of the latter affords dihydrosinomenilan methine [CV] in the first step and sinomelan [CVI] in the second step. The methine may be reduced to dihydrosinomenilan dihydromethine [CVII], which yields dihydrosinomelan [CVIII] on degradation [77].

DISINOMENINE AND ψ-DISINOMENINE

The mild oxidation of sinomenine effects the linking of two molecules to give a mixture of two dimolecular alkaloids, disinomenine and ψ-disinomenine, the former of which also occurs with sinomenine in nature [9]. The reagents that promote this oxidation are dilute potassium permanganate, ferric chloride, auric chloride, silver nitrate, and alkaline potassium ferricyanide [5]; the best yield of dimolecular alkaloids is obtained by adding sodium carbonate to a solution of sinomenine hydrochloride and potassium ferricyanide [9, 78]. The two bases so produced have similar properties, but differ markedly in optical rotatory power and in the solubilities of their hydrochlorides, through which salts they may be separated [78].

Disinomenine was first isolated by Goto (who called it dehydrosinomenine) and given the composition $C_{19}H_{21}O_4N$ [5, 9]; its dimolecular nature was first proved by molecular weight determination [79]. Both disinomenine and ψ-disinomenine on acetolysis yield ethylmethylamine and tetraacetyldisinomenol, which may be hydrolysed to disinomenol, the derivatives of which are identical with those obtained from the 1:1'-disinomenol obtained by heating sinomenine with 66 per cent. potassium hydroxide [78].

The strong diazo-reaction evident with sinomenine is greatly diminished in the two bimolecular alkaloids as it is in 1-bromosinomenine, and further support for the hypothesis of a 1:1' linkage in disinomenine and ψ-disinomenine is provided by the facts that 1-bromosinomenine cannot be oxidized to a dimolecular base [78] and that disinomenine cannot be sulphonated by cold concentrated sulphuric acid, unlike sinomenine which is converted to sinomenine-1-sulphonic acid [67–68].

That the two substances are not enantiomorphs is shown by the easy separation of their hydrochlorides. The difference between the two is maintained on hydrogenation, when disinomenine gives tetrahydrodisinomenine and ψ-disinomenine gives tetrahydro-ψ-disinomenine; both the tetrahydro-derivatives are obtained by the oxidation of dihydrosinomenine [79–80].

On the basis of the above reactions disinomenine is allotted the structure of 1:1'-disinomenine, and ψ-disinomenine is believed to have

the same structure with an asymmetric centre inverted, or a different mode of linkage of the ethanamine chain [78].

The ultra-violet absorption spectrum of sinomenine (see Fig. 18) has been studied by Kitasato [81] and by Ochiai and Kondo [82].

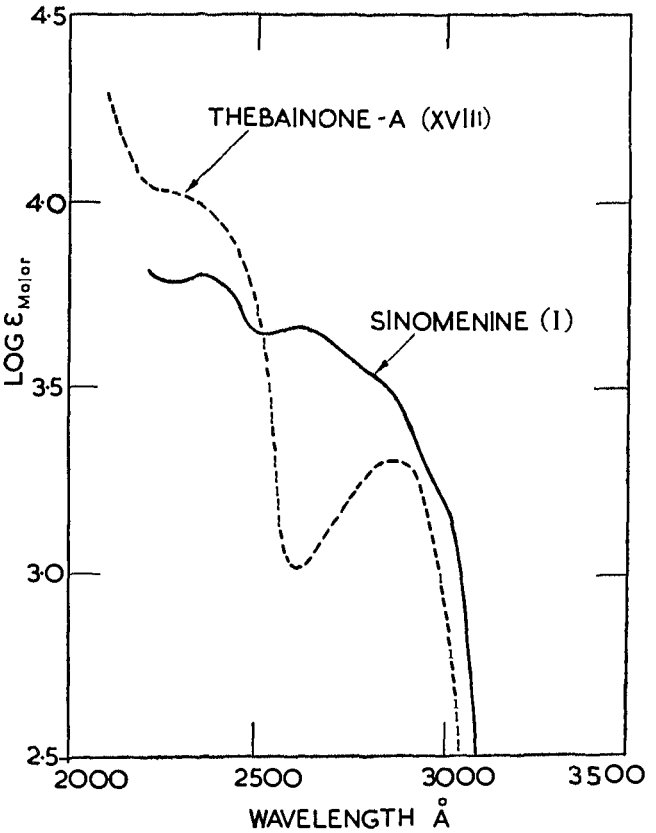


FIG. 18.

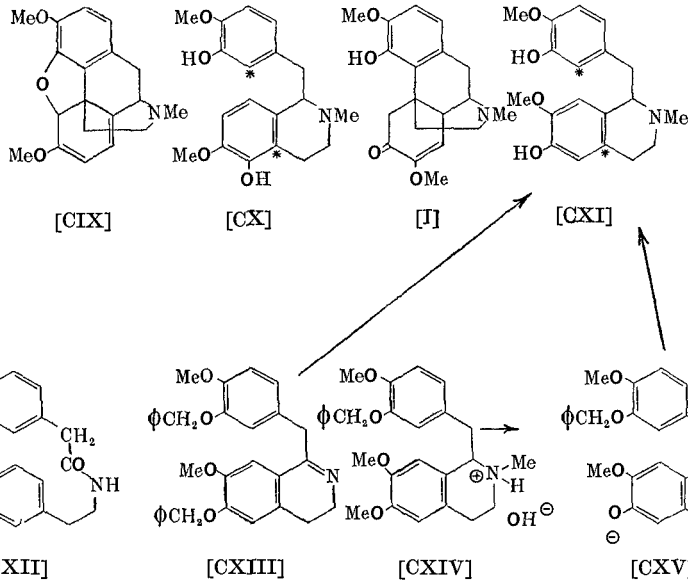
Sinomenine resembles quinine in its pharmacological properties [1, 83–85] and is useful clinically as an anti-rheumatic [83].

'PROTOSINOMENINE'

It was pointed out by Robinson [86] that thebaine [CIX] could be regarded as being derived from a laudanosine-type base by dehydration and coupling of the two aromatic nuclei in a way analogous to the polymerization of unsaturated substances, but that the orientation of the substituents in the hypothetical precursor [CX] is unusual. However, the positions of the substituents in sinomenine [I] is such that it could

theoretically arise in the plant by way of the normal type of laudanosine-base, 'protosinomenine' [CXI], by coupling in the positions marked in [CXI] by an asterisk. This 'protosinomenine' has been synthesized in two ways.

(*a*) Benzyl*iso*vanillin was converted through the azlactone and α-ketoacid to 3-benzyloxy-4-methoxyphenylacetic acid, the acid chloride of which on condensation with β-(3-benzyloxy-4-methoxyphenyl)-ethylamine gave the amide [CXII]. Bischler–Napieralsky cyclization of [CXII] under the influence of phosphorus pentachloride in chloroform afforded [CXIII], the methochloride of which on reduction and debenzylation yielded 'protosinomenine' [CXI] [87].



(*b*) Making use of an observation of Decker and Eichler [88] that 6-methoxy-N-alkylpapaverinium hydroxides can be made to lose methyl alcohol, the methyl group being derived from the 6-methoxyl group, [CXIV] was heated with barium hydroxide solution when the phenol-betaine [CXV] was formed. The latter was then converted to 'protosinomenine' [86–87].

'Protosinomenine' has not been converted to sinomenine [89]; it is probable that only some largely fortuitous discovery will reveal the conditions necessary for this conversion.

HASUBANONINE

Recently a new alkaloid obtained from *Stephania japonica* Miers ('hasunohakazura') has been investigated and shown to be very

probably of the morphine-sinomenine type [90]. This alkaloid, hasubanonine, was originally believed to be produced in the plant in place of protostephanine at certain seasons [91–92], but this is now known to be untrue [90].

Hasubanonine, which is best isolated as its nitrate, is present to the extent of about 0·04 per cent. of the dried plant shortly after collection, but the amount decreases with time and reaches 0 per cent. after about one year [90].

The alkaloid gives the following colour reactions [90].

Reagent	*Colour*
conc. H_2SO_4	colourless
conc. H_2SO_4 + H·CHO	orange-red → green → blue
dil. H_2SO_4 + base, add conc. HNO_3	yellowish-green → yellowish-brown
conc. HNO_3	colourless
diazo-reaction	pale brown
$FeCl_3$	yellow

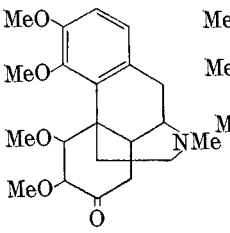
Hasubanonine has the composition $C_{21}H_{29}O_5N$, is non-phenolic, contains one carbonyl group and four methoxyl groups. On distillation with zinc-dust it gives phenanthrene, and on oxidation it yields hemipinic acid [90].

Hofmann degradation of the methiodide affords a methine base that is very unstable and can only be recrystallized from benzene. This methine base has the composition $C_{21}H_{27}O_4N$, and contains one phenolic (?) hydroxyl group and three methoxyl groups. It cannot successfully be degraded by Hofmann's method, but on heating with acetic anhydride it yields β-dimethylaminoethanol and a nitrogen-free product the ultra-violet absorption spectrum of which shows the bands characteristic of phenanthrene derivatives. Only alkaloids of the morphine-sinomenine group are known to suffer this type of degradation, and on this evidence hasubanonine is classed as a morphine alkaloid [90].

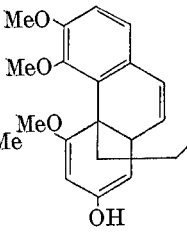
The nitrogen-free substance has the composition of a trimethoxyacetoxyphenanthrene, $C_{19}H_{18}O_4$, and can be hydrolysed to a trimethoxyhydroxyphenanthrene which on methylation with diazomethane yields a tetramethoxyphenanthrene [90] that is not identical with dimethylsinomenol (3:4:6:7-tetramethoxyphenanthrene). The acetolysis of the methine also affords a small quantity of the acetylated methine [90].

Only a limited number of formulae are possible for hasubanonine. The aromatic nucleus in the basic morphine skeleton must have methoxyl groups at positions 3 and 4, or (less likely) 2 and 1; it seems probable that the methine base is not a true phenol but contains a readily enolized carbonyl group (this would account for the fact that the methine does not show the expected intense diazo-reaction characteristic of phenols).

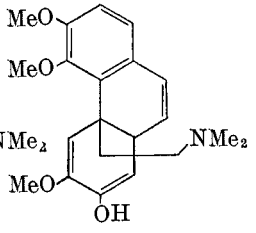
Hasubanonine could therefore have the structure [CXVI] which could suffer loss of the 6-methoxyl group during the Hofmann degradation to give the methine [CXVII]; the structure [CXVIII] for the methine is untenable as acetolysis, hydrolysis, and methylation of this would give dimethylsinomenol. Alternatively hasubanonine could be [CXIX] and the methine [CXX]. Further speculations, however, are pointless until the chemistry of the alkaloid has been more fully investigated.



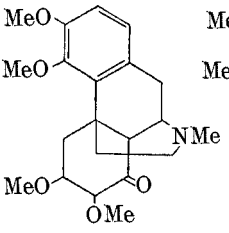
[CXVI]



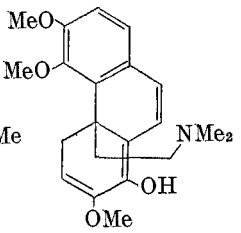
[CXVII]



[CXVIII]



[CXIX]



[CXX]

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Sinomenine	161 and 182	..	needles	−70·7	26	EtOH	1, 6
— hydrochloride·2H_2O	D. 231	..	..	−82·4	17	H_2O	5–6
— hydrobromide	231	..	..	..	..	..	5
— hydriodide	233	..	..	..	..	..	5
— nitrate	215	..	..	..	..	..	5
— aurichloride	..	..	amorph.	..	..	..	6
— picrate	c. 140	..	..	..	..	..	1
— methiodide	251	..	prisms	..	..	..	17, 38
— methomethylsulphate	265	H_2O	..	..	..	..	40
— oxime	254d.	..	..	..	..	..	5, 7
— semicarbazone	264d.	..	..	..	..	..	7
Methylsinomenine	179	..	needles	−29·6	14	$CHCl_3$	66
— methiodide	141	H_2O	..	..	..	..	66
— methomethylsulphate	245	MeOH	prisms	..	..	..	40
— oxime	139	..	prisms	..	..	..	66
Benzoylsinomenine	224	Et_2O+ benzene	prisms	−85·0	4	$CHCl_3$	66
— methiodide	237d.	H_2O	prisms	..	..	..	66
— oxime	249d.	MeOH	prisms	..	..	..	66
1-bromosinomenine	153	..	..	−2·6 −8·9	25 6	.. $CHCl_3$	5 53
— hydrochloride·3H_2O	116	H_2O	..	..	..	..	53
— hydrochloride (anhyd.)	231	..	..	..	..	..	5
— hydrobromide	202	MeOH	..	..	..	..	53
— methiodide	80	..	..	..	..	..	53
— oxime	softens 108 D. 211	..	..	..	..	..	53

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
1:5-dibromosinomenine	197d.	..	amorph.	..	..	..	55
— hydrobromide	220d.	..	..	..	..	..	55
1-bromomethylsinomenine	..	..	not cryst.	..	..	..	44
— methiodide	257	..	..	..	..	..	42, 44
1-bromoethylsinomenine	..	..	..	..	..	..	..
— ethiodide	234	..	..	..	..	..	43
Sinomenine *achro*methine	179	none	prisms	+72·6	16	$CHCl_3$	38
— hydriodide	115–118	..	prisms	..	..	..	38
— methiodide	212	..	..	−33·0	17	H_2O	38
— oxime	204–205	MeOH	prisms	..	..	..	38
Sinomenine *roseo*methine	163	..	..	+135·7	16	$CHCl_3$	38
— methiodide	277	MeOH	..	−48·3	17	H_2O	38
Sinomenine *violeo*methine	172–173	$CHCl_3$ + Et_2O	prisms	+437·8	17	$CHCl_3$	38
— methiodide	209	H_2O	..	+373·4	17	H_2O	38
Methylsinomenine *roseo*methine methomethylsulphate	178	..	plates	..	..	..	40
Methylsinomenine *violeo*methine methomethylsulphate	204d.	EtOH	prisms	+478·0 +581·6	13 20	H_2O $CHCl_3$	40
1-bromosinomenine methine	185d.	MeOH	yellow prisms	+15·9	24	$CHCl_3$	35
5-(hydroxymethyl)sinomenine	260	MeOH	prisms	−40·7	29	$CHCl_3$	37
— methiodide	233	MeOH	needles	..	..	..	37
— oxime	240–245	..	amorph.	..	..	..	37
1:5-di-(hydroxymethyl)-sinomenine	242	EtOH	..	−74·4	30	MeOH	37
— methiodide	210	MeOH	..	..	..	..	37
— oxime	200–215	..	amorph.	..	..	..	37
1-benzeneazosinomenine	253d.	ϕNO_2	red plates	..	..	..	36
Cyanonormethylsinomenine	257	..	..	−14·4	14	..	24
Cyanonorbenzoylsinomenine	245–246	..	..	+39·3	14	..	24
$C_{25}H_{32}O_5NCl$ from sinomenine and ethyl chloroformate	183	..	..	−108·4	..	..	7
Dihydrosinomenine	198	MeOH	needles	+33·1 +193·6	24 25	dil. HCl $CHCl_3$	22 5, 22
— methiodide	268d.	..	..	..	..	..	5, 22
— oxime	211d.	..	..	..	..	..	5, 22
— semicarbazone	209d.	..	..	..	..	..	22
Methyldihydrosinomenine	..	..	oil	..	..	..	31
— hydrochloride·$2H_2O$	150	H_2O	..	+35·1	14	H_2O	31
— semicarbazone	220	..	needles	..	..	..	31
1-bromodihydrosinomenine	237d.	$CHCl_3$	prisms	+102·4	24	$CHCl_3$	21, 32
— hydrobromide	229–232	..	..	..	..	..	21
— methiodide	225d.	prisms	..	..	..	..	21
— semicarbazone	D. 250	MeOH	prisms	..	..	..	21
1-benzeneazodihydrosinomenine	231	MeOH	red prisms	..	..	..	36
1-aminodihydrosinomenine hydrochloride	> 300	..	..	..	..	..	36
5-(hydroxmethyl)-dihydrosinomenine	244	MeOH	prisms	+73·0	29	MeOH + $CHCl_3$	37
— methiodide	205–220	MeOH	..	..	..	..	37
— oxime	215–225	..	amorph.	..	..	..	37
Dihydrosinomenine methine	173	Et_2O	prisms	−84·3	18	$CHCl_3$	45
Dihydrosinomenine dihydromethine	133	Et_2O	prisms	+2·1	18	$CHCl_3$	45
Desmethoxydihydrosinomenine	138	..	prisms	+59·2	..	..	23
— hydrochloride	..	..	..	+48·9	..	..	23
— methiodide	231* 120	..	..	..	..	..	23
— semicarbazone	235	..	..	..	..	..	23
Bis-8:8′-desmethoxydihydrosinomenine	304	..	prisms	−24·5	..	..	23
1-bromodesmethoxydihydrosinomenine	190–193* 119	..	..	..	..	..	29
		acetone	prisms	+57·6	13	EtOH	33–34
— methiodide	127d.	H_2O	prisms	..	..	..	33–34
— oxime	236	..	prisms	..	..	..	33–34
1:1′-dibromobis-8:8′-desmethoxydihydrosinomenine	227	acetone	..	+19·0	13	EtOH	33–34
dihydrosinomenine	..	..	..	..	..	..	..
— methiodide	253–255	H_2O	prisms	..	..	..	33–34
— oxime	217d.	..	..	..	..	..	33–34

* Indicates racemate with optical antipode.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
Desmethoxydihydrosinomenine methine	158*	..	..	..	..	..	49
	182	H_2O+ MeOH	prisms	−54·9	20	$CHCl_3$	46
Desmethoxydihydrosinomenine dihydromethine	184*	..	..	..	..	..	49
	156·5	Et_2O	prisms	+67·8	18	$CHCl_3$	46
— methiodide	226–229	MeOH	prisms	..	..	..	46
Bis-1:1′-desmethoxydihydrosinomenine methine	240–243*	..	..	..	..	..	49
	252	..	prisms	+45·1	19	$CHCl_3$+ MeOH	49
— methiodide	..	..	amorph.	..	..	..	49
Bis-1:1′-desmethoxydihydrosinomenine dihydromethine	245–248*	..	..	..	..	..	49
	248–249	..	prisms	+33·2	20	$CHCl_3$+ MeOH	49
1-bromodesmethoxydihydrosinomenine dihydromethine	175–177*	..	prisms*	..	..	..	47
	192	MeOH	prisms	+61·6	17	..	47
— hydrobromide	257	..	..	..	..	..	47
— methiodide	273	..	..	..	..	..	47
1-bromodesmethoxydihydrosinomenine methine	189–192*	..	..	..	..	..	47
	200–201	MeOH	prisms	−8·7	17	..	47
— methiodide	243	H_2O	..	..	..	..	47
Desmethoxydihydrosinomeninol-A·½H_2O	138	..	..	+45·1	23	..	24
Desmethoxydihydrosinomeninol-B	158	..	..	..	..	..	24
— methiodide	221–224	..	..	..	..	..	24
Sinomeninol	127	MeOH	..	−23·7	28	$CHCl_3$	22
— methiodide	272	H_2O	prisms	..	..	..	22
Dihydrosinomeninol	162	MeOH	prisms	+1·9	30	MeOH	22
— methiodide	249d.	..	plates	−6·7	28	H_2O	22
Desmethoxydesoxydihydrosinomenine·½H_2O	148	..	plates	..	..	..	23
— hydriodide	245	..	..	..	..	..	23
— methiodide	267	..	..	..	..	..	23
1-bromodesmethoxydesoxydihydrosinomenine	127	acetone	prisms	+40·4	12	EtOH	33–34
— methiodide	253–255	..	..	..	..	..	33–34
Methyldesmethoxydesoxydihydrosinomenine	..	..	oil	..	..	..	31
— hydriodide·H_2O	104–106	H_2O	needles	..	..	..	31
— methiodide	257–258	..	..	..	..	..	31
Desmethoxydesoxydihydrosinomenine methine	133–136*	..	..	..	..	..	50
	145–148	..	..	−65·2	19	..	49–50
Desmethoxydesoxydihydrosinomenine dihydromethine	135–140	..	..	..	..	..	50
	161	..	..	−77·9	19	..	49–50
1:9 ?-dibromodesmethoxydesoxydihydrosinomenine dihydromethine	205d.	MeOH	..	..	..	..	51–52
— perbromide	112–113	..	..	..	..	..	51–52
Bis-1:1′-desmethoxydesoxydihydrosinomenine	255–260*	..	..	..	..	..	50
	230–237	benzene	prisms	+91·6	20	EtOH	50
— dihydrochloride	293–297	H_2O	..	..	..	..	50
— methiodide	275–279	H_2O	prisms	..	..	..	50
1-bromosinomeneine	217	EtOH	prisms	−83·0	9	$CHCl_3$	53
— hydrochloride	231d.	..	..	..	..	..	53
— hydrobromide	229	..	..	..	..	..	53
— methiodide	211–212	..	..	..	..	..	53
— oxime	162	..	..	..	..	..	53
— oxime hydrochloride	280	..	..	..	..	..	53
1-bromodiacetylsinomeneine	125–135	MeOH	yellow prisms	+8·8	20	$CHCl_3$	59
1-bromosinomeneine methine	187	MeOH	prisms	+112·3	24	$CHCl_3$	35
— methiodide	213–214	..	..	..	..	..	35
1-bromodehydrometasinomenine methine	199–201	..	..	..	..	..	60
1-bromodesmethoxydihydrosinomeneine	190·5*	MeOH	prisms	+161·0	21	$CHCl_3$	35
	206						
— hydrobromide	217	..	..	..	..	..	35
(+)-dihydrocodeinone	163*	EtOH	..	+207·4	26	$CHCl_3$	35
	193						
— oxime	264–265	EtOH	prisms	..	..	..	35
(+)-dihydrocodeinone methiodide	114–116*	..	prisms	+4·0	11	MeOH	29
	120						

* Indicates racemate with optical antipode.

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
(+)-dihydrocodeinone dihydromethine	113–116* / 93–97	Et_2O+ EtOH	prisms	+50·0	11	MeOH	29
1-bromo-(+)-dihydrocodeinone methine	148*	..	..	+7·0	11	MeOH	29
— methiodide	130 278–279	..	..	..	..	..	29
(+)-dihydrocodeine (anhyd.)	105* / 110	..	..	+146·4	30	EtOH	56–57
(+)-dihydrocodeine·$2H_2O$	87–88	..	..	..	..	..	56–57
— methiodide	257* / 257	MeOH EtOH	..	+80·1	30	H_2O	56–57
(+)-dihydromorphine	154* 159	..	..	+151·5	29	EtOH	56–57
— hydriodide	261*	..	..	+87·9	29	H_2O	56–57
— methiodide	267*	..	..	+74·9	31	H_2O	56–57
(+)-6-chlorodihydrocodide	146* / 173	..	..	+177·2	28	..	56–57
— methiodide	253* / 248	MeOH	..	+114·8	7	H_2O	56–57
(+)-desoxycodeine-C	85* / 103	..	..	+179·6	20	..	57
— methiodide	218* / 238	MeOH	..	+102·4	13	..	57
(+)-7-hydroxydihydrocodeine	225	..	..	..	..	..	58
Sinomenine hydrate	139 (160)	..	prisms	+40·8	26	$CHCl_3$	61, 53
— methiodide	192–195	..	..	..	..	..	53
— dioxime	231d.	..	..	..	..	..	61
— disemicarbazone	191d.	..	..	..	..	..	61
1-bromosinomeninone	227d.	MeOH	prisms	+54·5	16	EtOH	63
— methiodide	244–246	H_2O	..	..	..	..	63
— semicarbazone	D. 118	..	..	..	..	..	63
— mono-imide	300	..	prisms	+110·2	16	$CHCl_3$	63
— mono-imide oxime	D. 300	..	..	..	..	..	63
— monoxime	199	..	needles	..	..	..	63
— dioxime	c. 189 d.	..	prisms	..	..	..	63
1:5:8-tribromosinomeninone hydrobromide	235	..	prisms	..	..	..	69
Methylsinomeninone	188	MeOH	prisms	+18·7	14	$CHCl_3$	66
— methiodide	D.225–227	..	prisms	..	..	..	66
— oxime	c. 170	..	..	..	..	..	66
1-bromomethylsinomeninone	110	..	..	..	..	..	44
Sinomeninone furazan	223–225	MeOH	prisms	+136·2	..	..	48
— methiodide	218–220	MeOH	prisms	..	..	..	48
1-bromosinomeninone furazan	D. 262	..	prisms	..	..	..	51–52
Sinomeninone furazan methine	226–227	MeOH	prisms	+49·9	19	..	48
— methiodide	..		not cryst.	..	..	..	48
Sinomeninone furazan dihydromethine	205–207	MeOH	prisms	+21·9	19	..	48
1-bromosinomeninone furazan methine	225d.	..	prisms	..	..	..	51–52
1:9 ?-dibromosinomeninone furazan methine	D. 212	MeOH	prisms	..	..	..	51–52
1-bromosinomeninone furazan dihydromethine	221–223	acetone	prisms	..	..	..	51–25
— hydrobromide	259	H_2O	needles	..	..	..	51–52
1:9:10-tribromosinomeninone furazan dihydromethine	D. 146	..	..	..	..	..	51–52
(−)-thebenone	120*, 134	EtOH	prisms	−78·6	18	$CHCl_3$	49, 46
— oxime	204·5	MeOH	prisms	..	..	.	46
bis-1:1′-(−)-thebenone	250–254* / 230–233	.. ..	.. ..	.. −163·3	.. 20	$CHCl_3$+ MeOH	.. 49
(−)-thebenone ketone	187	MeOH	prisms	..	..	..	48
— dioxime	D.225–260	MeOH	..	..	..	..	48
*Iso*nitroso-(−)-thebenone	D. 165	.	..	..	..	..	48
— oxime	241–242	MeOH	..	.	..	..	48
7-methoxy-(−)-thebenone	128	Et_2O	prisms	−147·7	18	$CHCl_3$	45
— oxime	168	EtOAc	plates	..	..	..	45
— *iso*nitroso-derivative	..	..	resin	..	..	..	45
9:10-dohydro-(−)-thebenone	158* / 113	.. ..	.. prisms	.. −206·9	.. 18	.. $CHCl_3$	49 46
bis-1:1′-9:10-dohydro-(−)-thebenone	202–205* / 208–212	..	prisms	−201·9	20	$CHCl_3$+ MeOH	49

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Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
1-bromo-9:10-dehydro-(−)-thebenone	{159–162*	MeOH	..	..	..	..	47
	{145	MeOH	prisms	−186·8	17	$CHCl_3$	47
9?-bromo-9:10-dehydro-(−)-thebenone	{156–158*	..	..	..	..	..	47
	{125–133	..	..	−113·3	17	acetone	47
7-methoxy-9:10-dehydro-(−)-thebenone	118	Et_2O	prisms	−286·0	18	$CHCl_3$	45
— oxime	180d.	EtOH	prisms	..	..	..	45
(−)-thebenone ketone furazan	148	MeOH	..	−120·4	19	..	48
1-bromo-(−)-thebenone ketone furazan	202–203	..	..	..	..	..	51–52
9:10-dehydro-(−)-thebenone ketone furazan	197	MeOH	prisms	−485·2	19	..	48
1-bromo-9:10-dehydro-(−)-thebenone ketone furazan	191	..	..	..	..	..	51–52
9?-bromo-9:10-dehydro-(−)-thebenone ketone furazan	152–153	acetone	plates	..	..	..	51–52
1:9?-dibromo-9:10-dehydro-(−)-thebenone ketone furazan	210–211	..	prisms	..	..	..	51–52
(−)-thebenane	48–54	..	..	−3·14	17	..	48, 50
9:10-dehydro-(−)-thebenane	107–112	..	..	−175·7	19	..	48, 50
α-dihydrosinomeninone	128	MeOH	prisms	+64·8	26	$CHCl_3$	61, 70
— methiodide	284d.	MeOH	prisms	..	..	..	61, 70
— oxime	170d.	H_2O	prisms	..	..	..	61, 70
— phenylhydrazone	146	..	..	..	..	..	61
— semicarbazone	191d.	..	..	..	..	..	61
Dibenzoyl-α-dihydrosinomeninone	141	MeOH	prisms	..	..	..	70
β-dihydrosinomeninone	104	MeOH	needles	+95·2	26	$CHCl_3$	61, 70
— methiodide	281d.	..	..	..	..	..	..
— oxime	{anhyd. 145–150	..	..	..	..	..	70
	107	H_2O	..				
	80	MeOH	needles				
— semicarbazone	206d.	..	..	..	..	..	..
1-bromodihydrosinomeninone	231	EtOH	prisms	..	..	..	66
Dihydromethylsinomeninone	128	33% MeOH	prisms	+71·1	15	$CHCl_3$	66
— methiodide	248	MeOH	needles	..	..	..	66
— monoxime	117	MeOH	..	..	..	..	66
(+)-7-hydroxydihydrothebainol	..	..	..	..	..	..	58
(+)-tetrahydrosinomeninone	157	..	..	..	..	..	58
(+)-1-bromotetrahydrosinomeninone	136	..	..	..	..	..	58
'Diacetyl-1-bromodehydrosinomenine'	203	..	..	..	..	..	72
— methiodide	204	..	..	..	..	..	72
'Dimethyl-1-bromodehydrosinomenine' methiodide	201·5	..	..	..	..	..	72
Sinomeninic acid	291d.	..	prisms	+88·9	18	H_2O	73
— hydrochloride	278–280	..	plates	+81·0	18	H_2O	73
— methiodide	239	MeOH	prisms	+61·8	18	H_2O	73
1-bromosinomeninic acid	251	..	prisms	+70·3	18	H_2O	73
— hydrochloride	292d.	..	plates	..	..	..	73
— hydrobromide	306d.	..	plates	+54·8	18	H_2O	73
— methiodide	276d.	..	prisms	+49·7	20	H_2O	73
Methylsinomeninic acid	295	..	prisms	+12·4	18	H_2O	73
— barium salt	D. > 300	..	..	..	..	..	73
— imide	239–241	..	..	..	..	..	75
1-bromomethylsinomeninic acid	271	..	..	..	..	..	44
1-bromosinomeneinic acid	261–262	.	prisms	+34·6	18	H_2O	73
— methiodide	D. 249	H_2O	..	+45·8	18	H_2O	73
— barium salt	D. > 300	..	..	..	..	..	73
1-bromosinomenilic acid	285	MeOH	prisms	..	..	..	69
— ethyl ester	62	EtOH	prisms	..	..	..	69
— methiodide	D. > 180	H_2O	prisms	..	..	..	69
— barium salt	> 295	EtOH	prisms	..	..	..	69
Benzoyl-1-bromosinomenilic acid	267	MeOH	prisms	..	..	..	69
Acetyl-1-bromosinomenilic acid	265	EtOH	prisms	..	..	..	69
1:7-dibromosinomenilic acid	225	dil.HOAc	prisms	..	..	..	69
— methiodide	213d.	H_2O	prisms	..	..	..	69
— barium salt	213–230d.	H_2O	rosettes	..	..	..	69
— methyl ester hydrochloride	200–212	..	prisms	..	..	..	60
— ethyl ester	82	H_2O + MeOH	prisms	..	..	..	69

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Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
1:7-dibromosinomenilic acid ethyl ester hydrochloride	234–236	EtOH	prisms	..	..	..	69
Sinomenilone	176	EtOH	prisms	+442·1	24	$CHCl_3$	76
— oxime	238	..	polygons	..	..	..	76
1-bromosinomenilone	179	..	needles	+243·3	22	EtOH	69
— methiodide	220	H_2O	needles	..	..	..	69
— oxime	270d.	Et_2O	prisms	..	..	..	69
Dihydrosinomenilone	132	acetone	..	+207·8	24	$CHCl_3$	76
— methiodide	D.220–240	..	prisms	..	..	..	76
— oxime	155–156	..	..	..	..	..	76
1-bromodihydrosinomenilone	224	EtOH	prisms	..	..	..	76
— methiodide	220d.	..	..	..	..	..	76
— oxime	222	EtOH	..	..	..	..	76
— oxime hydrochloride	280	..	..	..	..	..	76
Benzoyl-1-bromodihydrosinomenilone	180	..	prisms	..	..	..	76
Dihydrosinomenilone methine	220	EtOH	plates	+18·6	24	$CHCl_3$	76
Dihydrosinomenilone dihydromethine	175	acetone	plates	−24·6	24	$CHCl_3$	76
Anhydrobis-sinomelone	266	EtOH	prisms	−522·7	24	$CHCl_3$	76
Anhydrobis-dihydrosinomelone	247	EtOH	prisms	..	..	..	76
6:6-dichlorodihydrosinomenilan	110–116	MeOH	prisms	..	..	..	77
Dihydrosinomenilan	145–150	acetone	plates	+34·2	28	EtOH	77
— methiodide	85–87	H_2O	..	..	..	..	77
Dihydrosinomenilan methine	183–185	EtOH	prisms	−98·2	28	EtOH	77
— methiodide	225–227	H_2O	prisms	..	..	..	77
Dihydrosinomenilan dihydromethine	143–146	acetone	prisms	+45·6	28	EtOH	77
— methiodide	..	..	amorph.	..	..	..	77
Sinomelan	85–90	Et_2O	prisms	−178·0	28	EtOH	77
Dihydrosinomelan	55	Et_2O	prisms	−104·6	28	EtOH	77
Bis-desmethoxysinomenylidene	> 312	..	prisms	..	..	..	23
— hydrochloride	..	..	..	+335·5	..	..	23
— methiodide	> 300	..	..	..	..	..	23
— dioxime	> 300	..	..	..	..	..	23
— monosemicarbazone	> 300	..	..	..	..	..	23
Disinomenine	222	MeOH	plates	+150·0	..	..	78
— hydrochloride	> 290	H_2O	..	..	..	..	78
— methiodide	263d.	H_2O	prisms	..	..	..	78
— oxime	265d.	..	..	..	..	..	78
— semicarbazone	> 290	..	..	..	..	..	78
ψ-disinomenine	228	MeOH	needles	−127·0	..	..	78
— hydrochloride	> 290	..	..	..	..	..	78
— methiodide	267–268	H_2O	polyhedra	..	..	..	78
— oxime	> 280	..	..	..	..	..	78
— semicarbazone	> 290	..	..	..	..	..	78
Fully aromatic degradation products; *see* Chap. XXVIII							
Hasubanonine	116	MeOH	prisms	−219·5	25	EtOH	90
— hydrobromide	207–208	MeOH	rhombs.	−169·6	26	$CHCl_3$	90
— nitrate	222d.	MeOH	prisms	..	..	..	90
— nitrite	214	..	..	..	..	..	90
— picrate	210	MeOH	prisms	..	..	..	90
— methiodide	177–178	MeOH	plates	..	..	..	90
— oxime	141–142	..	..	..	..	..	90
— oxime hydrochloride	242–243	..	..	..	..	..	90
— methine base	158	benzene	needles	..	..	..	90
— methine base methiodide	..	..	not cryst.	..	..	..	90
— acetylated methine base methiodide	230d.	MeOH	prisms	..	..	..	90

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XXVII

DERIVATIVES OF PHENANTHRENE OBTAINED BY DEGRADATION OF THE MORPHINE ALKALOIDS

MANY degradations of alkaloids of the morphine group proceed with extrusion of the whole of the nitrogen-containing side-chain and production of a fully aromatic phenanthrene derivative. These reactions are of great value in the study of the constitutions of the alkaloids, as the readily determined positions of the substituents in the resulting aromatic compound indicates the nature of the basic alkaloid structure, and the ready extrusion of the basic side-chain led Gulland and Robinson to advance the now-accepted and proved mode of attachment of this chain to the hydrogenated phenanthrene skeleton in morphine and related bases.

Such degradations may be achieved in several ways, namely by heating the base or its quaternary salt with acetic anhydride, hydrochloric acid, or sodium ethoxide and ethyl alcohol at temperatures above 130–160° C. or by Hofmann's exhaustive methylation method.

Extrusion of the side-chain is never observed independently of the formation of a fully aromatic phenanthrene derivative, and always accompanies the formation of the latter except in the degradation of apomorphine, morphothebaine, isothebaine, and thebenine, bases that are known not to contain the typical morphine skeleton.

These important phenanthrene derivatives are conveniently considered together. They can be divided into five groups, namely:

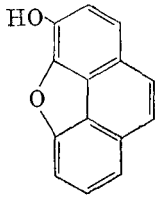
(*a*) Derivatives of 3-hydroxy-4:5-phenanthrylene oxide;
(*b*) Derivatives of 3:4-dihydroxyphenanthrene;
(*c*) Derivatives of 3:4:6-trihydroxyphenanthrene;
(*d*) Derivatives of 3:4:8-trihydroxyphenanthrene;
(*e*) Derivatives of 3:4:6:7-tetrahydroxyphenanthrene;

and they will be discussed in that order.

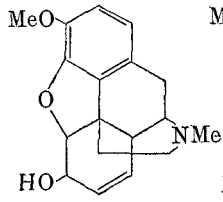
DERIVATIVES OF 3-HYDROXY-4:5-PHENANTHRYLENE OXIDE (MORPHENOL) [I]

Hofmann degradation of codeine [II] methiodide affords α-codeimethine [III] [2–3], which can be isomerized to β-codeimethine [IV] [4–6], and further degradation of these bases by Hofmann's method yields methylmorphenol [V] [7–9], the degradation being best effected by heating the methine methomethylsulphates with sodium ethoxide in

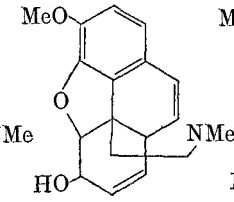
*cyclo*hexanol at 130° C., when the decomposition is rapid and the yield of methylmorphenol is 65–70 per cent., compared with 0–10 per cent. when the reaction is carried out in water [9]. Another substance, of the thebenol type, is obtained in about 1 per cent. yield during this degradation (see later under 'thebenol').



[I]



[II]



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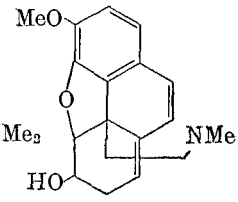
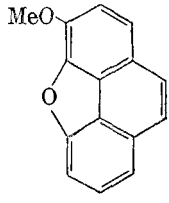


[IV]



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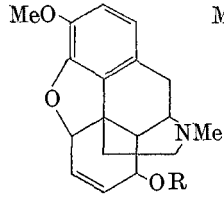
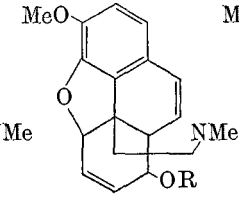
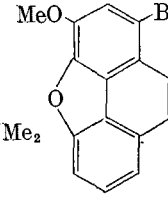


[VI]



[VII]



[VIII]

β-Codeimethine methohydroxide is stable in boiling water, even in the presence of alkali, but on evaporation to dryness the solution leaves a lacquer that at once decomposes to an amine and methylmorphenol on treatment with water. It has been suggested that the process of drying changes the methohydroxide to a compound of unknown constitution, having the side-chain so loosely attached that hydrolysis occurs under extremely mild conditions, causing aromatization [9].

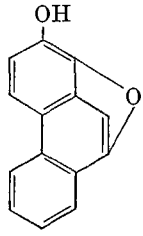
Methylmorphenol is also obtained as the final product of exhaustive methylation of codeine ethiodide [10], γ-codeimethine (the C-6 epimer of [III]) [11] and ϵ-codeimethine methyl ether [VII, R = CH_3] (obtained by the degradation of ψ-codeine methyl ether [VI, R = CH_3]) [12–13]; the other substances produced during the degradation of [VII, R = CH_3] are trimethylamine, ethylene, and methyl alcohol [12]. 1-Bromomethylmorphenol [VIII] arises in like manner by the degradation of 1-bromocodeine [10, 14–16] and ethylmorphenol from morphine-3-ethyl ether [17].

Morphenol [I]

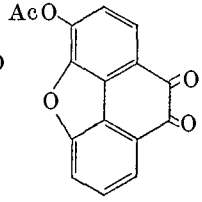
Though an early attempt to demethylate methylmorphenol failed [17], this can be accomplished quantitatively by hydrobromic acid [9], and presumably could also be effected by hot alcoholic alkali, as morphenol itself is obtained on heating the methiodides of α-codeimethine [III] [18, 21], ϵ-codeimethine [VII, R = H] [19], and β-codeimethine

methyl ether [20] with alcoholic potassium hydroxide at 150–160° C.; demethylation also accompanies hydriodic acid reduction of 1-bromomethylmorphenol [VIII], morphenol being the product of this reaction [14].

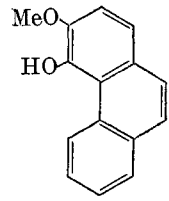
Morphenol is a phenol and gives acetyl and benzoyl esters [21]. On distillation with zinc-dust the phenol and its ethers are converted to phenanthrene [10, 22], a reaction that led Vongerichten [23] to suggest the structure [IX] for morphenol, but this was subsequently modified to [I] when it was found that acetylmorphenol can be oxidized to a quinone [X] without loss of groups or modification of the ether link, showing that the 9:10-positions carry no substituent [21, 24]. The 4:5-ether bridge of methylmorphenol [V] can be opened by reduction with sodium and alcohol, the product being methylmorphol [XI], the acetyl and benzoyl esters of which can be oxidized to quinones without loss of groups [22] (see below).



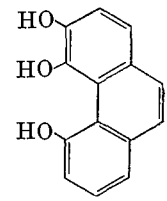
[IX]



[X]

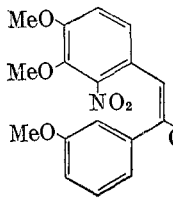


[XI]



[XII]

3:4:5-trihydroxyphenanthrene [XII] results from the fusion of morphenol with potassium hydroxide at 250° C.; it gives a triacetyl-derivative oxidizable to a quinone without loss of groups, and was identified by conversion to 3:4:5-trimethoxyphenanthrene [25], found to be identical with an authentic specimen prepared as follows [26]. 2-Nitroveratric aldehyde was condensed with 3-methoxyphenylacetic acid to give [XIII], which on reduction and phenanthrene ring-closure afforded two substances [XIV] and [XV], one of which [XIV] was also obtained by ring-closure and debromination of [XVI], and on decarboxylation this isomer yielded 3:4:5-trimethoxyphenanthrene.



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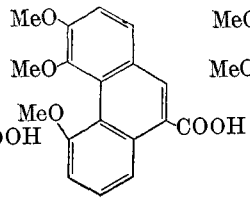

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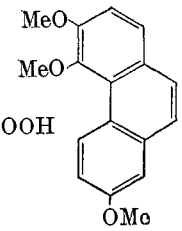

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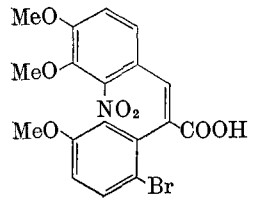
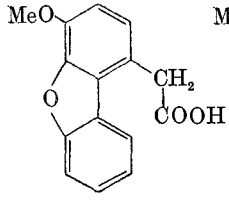


[XVI]

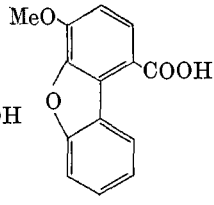
Though the structure of morphenol is sufficiently demonstrated by these reactions, its confirmation by synthesis has not been achieved, though it has been attempted by cyclization of the acid [XVII], prepared by the Arndt–Eistert reaction from [XVIII], but this cyclization failed to give a phenanthrene derivative [27].

The bromination of acetylmorphenol gives acetylbromomorphenol, hydrolysis of which gives β-bromomorphenol, and methylation of this yields β-bromomethylmorphenol isomeric with 1-bromomethylmorphenol, which is formed by the degradation of 1-bromocodeine. The two isomers behave differently on oxidation, when the β-isomer gives no crystalline products, while 1-bromomethylmorphenol gives the diphenanthryl-derivative $(C_{15}H_7O_2Br)_2O$, which is converted to dibromomethylmorphenol on bromination. β-Bromomethylmorphenol appears to give the same dibromo-compound on bromination in carbon-disulphide. The oxidation of acetylbromomorphenol gives acetylbromomorphenolquinone [15].

6-Methylmorphenol methyl ether [XIX] can be prepared by the exhaustive methylation of 6-methylcodeine [128].



[XVII]



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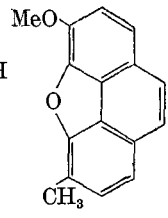
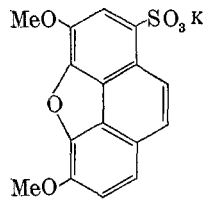


[XIX]



[XX]

If codeine sulphonic acid is allowed to stand for some time with methyl iodide and aqueous potassium hydroxide and the mixture then heated, a substance $C_{16}H_{11}O_6SK$, believed by Freund [28] to be [XX], is formed, but it is difficult to see how [XX] could arise.

DERIVATIVES OF 3:4-DIHYDROXYPHENANTHRENE (MORPHOL) [XXI]

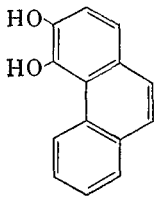
Acid-degradation of many of the morphine bases and their quaternary salts, and degradation by heating with sodium ethoxide and ethyl alcohol at 160° C., results in opening of the cyclic ether link and the production of phenanthrene derivatives having a substituted or free hydroxyl group at C-4.

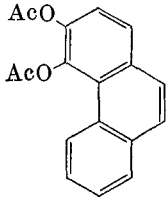
When morphine methiodide is heated with acetic anhydride and sodium acetate, diacetylmorphol [XXII] is obtained [29], and this compound is also obtained in the same way from α-isomorphine [30]. Morphol [XXI] is produced by the hydrolysis of [XXII] [29] and also from

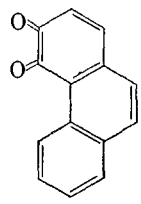
heating α-codeimethine [III] with hydrogen chloride at 180° C., the other products of this degradation being methyl chloride, β-dimethylaminoethanol, and β-codeimethine [IV], which is more stable than the α-isomer [4].

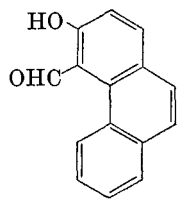
MORPHOL

Morphol [XXI] is a readily oxidizable phenol that will reduce ferric chloride and Fehling's solution [29]. It can be oxidized to 3:4-phenan-


[XXI]

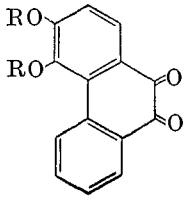

[XXII]

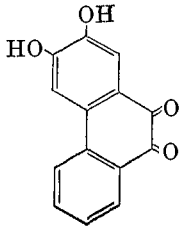

[XXIII]

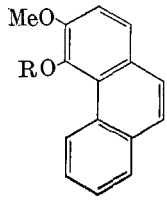

[XXIV]

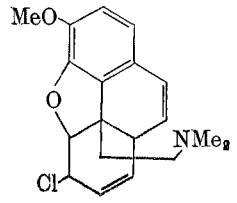
threne quinone [XXIII] by silver oxide, the reverse change being effected by sulphur dioxide [31–33]. Morphol itself has been synthesized by heating the aldehyde [XXIV] (prepared by the Gattermann method from 3-hydroxyphenanthrene [34]) with pyridine, hydrogen peroxide, and potassium hydroxide under hydrogen [31], and the quinone has been synthesized by coupling 3-hydroxyphenanthrene with a diazonium salt and reducing the resulting azo-compound to 3-hydroxy-4-aminophenanthrene followed by oxidation of the latter [32–33].

Diacetylmorphol [XXII] may be oxidized with chromic acid to diacetylmorpholquinone [XXV, R = Ac] without loss of groups [29, 35], and the latter may be hydrolysed to morphol-9:10-quinone [XXV, R = H], the monomethyl ether of which (see below) can be further oxidized to phthalonic and phthalic acids [36], showing that both hydroxyl groups of morphol-9:10-quinone are in the same aromatic nucleus. That the hydroxyl groups are adjacent is indicated by the facts that whereas morphol-9:10-quinone is an excellent mordant dye [35] its monomethyl ether is not [32]; analogy for this is to be found in the behaviour of other orthodihydroxycompounds.


[XXV]


[XXVI]


[XXVII]


[XXVIII]

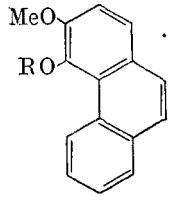
Morphol-9:10-quinone has been synthesized together with the 2:3-dihydroxy-isomer [XXVI] from 3-hydroxyphenanthrene-9:10-quinone by nitration, reduction, and conversion of the isomeric amino-compounds to the hydroxy-compounds through the diazonium salts [37].

3-Methyl-4-acetylmorphol [XXVII, R = Ac] is formed when codeine methiodide [29], α-codeimethine [III] [29, 38], α-codeimethine methiodide [7], ε-codeimethine [VII, R = H] [19], α-chlorocodeimethine [XXVIII] [39], and α-chlorocodeimethine methiodide [39] are heated with acetic anhydride, the basic products of these degradations being β-dimethylaminoethanol [7, 39] and, in the last two cases, tetramethylethylenediamine (see below) [39].

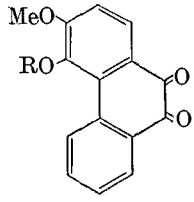
The appearance of β-dimethylaminoethanol (or its acetyl-derivative) in so many degradations of the morphine alkaloids led Knorr to believe that these alkaloids contain an oxazine system, and that the oxygen atom lost during the morphol scission appears in basic product as a hydroxyl group (see below) [40].

The hydrolysis of 3-methyl-4-acetylmorphol yields 3-methylmorphol [XXIX, R = H] [29], which also results from heating codeine methiodide [41] and α-codeimethine [41] with sodium ethoxide at 160° C., and α-chlorocodeimethine with ether and ethyl alcohol at 100° C. [42], the basic products being β-dimethylaminoethyl ethyl ether [41] and tetramethylethylenediamine [42].

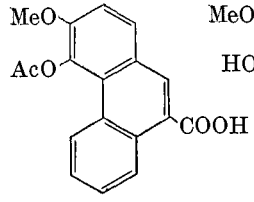
3-Methyl-4-acetylmorpholquinone [XXX, R = Ac] is the product when 3-methyl-4-acetylmorphol is oxidized with chromic acid [22, 24]; it is readily hydrolysed to 3-methylmorpholquinone [XXX, R = H], which as already stated can be oxidized to phthalic acid [36].



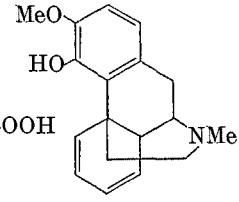
[XXIX]



[XXX]



[XXXI]



[XXXII]

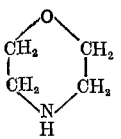
[XXX, R = Ac] has been synthesized from 2-nitro-3-acetoxy-4-methoxybenzaldehyde and phenylacetic acid, by condensation, reduction, phenanthrene ring-closure, and oxidation of the resulting acid [XXXI] [43]. 3-Methyl-4-benzoylmorpholquinone [XXX, R = $\phi \cdot CO$] is obtained by the oxidation of 3-methyl-4-benzoylmorphol [XXVII, R = $\phi \cdot CO$] [22].

Dimethylmorphol [XXVII, R = CH_3], prepared by the hydrolysis of 3-methyl-4-acetylmorphol [44], has been shown to be identical with 3:4-dimethoxyphenanthrene, synthesized in the usual way from

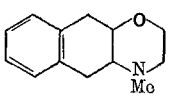
2-nitroveratric aldehyde and phenylacetic acid by Pschorr and Sumuleanu [45], who also synthesized 3-hydroxy-4-methoxyphenanthrene and showed it to be different from 3-methylmorphol [XXVII, R = H]. Dimethylmorphol also results from the degradation of metathebainone [46] (see below) and desoxycodeine-A [XXXII] [47].

1-Bromo-3-methyl-4-acetylmorphol results from the degradation of 1-bromocodeine to 1-bromo-α-codeimethine followed by acetolysis of the latter [16, 48]; on hydrolysis and methylation it is converted into 1-bromo-3:4-dimethoxyphenanthrene, identical with an authentic specimen prepared by synthesis [16]. In this way the bromine atom in 1-bromocodeine and 1-bromomorphine was shown to occupy position 1 (and not position 2 as had originally been assumed [48]).

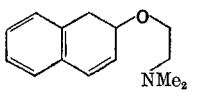
The Knorr oxazine theory of morphine structure led to the preparation of a series of bases derived from morpholine [XXXIII], so called on account of its supposed relationship to morphine [49–50]. In particular it was found that N-methylnaphthalanmorpholine [XXXIV] undergoes Hofmann degradation to a methine base [XXXV] that can be degraded further to naphthalene and β-dimethylaminoethanol. The extraordinary ease with which this last stage takes place led Knorr to believe that an *ortho*-attachment of the nitrogen side-chain to the phenanthrene residue in the morphine alkaloids was improbable, and he accordingly advanced the structure [XXXVI] [51]).



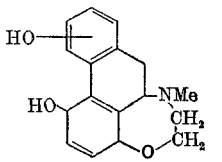
[XXXIII]



[XXXIV]

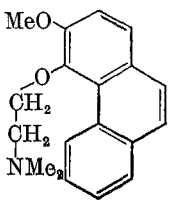


[XXXV]

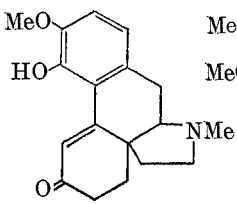


[XXXVI]

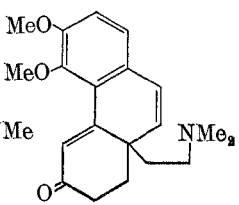
In addition 3-methylmorphol was condensed with β-dimethylaminoethyl chloride to give 3-methyl-4-(β-dimethylaminoethyl)-morphol [XXXVII], which was unaffected by sodium ethoxide at 150° C., but was degraded to 3-methyl-4-acetylmorphol [XXVII, R = Ac] and β-dimethylaminoethanol on heating with acetic anhydride, and to morphol [XXI], β-dimethylaminoethanol, and tetramethylethylenediamine on heating with hydrogen chloride [52].



[XXXVII]



[XXXVIII]



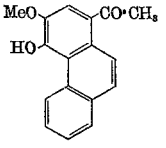
[XXXIX]

However, all support for an oxazine structure for morphine was removed when it was discovered that metathebainone (now known to be [XXXVIII]), in which the function of all three oxygen atoms was known, can be degraded to a methine base, the methyl ether of which [XXXIX], on heating with acetic anhydride, affords dimethylmorphol [XXVII, R = CH_3] and β-dimethylaminoethanol, proving that the latter can arise as a result of the scission of a carbon-carbon link [46].

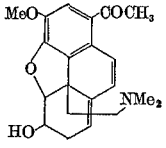
Other derivatives of morphol may be obtained by acid degradation of substituted morphines and codeines as follows.

1-Acetyl-3-methylmorphol [XL] results from heating 1-acetyl-β-codeimethine [XLI] (see Chap. VI) with sodium ethoxide and ethyl alcohol at 160° C., the basic product being β-dimethylaminoethyl ethyl ether [53]. The corresponding derivative of morphenol can be prepared by Hofmann degradation of [XLI] [54].

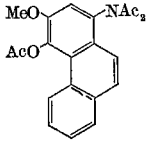
1-Diacetylamino-4-acetyl-3-methylmorphol: apparently [XLII] results from heating diacetylaminocodeine [XLIII] with silver acetate and acetic anhydridide [55–56]; it can be oxidized to a nitrogen-containing quinone [55]. (N.B. The analytical data found for this product and calculated for [XLII] correspond to $C_{21}H_{19}O_5N$ not $C_{21}H_{21}O_5N$ as given in the literature [55], in which the product is called 'triacetylaminomorphol' [55–56].)



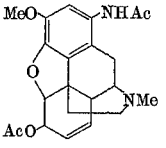
[XL]



[XLI]



[XLII]



[XLIII]

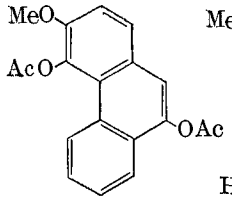
Bis-diacetylmorphol is obtained when the dimolecular alkaloid pseudomorphine methiodide is heated with acetic anhydride, sodium acetate, and silver acetate at 180° C. for twenty-four hours. It has been allotted the bis-2:2′ structure [57], but as the structure of pseudomorphine is by no means certain it may equally well be a bis-1:1′ compound (see Chap. III). It has been hydrolysed and methylated to bis-[3:4-dimethylmorphol] [57].

Bis-1:1′-[3-methyl-4-acetylmorphol] is prepared by the acetolysis of both isomers of 1:1′-dimetathebainone (formed by the oxidation of [XXXVIII]—see Chap. XVI), a dimolecular base in which the link is clearly in the 1:1′-position [57]. No attempt was made to convert this into the corresponding bis-dimethylmorphol for comparison with that obtained from pseudomorphine.

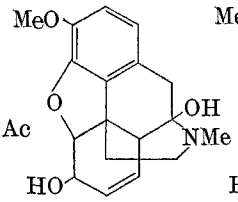
3-Methoxy-4:9 (or 10)-diacetoxyphenanthrene [XLIV ?] may conveniently be considered as a derivative of morphol. It is formed by

the acetolysis of the methine base [XLVI ?] derived from 9 (or 10)-hydroxycodeine [XLV ?] [58–59]. An oxidation with chromic acid it is converted into 3-methyl-4-acetylmorpholquinone [XXX, R = Ac], showing that one of the acetoxy groups of [XLIV ?] must be in the 9 or 10 position [60]. These reactions are of considerable importance as they indicate the point of attachment of the nitrogen end of the basic side-chain in the morphine alkaloids. As the new hydroxyl group of hydroxycodeine appears as an acetoxy group in the degradation product and as this group is lost on oxidation, the hydroxyl group in question must occupy position 9 or position 10 in hydroxycodeine. Moreover, as this hydroxyl group appears as a carbonyl group in the methine base [XLVI] the nitrogen atom must also be attached to C-9 or C-10 [59].

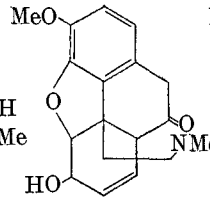
Two methods of fixing the position of the new hydroxyl group in hydroxycodeine can be envisaged. The methine base [XLVI] can be condensed with methylmagnesium iodide and the product degraded to 3:4-dimethoxy-9 (or 10)-methylphenanthrene, or [XLIV ?] can be converted to 3:4:9- or 3:4:10-trimethoxyphenanthrene, the final product in either case being compared with synthetic material of known constitution.



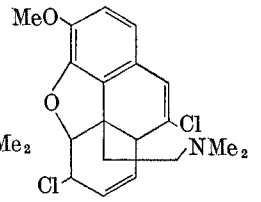
[XLIV]



[XLV]



[XLVI]

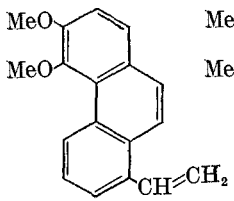


[XLVII]

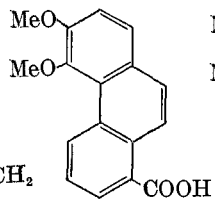
3:4-Dimethoxy-9-methylphenanthrene has been synthesized for this purpose by the Wolff–Kishner reduction of the 9-aldehyde obtained from the 9-carboxylic acid [61], and 3:4:9-trimethoxyphenanthrene has been synthesized via the 9-hydroxycompound by the Bücherer reaction on 3:4-dimethoxy-9-aminophenanthrene [62]. It is of interest to note that, contrary to expectations based on [XLV], Holmes and Lee [63] were unable to detect any properties of hydroxycodeine consistent with a carbinolamine structure.

3-Methoxy-4:9 (or 10)-diacetoxyphenanthrene may also be prepared by the acetolysis of dichlorocodeimethine [XLVII ?] [39] (see Chap. VI).

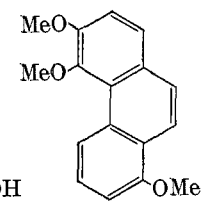
3:4-Dimethoxy-8-vinylphenanthrene [XLVIII] is the end-product of exhaustive methylation of apomorphine dimethyl ether. It can be oxidized to the 8-carboxylic acid [XLIX] [64–65], which can be converted via the amine to 3:4:8-trimethoxyphenanthrene [L] [66], identical with an authentic specimen [67] (see Chap. XXII).



[XLVIII]



[XLIX]

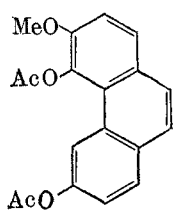


[L]

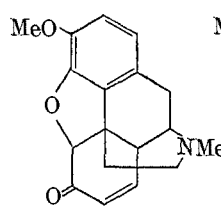
DERIVATIVES OF 3:4:6-TRIHYDROXYPHENANTHRENE

Whereas derivatives of codeine and morphine must undergo dehydration and loss of the hydroxyl group at C-6 for aromatization to occur, thebaine and codeinone can be degraded to aromatic compounds with retention of the oxygen substituent at C-6.

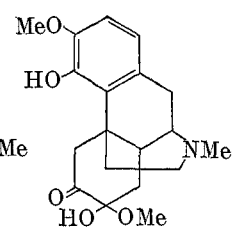
3-Methoxy-4:6-diacetoxyphenanthrene [LI] is formed when codeinone [LII] [68] and sinomenine hydrate [LIII] [69] are heated with acetic anhydride and sodium acetate; a second product in the degradation of [LIII] is triacetyl*iso*thebenine [LIV ?]. The 1-bromo-derivative can be obtained in like manner from the antipodes of 1-bromosinomeninone [69–70] and reduced catalytically to [LI]. Hydrolysis of [LI] affords the corresponding 4:6-dihydroxy-compound, which results from heating codeinone methiodide with ethanol at 160° C. [71]; both compounds have been identified by conversion to 3:4:6-trimethoxyphenanthrene [68].



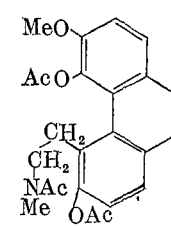
[LI]



[LII]

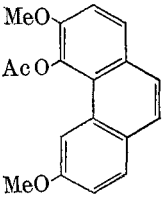


[LIII]

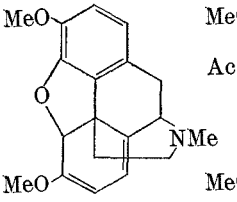


[LIV]

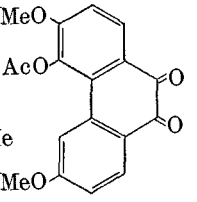
3:6-Dimethoxy-4-acetoxyphenanthrene (acetylthebaol) [LV]. This compound is the product of acetolysis of thebaine [LVI] [68, 72–73] or thebaine methiodide [72–73]. Benzoylthebaol is formed by heating thebaine with benzoyl chloride [74]. Acetylthebaol is not easily hydrolysed by aqueous alkali, but on heating with alcoholic sodium ethoxide it is converted into thebaol (3:6-dimethoxy-4-hydroxyphenanthrene) [72–73], which is obtained directly from thebaine methiodide by the action of sodium ethoxide at 160° C. [71]. (Freund earlier had failed to isolate thebaol from this reaction [73], whilst Howard and Roser claimed the production of a compound $C_{14}H_{12}O_3N$ [75].)



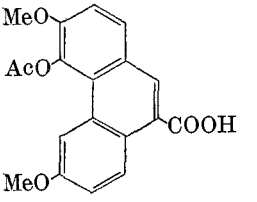
[LV]



[LVI]



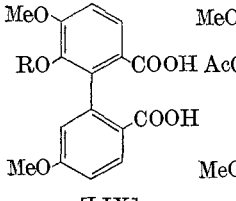
[LVII]



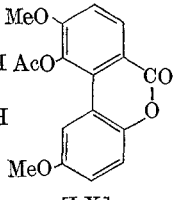
[LVIII]

Bromination of acetyl thebaol affords a dibromide [73], and oxidation affords acetylthebaolquinone [LVII] without loss of groups [72–73]. Benzoylthebaol likewise gives benzoylthebaolquinone [74]. Both quinones can be hydrolysed to thebaol-9:10-quinone [72–74]. Acetylthebaolquinone has been synthesized in a way similar to that used for the synthesis of 3-methyl-4-acetylmorpholquinone, starting from 2-nitro-3-acetoxy-4-methoxybenzaldehyde and 4-methoxyphenylacetic acid, and oxidizing the intermediate acid [LVIII] [76].

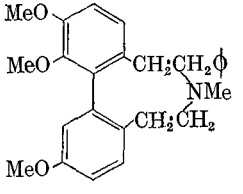
Further oxidation of acetylthebaolquinone [LVII] with hydrogen peroxide in hot glacial acetic acid affords two substances, 6-acetoxy-5:5′-dimethoxydiphenic acid [LIX, R = Ac] and 4′-acetoxy-6:3′-dimethoxy-3:4-benzocoumarin [LX], in approximately equal amounts. The first of these can be hydrolysed to the 2-hydroxy acid and methylated to 5:6:5′-trimethoxydiphenic acid [LIX, R = Me], identical with a product of degradation of phenyldihydrothebaine methyl ether [LXI] (see Chap. XX). 5:6:5′-Trimethoxydiphenic acid can be cyclized to 1:5:6-trimethoxyfluorenone-4-carboxylic acid [LXII] by heating with concentrated sulphuric acid at 50° C., but under the same conditions 6-acetoxy-5:5′-dimethoxydiphenic acid and the 6-hydroxy-acid suffered decarboxylation and were converted to the lactone [LXIII], i.e. 8:3′-dimethoxy-3:4-benzocoumarin [77–78].



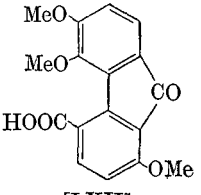
[LIX]



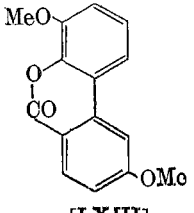
[LX]



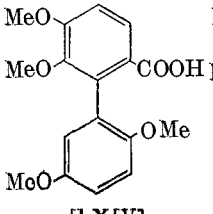
[LXI]



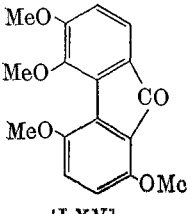
[LXII]



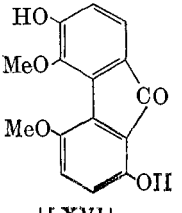
[LXIII]



[LXIV]



[LXV]



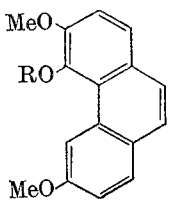
[LXVI]

[LX] was identified by hydrolysis and methylation to 5:6:2′:5′-tetramethoxydiphenyl-2-carboxylic acid [LXIV], the acid chloride of which with stannic chloride in benzene gave 1:4:5:6-tetramethoxyfluorenone [LXV] and with aluminium chloride in carbon disulphide yielded 1:6-dihydroxy-4:5-dimethoxyfluorenone [LXVI] [78].

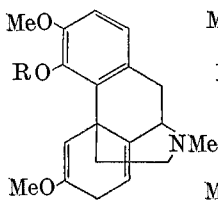
Further oxidation of thebaol-9:10-quinone affords an acid claimed by Freund to be 3-methoxyphthalic acid [73], but that is clearly 4-methoxyphthalic acid.

Thebaol [LXVII, R = H] can be converted to β-dimethylaminoethylthebaol [LXVII, R = $CH_2 \cdot CH_2 \cdot NMe_2$], which is degraded to acetylthebaol [LV] by hot acetic anhydride [43]. Methylation of thebaol affords 3:4:6-trimethoxyphenanthrene [LXVII, R = Me] [79], identical with an authentic specimen prepared in the usual way from 2-nitroveratric aldehyde and 4-methoxyphenylacetic acid [76].

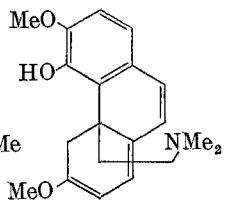
3:4:6-Trimethoxyphenanthrene [LXVII, R = Me] is also obtainable by the exhaustive methylation, in two steps, of dihydrothebaine-φ methyl ether [LXVIII, R = Me] [80]. It is of interest to note that dihydrothebaine-φ [LXVIII, R = H] can be degraded to β-dihydrothebaine methine [LXIX], further degradation of which results in retention of the residue of the nitrogen-containing side-chain, which undergoes cyclization with the phenolic hydroxyl group, the product being 6-methoxythebentriene [LXX], not thebaol [77, 81]. It is reasonable to suppose that in this degradation a vinyl group never appears as such at C-13 as no mechanism is known whereby such a group could undergo cyclization with the phenolic hydroxyl in alkaline solution; moreover a vinyl group at C-13 would immediately be lost, as in the degradation of the methyl ether of [LXIX]. The mechanism of the degradation of [LXIX] to [LXX] is discussed in Chapter XIV.



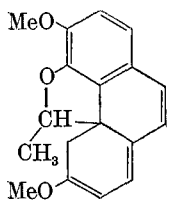
[LXVII]



[LXVIII]



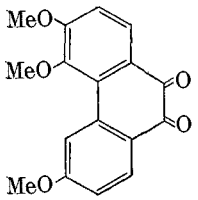
[LXIX]



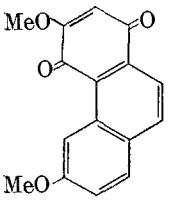
[LXX]

3:4:6-Trimethoxyphenanthrene-9:10-quinone [LXXI] has not been prepared. The chromic acid oxidation of 3:4:6-trimethoxyphenanthrene gives instead 3:6-dimethoxyphenanthrene-1:4-quinone, clearly identified as [LXXII] by its production in the same way from thebaol [LXVII, R = H]. This quinone condenses with *o*-phenylenediamine only with difficulty, losing a methoxyl group and giving 2-hydroxy-3:4′-(7′-methoxynaphtho-1′:2′)-phenazine [LXXIII], which is soluble in

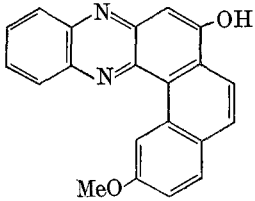
alkali. Oxidation of [LXXII] with hydrogen peroxide in hot glacial acetic acid gives 8-carboxy-7-(β-carboxyvinyl)-2-methoxy-1:4-naphthoquinone [LXXIV] in poor yield, the main product being a water-soluble acid, presumably the dihydroxy-compound derived from [LXXIV]. Both acids are oxidized further by potassium permanganate to benzene-1:2:3:4-tetracarboxylic acid [77–78].



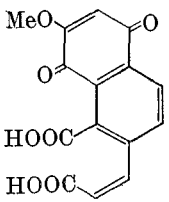
[LXXI]



[LXXII]

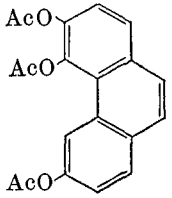


[LXXIII]

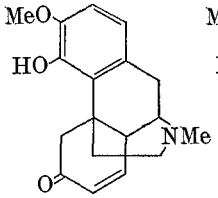


[LXXIV]

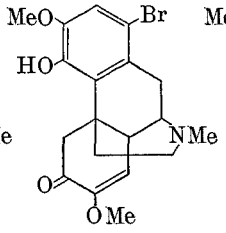
3:4:6-Triacetoxyphenanthrene [LXXV]. Acetolysis of thebainone-A [LXXVI] methiodide affords 3:4:6-triacetoxyphenanthrene, identical with the product of successive demethylation and acetylation of acetylthebaol [LV] [82]. It is curious that whereas thebainone-A retains the oxygen function at C-6 and suffers demethylation of the 3-methoxyl group during degradation, metathebainone [XXXVIII], which is in the same state of oxidation as thebainone-A, loses the oxygen at C-6 and suffers no demethylation (see above).



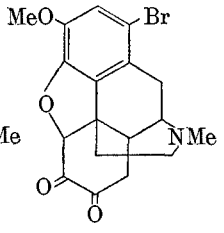
[LXXV]



[LXXVI]



[LXXVII]



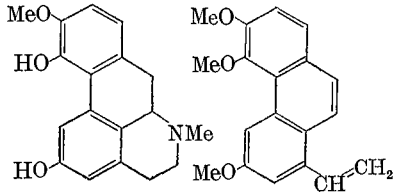
[LXXVIII]

Acetolysis of 1-bromosinomenine [LXXVII] and of 1-bromosinomeneine ketone [LXXVIII] gives 1-bromo-3:4:6-triacetoxyphenanthrene, which can be reduced to [LXXVI] [83]. (N.B. These two products were assigned the 3:4:7-triacetoxy-structure by Goto and Shishido [83], but the properties of the halogen-free substance agree with those recorded for 3:4:6-triacetoxyphenanthrene derived from thebainone-A.)

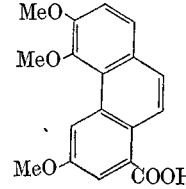
3:4:6-Trihydroxyphenanthrene derivatives can arise from certain codeine compounds as follows. The bromination of α-codeimethine [III] in chloroform leads to α-bromohydroxydihydrocodeimethine, $C_{19}H_{24}O_4NBr$, a substance containing a new hydroxyl group, the acetyl-derivative of which on heating with acetic anhydride loses hydrogen

bromide, water, and the basic side-chain, giving 3-methoxy-4:6-diacetoxyphenanthrene, identical with the product obtained from codeinone [84]. Similarly the introduction of a new hydroxyl group into α-codeimethine methyl ether by bromination to bromoacetoxydihydro-α-codeimethine methyl ether permits degradation to an aromatic compound to be achieved with retention of the 6-methoxyl group, aromatization occurring with loss of the new hydroxyl group, the product of acetolysis of the bromo-compound being acetylthebaol [LV [85].

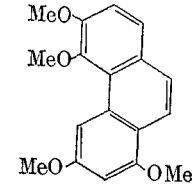
3:4:6-Trimethoxy-8-vinylphenanthrene [LXXX] arises as end-product in the exhaustive methylation of morphothebaine [LXXIX] [86]. It can be oxidized to the 8-carboxylic acid [LXXXI] which can be decarboxylated to 3:4:6-trimethoxyphenanthrene [LXVII, R = Me] [86–87], and also converted through the azide and amine to 3:4:6:8-tetramethoxyphenanthrene [LXXXII] [87], identical with an authentic specimen prepared in the usual way from 2-nitroveratric aldehyde and 2:4-dimethoxyphenylacetic acid [88] (see Chap. XXIII).



[LXXIX] [LXXX]



[LXXXI]



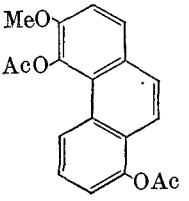
[LXXXII]

DERIVATIVES OF 3:4:8-TRIHYDROXYPHENANTHRENE

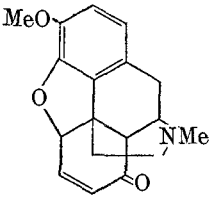
3-Methoxy-4:8-diacetoxyphenanthrene [LXXXIII]. β-Dimethylaminoethanol and [LXXXIII] are formed when ψ-codeinone [LXXXIV] is heated with acetic anhydride, but the main product of this reaction is triacetylthebenine [LXXXV, R = Ac] [89]. ψ-Codeinone methiodide and ethanol at 160° C. give 3-methoxy-4:8-dihydroxyphenanthrene [89–90], which on methylation affords 3:4:8-trimethoxyphenanthrene [90], identical with an authentic specimen prepared in the usual way from 2-nitroveratric aldehyde and 2-methoxyphenylacetic acid [67]. In this way the location of the hydroxyl group in ψ-codeine and allo-ψ-codeine, at C-8, was proved.

Bromination of ε-codeimethine methyl ether [VII, R = Me] affords bromohydroxydihydro-ε-codeimethine methyl ether, which on acetolysis gives 3:8-dimethoxy-4-acetoxyphenanthrene [85].

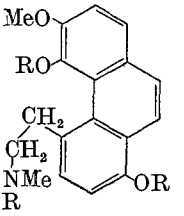
3:4:8-Trimethoxy-5-vinylphenanthrene. Thebenine [LXXXV, R = H], itself a fully aromatic phenanthrene derivative, can be degraded to 3:4:8-trimethoxy-5-vinylphenanthrene [LXXXVI] [91–92],



[LXXXIII]



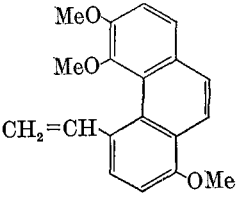
[LXXXIV]



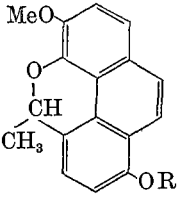
[LXXXV]

which can be reduced to 3:4:8-trimethoxy-5-ethylphenanthrene, identical with material prepared by synthesis [93], and oxidized to 3:4:8-trimethoxyphenanthrene-5-carboxylic acid, decarboxylation of which affords 3:4:8-trimethoxyphenanthrene [92]. Thebenine may also be degraded to 3:4-dimethoxy-8-ethoxy-5-vinylphenanthrene and 3:4-dimethoxy-8-ethoxyphenanthrene [92], the structure of the latter being confirmed by synthesis [94].

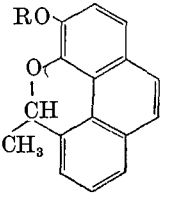
Thebenol [LXXXVII, R = H], methebenol [LXXXVII, R = Me], ethebenol [LXXXVII, R = Et], and prothebenol [LXXXVII, R = Pr] can also be prepared by the degradation of thebenine and its derivatives [73, 95–96]. They give pyrene on distillation with zinc-dust. The derivatives of thebenine are discussed in detail in Chapter XXV.



[LXXXVI]



[LXXXVII]



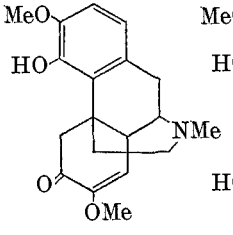
[LXXXVIII]

When codeine is degraded to methylmorphenol by heating the codeimethine methomethylsulphates with sodium ethoxide in *cyclo*-hexanol at 130° C., a compound of the thebenol type is obtained in about 1 per cent. yield. It has the composition $C_{17}H_{14}O_2$, is indifferent to hydrogenation and permanganate oxidation, and contains a C-methyl group. It has been assigned the structure of 3-methoxy-5-methyl-5-phenanthro-[4:5 *bcd*]-pyran [LXXXVIII, R = Me], and its production is doubtless the result of the violent conditions of the degradation and is of no structural significance. [LXXXVIII, R = Me] on demethylation with hydriodic acid gives the 3-hydroxy-compound [LXXXVIII, R = H] and on distillation with zinc-dust it affords pyrene. All attempts to convert thebenol [LXXXVII, R = H] to [LXXXVIII, R = Me] have failed [97].

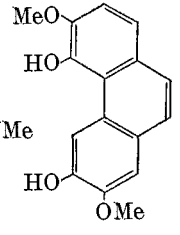
DERIVATIVES OF 3:4:6:7-TETRAHYDROXYPHENANTHRENE

These are all obtained by the degradation of derivatives of sinomenine [LXXXIX] by methods similar to those used in the morphine-thebaine series.

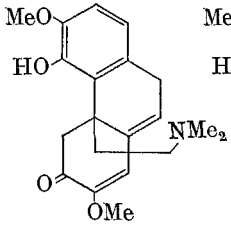
3:7-Dimethoxy-4:6-dihydroxyphenanthrene (sinomenol) [XC] is obtained when sinomenine [LXXXIX] [98–99], and when the three sinomenine methines, [XCI], [XCII], and [XCIII] [100], are boiled with 66 per cent. potassium hydroxide. It gives a dimethyl ether [dimethylsinomenol] [98], also accessible from sinomenine methyl ether [101], and a dibenzoyl-derivative [98], which also results when sinomenine or the achro-methine [XCI] is heated with benzoic anhydride at 160° C. [100–102].



[LXXXIX]



[XC]



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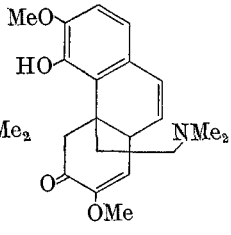
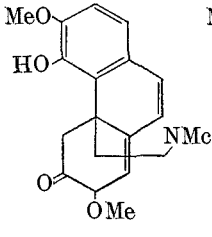
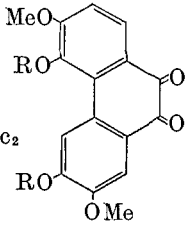


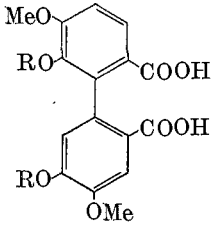
[XCII]



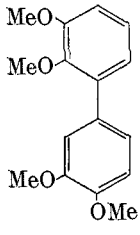
[XCIII]



[XCIV]



[XCV]

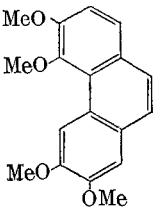


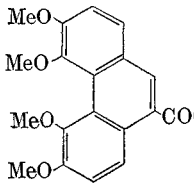
[XCVI]

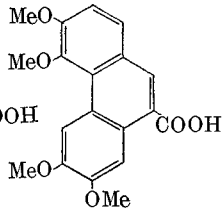
4:6-Dibenzoylsinomenol and 4:6-diacetylsinomenol can be oxidized with chromic acid to dibenzoyl- and diacetylsinomenolquinones, [XCIV, R = ϕCO] and [XCIV, R = Ac] respectively, without loss of groups [98, 103], showing that in sinomenine the oxygen substituents are not located at C-9 or C-10. The quinone esters can be hydrolysed to sinomenolquinone [XCIV, R = H] and converted to dimethylsinomenolquinone [XCIV, R = Me] and diethylsinomenolquinone [XCIV, R = Et] [103].

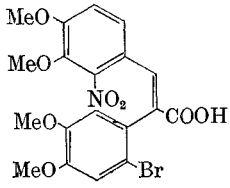
Further oxidation of dibenzoylsinomenolquinone [XCIV, R = $\phi \cdot$CO] with 30 per cent. hydrogen peroxide in glacial acetic acid affords 4:5′-dimethoxy-5:6′-di-(benzoyloxy)-diphenic acid [XCV, R = $\phi \cdot$CO],

which on hydrolysis and methylation is converted to 4:5:5′:6′-tetramethoxydiphenic acid [XCV, R = Me]. The latter can be decarboxylated to 2:3:3′:4′-tetramethoxydiphenyl [XCVI] by boiling with copper powder in quinoline [104].


[XCVII]

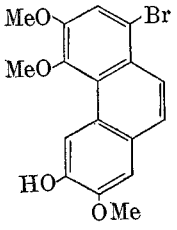

[XCVIII]

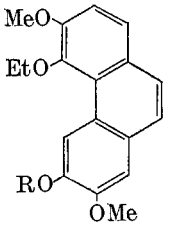

[XCIX]

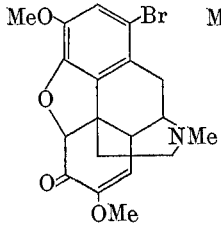

[C]

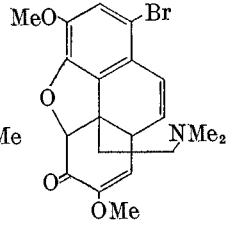
The positions of the oxygen substituents in sinomenine was demonstrated by the identity of dimethylsinomenol [XCVII] with 3:4:6:7-tetramethoxyphenanthrene. This was synthesized by Pschorr's method from 2-nitroveratric aldehyde and 3:4-dimethoxyphenylacetic acid, a synthesis that afforded two tetramethoxyphenanthrene-9-carboxylic acids, [XCVIII] and [XCIX], one of which, [XCVIII], being also accessible from the bromo-acid [C] must be the 3:4:5:6-isomer; the other [XCIX], which must therefore be the 3:4:6:7-isomer, gave dimethylsinomenol on decarboxylation [103, 105–6].

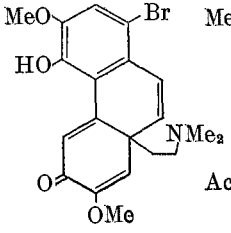
The exhaustive methylation of 1-bromosinomenine methyl ether ultimately leads to 1-bromo-4-methyl-sinomenol [CI] [107–9], and the corresponding 4-ethyl-derivative is accessible from 1-bromosinomenine ethyl ether [110]. Reductive debromination of these affords a method of

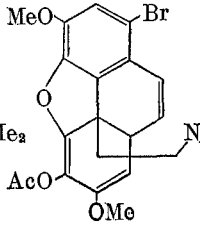

[CI]

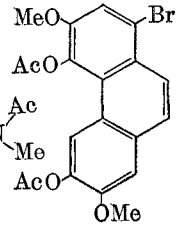

[CII]

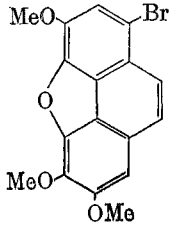

[CIII]


[CIV]


[CV]


[CVI]


[CVII]


[CVIII]

preparation of 4-ethylsinomenol [CII, R = H], 4-ethyl-6-methylsinomenol [CII, R = Me], and 4-ethyl-6-benzoylsinomenol [CII, R = ϕ·CO] [110].

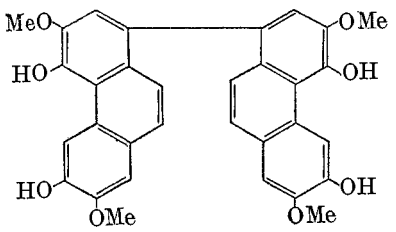
In marked contrast to codeinone [LII], of which it is a derivative, 1-bromosinomeneine [CIII] can be degraded to methine bases, of which two are known, viz. 1-bromosinomeneine methine [CIV] [107] and 1-bromodehydrometasinomenine methine [CV] [111]. The acetolysis of 1-bromosinomeneine [CIII] affords 1-bromodiacetylsinomeneine [CVI] together with a small quantity of 1-bromodiacetylsinomenol [CVII], which is also obtained by the acetolysis of 1-bromosinomenine, 1-bromosinomenine methine, 1-bromosinomeneine methine [CIV] [112], and 1-bromodehydrometasinomenine methine [CV] [111]. Catalytic reduction of [CVII] yields diacetylsinomenol [112].

When 1-bromosinomeneine methiodide is boiled with methyl sulphate and alkali, a derivative of morphenol—1-bromo-6:7-dimethoxy-3-methymorphenol [CVIII]—is formed [107].

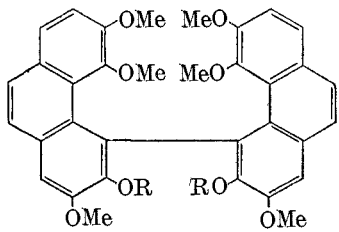
In addition to the simple sinomenol derivatives, dimolecular compounds of two types are also known.

Bis-1:1′-sinomenol derivatives. The two dimolecular alkaloids disinomenine and ψ-disinomenine on acetolysis yield ethylmethylamine and the same tetra-acetyl-1:1′-disinomenol, which may be hydrolysed to 1:1′-disinomenol [CIX] [113], also obtained in less than 15 per cent. yield when sinomenine is heated with 66 per cent. potassium hydroxide solution [98–99].

Bis-5:5′-sinomenol derivatives. Further degradation of sinomenine *violeo*methine [XCIII], methyl ether methomethyl sulphate with 2 per cent. alkali affords 4:4′-dimethyl-[bis-5:5′-sinomenol] [CX, R = H] [114], originally believed to be a trimethoxyketovinyl tetrahydrophenanthrene [115]. If sinomenine is allowed to stand with excess of methyl sulphate and alkali for several weeks tetramethyl-bis-5:5′-sinomenol [CX, R = Me] (originally believed to be α-tetramethoxyvinyldihydrophenanthrene [115]) is obtained, and from the mother liquors dimethylsinomenolquinone can be isolated after oxidation [114]. If sinomenine



[CIX]



[CX]

is boiled with alkali and methyl sulphate these two dimolecular derivatives, [CX, R = H] and [CX, R = Me], are obtained in varying amounts

together with dimethylsinomenol [114]. (The latter is identical with the β-tetramethoxyvinyldihydrophenanthrene of Goto [115].)

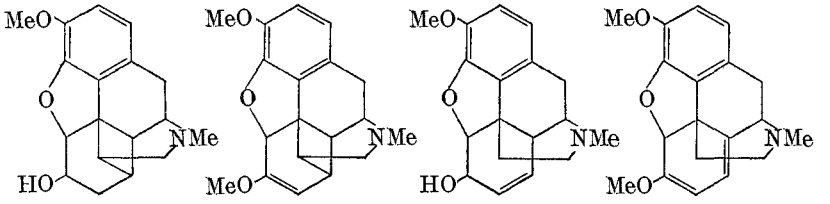
Sinomenine and sinomeninone suffer a similar degradation to 5:5′-diphenanthrene derivatives with alkali and ethyl sulphate, but such compounds are not obtained in the same way from 1-bromosinomenine [116].

The Degradation of Hasubanonine

A new alkaloid, hasubanonine, believed to be of the morphine type has recently been isolated and studied. It can be degraded to a methine base, the acetolysis of which gives a trimethoxyacetoxyphenanthrene, which has been converted to the corresponding trimethoxyhydroxy- and tetramethoxyphenanthrenes. The structure of these compounds is not yet known [117], but the properties of the tetramethoxyphenanthrene differ from those of dimethylsinomenol [XCVII].

THE MECHANISM OF DEGRADATION

The facts that the degradation of the morphine alkaloids to fully aromatic phenanthrene derivatives is always accompanied by loss of the whole of the basic side-chain, and that loss of the latter is never observed independently of formation of such an aromatic derivative, led Gulland and Robinson [1, 118] to perceive that the nitrogen-containing side-chain must be so located that its extrusion is a necessary part of aromatization. The only positions for the attachment of the carbon end of the side-chain on this assumption are C-13 and C-14 of the phenanthrene skeleton, and the formulae [CXI] for codeine and [CXII] for thebaine were accordingly advanced [1], later being modified to [CXIII] and [CXIV] respectively [118]. Such formulations allow the construction of plausible mechanisms for the degradation of the morphine alkaloids to phenanthrene derivatives.

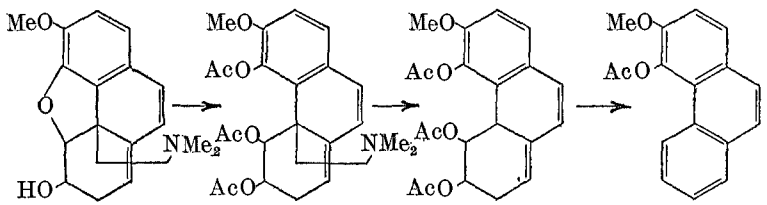


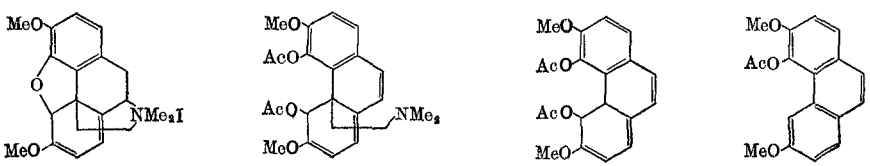
[CXI] [CXII] [CXIII] [CXIV]

The acetic anhydride degradation of morphine-type bases to give 4-acetoxyphenanthrene derivatives could proceed as follows. β-Codeimethine [CXV] undergoes acetylation of the hydroxyl group and addition of acetic anhydride to the cyclic ether system giving [CXVI], which could lose the side-chain as $CH_2{=}CH \cdot NMe_2$, whereupon the

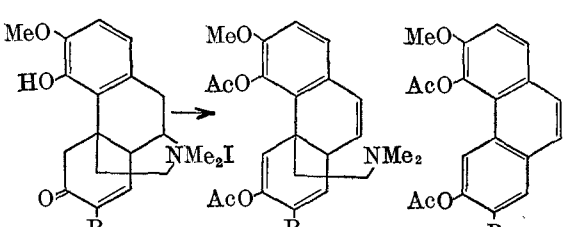
resulting [CXVII] could undergo aromatization by the loss of two molecules of acetic acid, the final product being 3-methyl-4-acetylmorphol [CXVIII]. Addition of acetic acid to the $CH_2{=}CH \cdot NMe_2$ would afford $AcO \cdot CH_2 \cdot CH_2 \cdot NMe_2$, or the latter might be formed directly during the extrusion of the side-chain [1].

In like manner acetylthebaol [CXXII] could arise from thebaine methiodide [CXIX] by fission of the nitrogen-containing ring, addition of acetic anhydride to the cyclic ether giving [CXX], loss of $CH_2{=}CH \cdot NMe_2$ from this and aromatization of the resulting [CXXI] with loss of acetic acid.



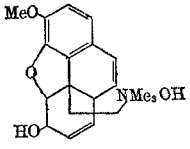


The degradation of sinomenine [CXXIII, R = OMe] and thebainone-A [CXXIII, R = H] with retention of the oxygen function at C-6 doubtless proceeds with formation of the enol acetate and scission of the nitrogen ring to give [CXXIV], followed by the loss of $CH_3 \cdot CH_2 \cdot NH \cdot Me$ instead of $CH_2{=}CH \cdot NHMe$ to yield [CXXV]. Ethylmethylamine has been isolated from the potash-fusion of sinomenine [98] and from the acetolysis of disinomenine and ψ-disinomenine [113].

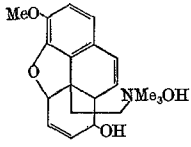


The state of oxidation of a tertiary base is increased by the formation of a methohydroxide, and the codeimethine methohydroxides are thus able to undergo degradation to a phenanthrene derivative without

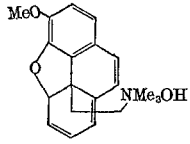
opening of the cyclic ether. α-Codeimethine methohydroxide [CXXVI] and the ε-isomer [CXXVII] could give [CXXVIII] on dehydration, and degradation of this would give a 13-vinyldihydrophenanthrene, which would at once lose ethylene and revert to methylmorphenol [CXXIX].



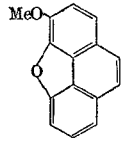
[CXXVI]



[CXXVII]



[CXXVIII]



[CXXIX]

The Basic Products of Degradation

The basic side-chain on extrusion appears in various forms according to the nature of the degradation, as follows:

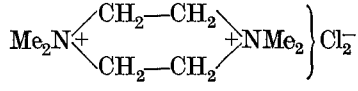
(*a*) Ethylene and trimethylamine during exhaustive methylation;

(*b*) β-methylamino- or β-dimethylaminoethanol, or their acetyl esters, during the acetolysis of the cyclic bases or their methiodides;

(*c*) β-dimethylaminoethyl ethyl ether during degradations with sodium ethoxide and ethyl alcohol;

(*d*) tetramethylethylenediamine during degradations with hydrochloric acid or in which the latter is liberated.

It has been suggested by Knorr that the initial basic product in each degradation (except exhaustive methylation) is vinyldimethylamine, $CH_2{=}CH\cdot NMe_2$ (or vinylmethylamine, $CH_2{=}CH\cdot NHMe$), which is subsequently converted to $AcO\cdot CH_2\cdot CH_2\cdot NMe_2$, $EtO\cdot CH_2\cdot CH_2\cdot NMe_2$, and $Cl\cdot CH_2\cdot CH_2\cdot NMe_2$ by the addition of acetic acid, ethanol, and hydrogen chloride respectively [71]. β-Dimethylaminoethyl chloride readily polymerizes to the piperazine salt [CXXX], which is decomposed by alkalis to tetramethylethylenediamine, acetylene, and β-dimethylaminoethanol [119].

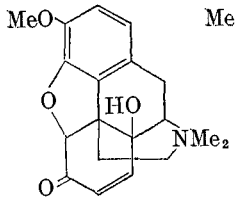


[CXXX]

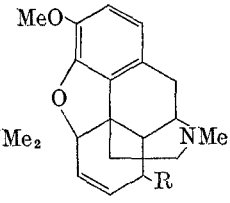
(*e*) In a few cases, as already stated, ethylmethylamine is the basic product of degradation.

Morphine derivatives that do not suffer degradation to aromatic phenanthrenes are those in which the degree of hydrogenation is too high for aromatization to be achieved simply by dehydration and extrusion of the side-chain, and those in which aromatization is blocked by the presence of a substituent at C-14—i.e. 14-hydroxycodeinone [CXXXI] [120]. Also the bases 8-piperidocodide [CXXXII, R = piperidyl] and 8-ethylthiocodide [CXXXII, R = SEt] give methine bases that

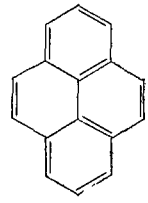
do not suffer degradation to aromatic derivatives [121–2], presumably due to the difficulty of elimination of piperidine and ethyl mercaptan between C-8 and C-14.

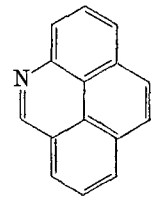


[CXXXI]



[CXXXII]


[CXXXIII]



[CXXXIV]

Miscellaneous Degradations

The distillation of morphine with zinc-dust affords phenanthrene [123–4] together with ammonia, trimethylamine, pyrroline, pyridine, quinoline [123], and 'morphidine' [118], which is a mixture of two bases $C_{17}H_{15}N$ and $C_{17}H_{13}N$ presumably of the phenanthridine type [125]. Thebaine on distillation with zinc-dust gives pyrene [CXXXIII], also obtained by the action of hydriodic acid and red phosphorus on the alkaloid [126]. Thebenidine [CXXXIV] is also produced during the zinc-dust distillation of thebaine [123]. It has been synthesized by heating 4-formamidophenanthrene with phosphorus pentoxide in xylene [127].

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Refs.*
Morphenol	145	Et_2O or EtOH	noedles	14, 17, 19, 18, 20
Acetylmorphenol	140	..	needles	14, 24
Benzoylmorphenol	123	HOAc	..	14, 21
Acetylbromomorphenol	208	..	needles	15
Methylmorphenol	65	EtOH	..	9–11, 7, 8
1-bromomethylmorphenol	118·5–119·5	..	..	10, 14–15, 16
— oxidation product $(C_{15}H_7O_2Br_2)_2O$	> 330	ϕNO_2	..	15
β-bromomothylmorphenol	124	..	needles	15
Ethylmorphonol	59	..	..	17
1-acetylmethylmorphenol	140·5	EtOAc	..	54
6-methylmorphenol methyl ether	89–90	MeOH	prisms	128
— picrate	138·5–139·5	MeOH	red prisms	128
Morphol	143	petrol	..	29, 31–32
Morphol-3:4-quinone (3:4-phenanthrene-quinone)	133d.	benzene+ petrol	red needles	32
Morphol-9:10-quinone	..	EtOH	brown needles	23
Diacetylmorphol	159	..	needles	29–30
Diacetylmorpholquinone	196	HOAc	yellow noedlos	23, 29
— azine	215–218	..	..	23
3-Methylmorphol	62–63	..	noodles	29, 41–42
— picrate	150	..	..	..

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Refs.
3-methyl-4-acetylmorphol	131	EtOH	needles	7, 19, 29 38–39
3-methyl-4-acetylmorpholquinone	205–207	HOAc	yellow needles	22–24
3-methyl-4-benzoylmorphol	..	..	not cryst.	22
3-methyl-4-benzoylmorpholquinone	228	..	yellow needles	22
Dimethylmorphol	44	MeOH	..	44–45
— picrate	104–105	..	..	44–45
— dibromo-derivative	125	..	..	44–45
3-methyl-4-(β-dimethylaminoethyl)-morphol	..	..	not cryst.	52
— hydrochloride	214–215	..	..	52
— picrate	189	..	..	52
— methiodide	196–198	..	..	52
1-bromo-3-methylmorphol	166	MeOH	needles	48
	141·5–142·5	petrol	rods	16
1-bromodimethylmorphol	..	..	oil	16
— picrate	113–114	EtOH	red needles	16
— styphnate	105–108	EtOH	red needles	16
1-bromo-3-methyl-4-acetylmorphol	163–165·5	..	..	16
1-acetyl-3-methylmorphol	161–162	..	needles	53
— semicarbazone	220	..	..	53
1-diacetylamino-3-methyl-4-acetylmorphol	178–179	Et_2O	needles	55–56
Bis-diacetylmorphol	255	H_2O+HOAc	prisms	57
Bis-[3:4-dimethylmorphol]	222	EtOH+EtOAc	prisms	57
Bis-1:1′-[3-methyl-4-acetylmorphol]	237	HOAc	needles	57
3-methoxy-4:9 (or 10)-diacetoxyphenanthrene	201	EtOH	..	58
3:4:5-trihydroxyphenanthrene	148	H_2O	..	25
3:4:5-triacetoxyphenanthrene	..	..	not cryst.	25
3:4:5-triacetoxyphenanthrenoquinone	..	..	not cryst.	25
— azine	..	..	cryst.	25
3:4:5-trimethoxyphenanthrene	..	..	oil	25
— picrate	166	..	leaflets	25
3:4:6-triacetoxyphenanthrone	165–167	EtOH	..	82–83
1-bromo-3:4:6-triacetoxyphenanthreno	216	..	..	83
3-methoxy-4:6-diacetoxyphenanthrene	162–163	HOAc	..	68
1-bromo-3-methoxy-4:6-diacetoxyphenanthrene	162	..	..	69
3-methoxy-4:6-dihydroxyphenanthrene	..	..	..	71
3:4-dimethoxy-4-hydroxyphenanthrene (thebaol)	93–94	EtOH	prisms	71, 72–3
Thebaolquinone	233	HOAc	..	72–73
— azine with o-tolylenediamine	192	..	..	72
Acetylthebaol	122	EtOH	prisms	72, 78
Dibromoacetylthebaol	179	HOAc	plates	73
Acetylthebaolquinone	205	HOAc	yellow needles	72, 78
— azine with o-phenylenediamine	265	ϕNO_2	prisms	78
— azine with o-tolylenediamine	201–203	..	..	72
Bromoacetylthebaolquinone	310	ϕNO_2	needles	73
Benzoylthebaol	160–161	H_2O+HOAc	needles	74
Dibromobenzoylthebaol	229	..	..	74
Benzoylthebaolquinone	216	..	..	74
4-(β-dimethylaminoethyl)-thebaol	..	..	oil	43
— picrate	186	..	..	43
— methiodide	199–200	..	..	43

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Refs.
3:4:6-trimethoxyphenanthrene	..	..	oil	80, 76, 79
— picrate	108–109	EtOH	..	80, 76, 79
6-acetoxy-5:5′-dimethoxydiphenic acid	229	H_2O + EtOH	needles	78
6-hydroxy-5:5′-dimethoxydiphenic acid	172 and 235	50% EtOH	prisms	78
5:6:5′-trimethoxydiphenic acid	215	H_2O + MeOH	prisms	78
1:5:6-trimethoxyfluorenone-4-carboxylic acid	256	H_2O + HOAc	yellow needles	78
— 2:4-dinitrophenylhydrazone	286	..	amorph.	78
8:3-dimethoxy-3:4-benzocoumarin	148–149	EtOH	noedles	78
4′-hydroxy-6:3′-dimethoxy-3:4-benzocoumarin	172	EtOH	prisms	78
4′-acetoxy-6:3′-dimethoxy-3:4-benzocoumarin	192	EtOH	needles	78
5:6:2′:5′-tetramethoxydiphenyl-2-carboxylic acid	162·5	EtOH	needles	78
1:4:5:6-tetramethoxyfluorenone	183	EtOH	prisms	78
— 2:4-dinitrophenylhydrazone	290	ϕNO_2	needles	78
1:6-dihydroxy-4:5-dimethoxyfluorenone ?	147	EtOH	needles	78
— 2:4-dinitrophenylhydrazone	285	HOAc	..	78
3:6-dimethoxyphenanthrene-1:4-quinone	223	HOAc	needles	78
2-hydroxy-3:4-(7′-methoxynaphtho-1′:2′)-phenazine	295–297	..	needles	78
8-carboxy-7-(β-carboxyvinyl)-2-methoxy-1:4-naphthoquinone	273–275	50% EtOH	prisms	78
3-methoxy-4:8-diacetoxyphenanthrene	155–156	..	..	89–90
3:8-dimethoxy-4-acetoxyphenanthrene	196	MeOH	..	85
3:4:8-trimethoxyphenanthrene	136–137	EtOH	plates	90
— picrate	127–129	..	needles	90
— dibromide	140–142	HOAc	needles	90
3-methoxy-5-methyl-5-phenanthro-[4:5 *bcd*]-pyran [LXXXVIII, R = Me]	118·5	EtOAc	..	97
— picrate	107–108	EtOH	purple rods	97
— 1-bromo-derivative	104–105	subl.	needles	97
3-hydroxy-5-methyl-5-phenanthro-[4:5 *bcd*]-pyran [LXXXVIII, R = H]	84–84·5	subl.	..	97
3:7-dimethoxy-4:6-dihydroxyphenanthrene (sinomenol)	172	..	..	100
Sinomenolquinone	259–263	EtOAc	needles	103
— phenazine	272	..	..	103
4:6-diacetylsinomenol	151	..	..	112
4:6-diacetylsinomenolquinone	217–219	EtOAc	needles	103
— phenazine	256	..	needles	103
4:6-dibenzoylsinomenol	206	..	..	98
4:6-dibenzoylsinomenolquinone	211	..	prisms	103
— phenazine	254	..	needles	103
3:4:6:7-tetramethoxyphenanthrene (dimethylsinomenol)	123–125	..	..	103 105–6
Dimethylsinomenolquinone	266	EtOAc	prisms	103
— phenazine	184	..	needles	103
Diethylsinomenolquinone	174	..	needles	103
— phenazine	188	..	needles	103
4-ethylsinomenol	135	..	..	110
4-ethyl-6-methylsinomenol	95	..	..	110
4-ethyl-6-benzoylsinomenol	104	..	..	110
1-bromo-4-methylsinomenol	134	$CHCl_3$	prisms	107–8, 109
1-bromo-4-ethylsinomenol	137	..	..	110
1-bromo-4:6′-diethylsinomenol	..	..	..	110
1-bromo-4:6-diacetylsinomenol	187	HOAc	prisms	112
1-bromo-6:7-dimethoxy-3-methylmorphenol	143	MeOH	prisms	107

Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Refs.
1:1′-disinomenol	> 310	..	..	113
Tetra-acetyl-1:1′-disinomenol	253	..	..	113
Tetrabenzoyl-1:1′-disinomenol	280	..	needles	113
Tetramethyl-1:1′-disinomenol	240	..	needles	113
Tetraethyl-1:1′-disinomenol	184	..	needles	113
4:4′-dimethyl-bis-5:5′-sinomenol	310	HOAc	prisms	114
4:4′-dimethyl-6:6′-diacetyl-bis-5:5′-sinomenol	230	MeOH	prisms	114
4:4′:6:6′-tetramethyl-bis-5:5′-sinomenol	283	acetone	prisms	114
4:5′-dimethoxy-5:6′-di(benzoyloxy)diphenic acid	233–235	..	rosettes	104
— dimethyl ester	170–173	MeOH	..	104
4:5:5′:6′-tetramethoxydiphenic acid	206–208	Et_2O	prisms	104
— dimethyl ester	132	MeOH	..	104
2:3:3′:4′-tetramethoxydiphenyl	96–100	MeOH	plates	104
FROM HASUBANONINE				
Trimethoxyhydroxyphenanthrene	187–188	MeOH	square crystals	117
Trimethoxyacetoxyphenanthrene	123–124	MeOH	plates	117
Tetramethoxyphenanthrene	155–157	MeOH	prisms	117
— picrate	131	MeOH	prisms	117

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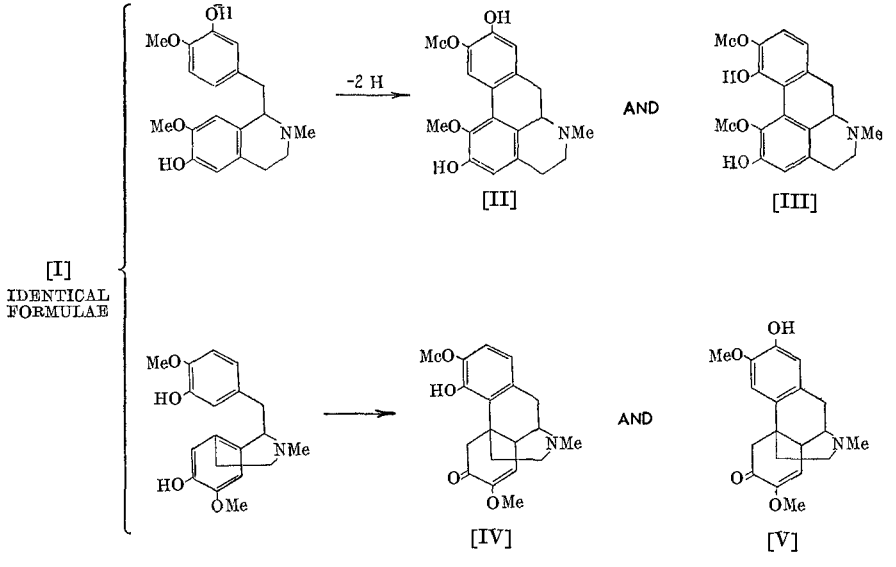
XXVIII

BIOSYNTHESIS AND SYNTHESIS IN THE MORPHINE-THEBAINE GROUP

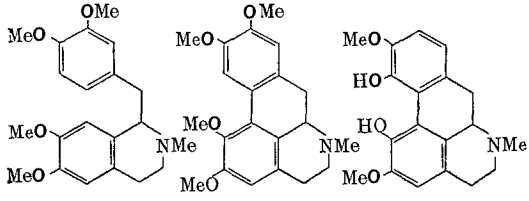
In view of the great chemical and pharmacological interest of the alkaloids of the morphine-thebaine group, the ultimate verification of the Gulland–Robinson formulae [1–2] by the synthesis of one of the alkaloids or of one of their derivatives by an unambiguous route, clearly showing the attachment of the nitrogen-containing bridge at positions 9 and 13 of the phenanthrene skeleton, has been of major importance.

The first attempts at synthesis were based on the view that the probable mode of biogenesis of these alkaloids is the union of the two aromatic nuclei of a laudanosine-type of benzyltetrahydro*iso*quinoline [3]. This union may be regarded as analogous to the formation of a terpene from isoprene or of vinylacetylene from acetylene. If the union occurs in such a position that hydrogen can subsequently be lost with reformation of an aromatic nucleus, then the product is a base of the aporphine type, whereas if union takes place in a position already bearing a substituent, loss of hydrogen cannot occur without migration, and the resulting base belongs to the morphine group.



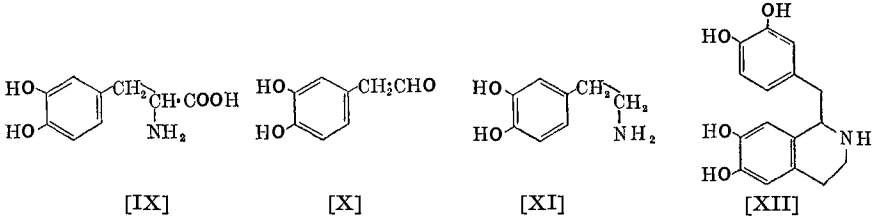
This theory may be illustrated by the base [I], which could hypothetically undergo union of the two aromatic nuclei in four different

ways, two of which would yield aporphine bases, [II] and [III], and the remaining two would give sinomenine [IV] and an isomer of sinomenine [V]. Sinomenine, benzyltetrahydro*iso*quinoline bases of type [I] (e.g. laudanosine [VI]) and aporphine bases of types [II] (e.g. glaucine [VII]) and [III] (e.g. corytuberine [VIII]) are known to occur in nature, but no morphine-type of alkaloid substituted as in [V] has yet been isolated.



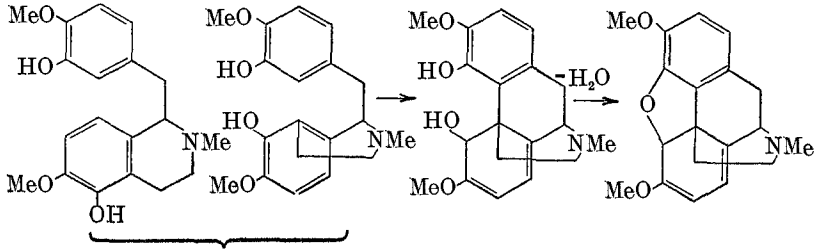
[VI] [VII] [VIII]

'Protosinomenine' [I] may be regarded as being formed in nature from 3:4-dihydroxyphenylalanine [IX], which could be converted in part to 3:4-dihydroxyphenylacetaldehyde [X] and in part to β-(3:4-dihydroxyphenyl)-ethylamine [XI], these two fragments finally uniting to give [XII]. At what stages the O- and N-methylations might occur is not known [3].



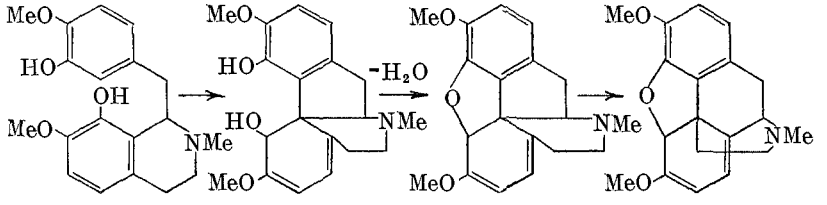
[IX] [X] [XI] [XII]

A similar scheme may be advanced for the biogenesis of thebaine [XV] as shown below [XIII] → [XV], but in this case the *iso*quinoline precursor [XIII] has an arrangement of substituents not found elsewhere in nature (neither of the two corresponding aporphine types occur naturally), and also for its formation would require two dissimilar fragments, namely 3:4-dihydroxyphenylacetaldehyde and β-(2:3:dihydroxyphenyl)-ethylamine.



[XIII] [XIV] [XV]

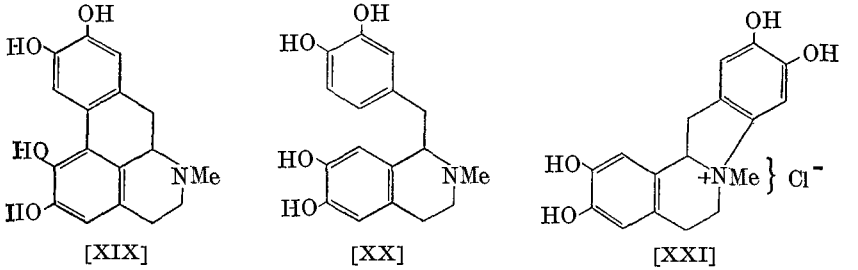
Robinson has suggested that a more probable course for the biogenesis of thebaine is by way of [XVI] (which could arise from the same intermediates as [I] with cyclization of the *iso*quinoline ring *ortho* instead of *para* to the hydroxyl group) and the further intermediates [XVII] and [XVIII], the latter finally undergoing transposition of the substituents at C-13 and C-14 to give thebaine [XV], a feasible migration [3]. In fact [XVIII] has been considered as a possible formula for thebaine [3–4], but rejected (see Chap. I).



[XVI] [XVII] [XVIII] [XV]

Thebaine occurs in the oriental poppy during the period of vigorous growth, but during the periods of withering and rest of the plant only *iso*thebaine, believed to be 3:5-dimethoxy-4-hydroxyaporphine (but see Chap. XXIV), can be isolated. The latter could arise from [XVI] by elimination of the elements of water.

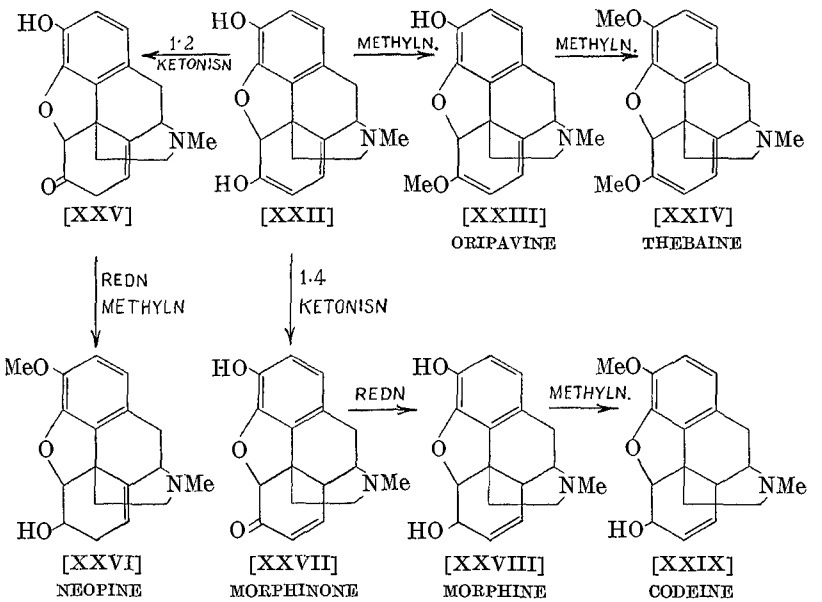
Attempts have been made to realize experimentally the conversion of laudanosine-type bases to bases of the aporphine and morphine series, so far without success. In an attempt to convert laudanosoline [XIX] to norglaucine [XX] it was discovered that the former is very readily oxidized to intractable materials, but that oxidation with chloranil [5–6] or tetrabromo-*o*-benzoquinone [7] affords, not the expected norglaucine, but 2:3:11:12-tetrahydro-8-methyldibenzotetrahydropyrrocolinium chloride [XXI]. 'Protosinomenine' [I] has been synthesized in two ways [3, 8], but the conditions required for the conversion of this base to sinomenine [IV] have not yet been realized and their discovery must be largely fortuitous [6].



[XIX] [XX] [XXI]

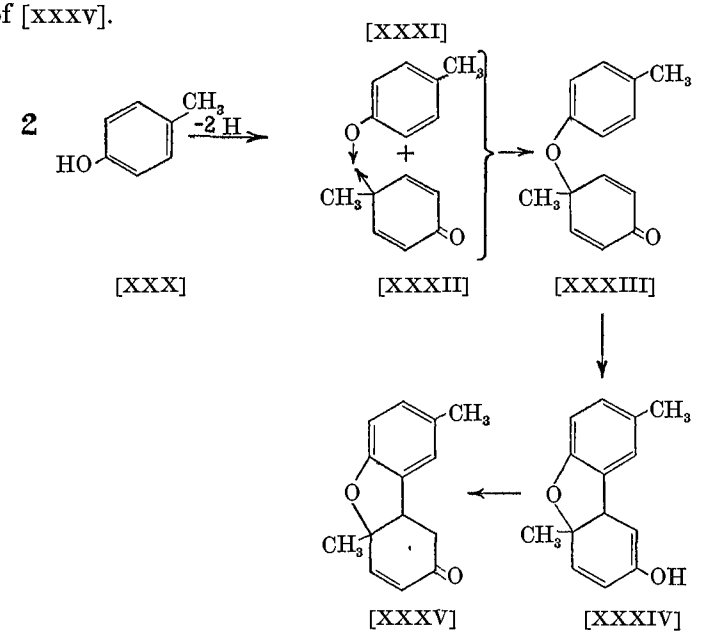
A new approach to the problem of the biogenesis of the morphine alkaloids has recently been made by Schöpf and kindly disclosed to the

author as a 'private communication' [9]. The characteristics of all the morphine alkaloids except sinomenine and hasubanonine are the phenolic (or phenol ether) nucleus, the dihydrofuran ring, the quaternary carbon atom, the aliphatic double bond, and oxygen substituent in the reduced six-membered ring, and all these are also characteristic of sinomenine with the exception of the dihydrofuran ring.



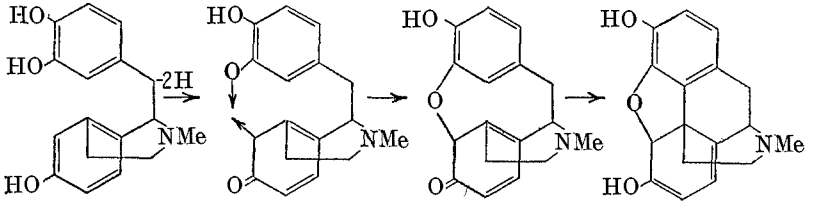
Schöpf believes that the intermediate in the biosynthesis of all the alkaloids of the morphine-thebaine group is [XXII], an enolic form of morphinone. Methylation of this would afford oripavine [XXIII] and thebaine [XXIV]; 1:2-ketonization would yield [XXV], which could be methylated and reduced to neopine [XXVI], whilst 1:4-ketonization would give morphinone [XXVII], reduction of which would give morphine [XXVIII], and this on biological methylation is converted to codeine [XXIX]. The intermediate [XXII] can, Schöpf believes, arise in one reaction from a suitable benzyltetrahydro*iso*quinoline, and analogous reactions are known to occur. *p*-Cresol [XXX] has been shown by Pummerer and his co-workers [10–11] to undergo oxidation with production of a compound having the constitution [XXXV], which has a dihydrofuran ring, an aromatic nucleus, a quaternary carbon atom, and a reduced ring containing a double bond and an oxygen substituent. This oxidation may be represented as a free radical process, the *p*-cresol being oxidized partly to the aroxyl radical [XXXI] and partly to the quinone-like radical [XXXII], combination of the free valencies of which

would lead to [XXXIII]. Finally cyclization of the α:β-unsaturated ketone and the aromatic nucleus would yield [XXXIV], which is an enol form of [XXXV].



[XXX] [XXXII] [XXXIII] [XXXV] [XXXIV]

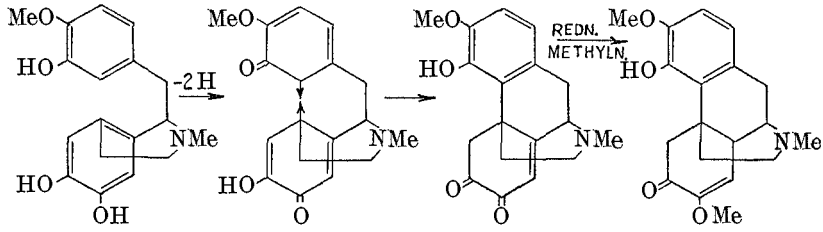
In a similar manner [XXII] could arise as a result of the oxidation of 1-(3':4'-dihydroxybenzyl)-6-hydroxy-2-methyltetrahydro*iso*quinoline [XXXVI]. Whilst *p*-cresol is oxidized *para* to the hydroxyl, if [XXXVI] is oxidized *ortho* to the 6-hydroxyl group the diradical [XXXVII] is obtained, and this can be converted through [XXXVIII] to [XXII] [9].



[XXXVI] [XXXVII] [XXXVIII] [XXII]

Similarly oxidation of [XXXIX] could give [XL] and [XLI], and reduction of the latter followed by methylation of the enol form of the product would yield sinomenine [IV] [9].

Waters, who has been thinking on identical lines in Oxford, has pointed out to the author that an extension of this free-radical mechanism can account for the production of curare alkaloids from those of the benzyltetrahydro*iso*quinoline series.



Schöpf has made numerous unsuccessful attempts to realize this biogenetic scheme in the laboratory. These attempts have been frustrated by the fact that [XXXVI] is invariably oxidized to the *o*-quinone, which then adds the nitrogen to give a tetrahydropyrrocolinium salt as in the oxidation of laudanosoline. Attempts to prevent this by using a variety of oxidizing agents, by converting [XXXVI] to the 4′-methyl ether [12], by blocking the 6′-position by a bromine atom, by using the N-oxide, or by using the N-acetyl-derivative of the corresponding secondary amine all failed. An attempt to couple 3:4-dihydroxyphenylacetaldehyde [13] with *β*-(3-hydroxyphenyl)-ethylamine with oxidation also failed to yield [XXV] or [XXVII] [9].

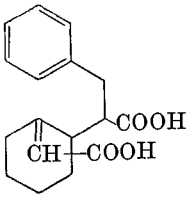
If this theory of the biogenesis of the morphine alkaloids is correct, the cell must be capable of preventing formation of an *o*-quinone on enzymatic oxidation of [XXXVI], and it seems probable that such an oxidation will only be achieved by the use of an enzyme system.

The biosynthesis of the alkaloids has also been discussed by Awe [14], and Emde [15] has advanced a hypothesis for the biogenesis of thebaine that has been described by Grewe [16] as 'fantastic'.

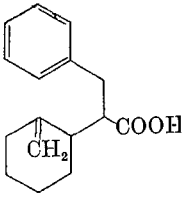
Many attempts have been made to synthesize 13-substituted phenanthrene-derivatives for comparison with possible degradation products of the morphine alkaloids, culminating in the synthesis of *dl*-tetrahydrodesoxycodeine by Grewe and of *dl*-*β*-dihydrodesoxycodeine-B methyl ether by Gates using a method that has finally afforded a total synthesis of morphine itself. Historically the most interesting of these is the former, as the final stage of the synthesis involves a reaction akin to the mode of biogenesis first postulated, namely the cyclization of a reduced benzyltetrahydro*iso*quinoline to a morphine-type of base, albeit under drastic conditions.

Grewe first investigated the production of 13-substituted phenanthrene-derivatives by the cyclization of various derivatives of *β*-phenylethyl*cyclo*hexene with phosphoric acid. The unsaturated acid [XLII] on heating with phosphoric acid yielded an unidentified monocarboxylic acid $C_{17}H_{18}O_3$ [17], but on heating with copper powder in quinoline it was converted to [XLIII], which, like [XLIV], yielded two isomers of the angular-substituted acid [XLV] on cyclization [18].

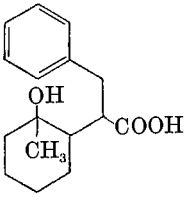
However, attempts to effect a similar cyclization of [XLVI] and [XLVII] appeared to result in an 8-substituted product [19–20], and Grewe concluded that only hydrocarbon residues can be introduced at C-13 in this way. This was subsequently found to be untrue. Cyclization of the allyl-derivative [XLVIII] gave 13-allyloctahydrophenanthrene [XLIX, R = $CH_2 \cdot CH{=}CH_2$], which was converted to the corresponding aldehyde [XLIX, R = $CH_2 \cdot CHO$] by ozonolysis [20].



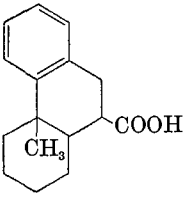
[XLII]



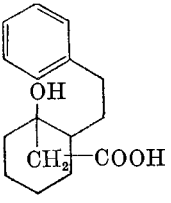
[XLIII]



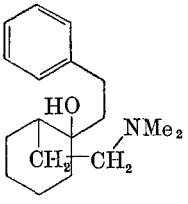
[XLIV]



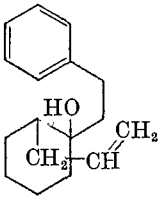
[XLV]



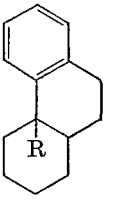
[XLVI]



[XLVII]

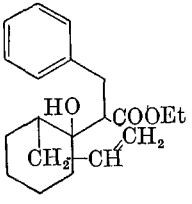


[XLVIII]

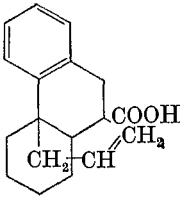


[XLIX]

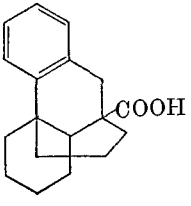
The Reformatsky reaction between 2-allyl*cyclo*hexanone and ethyl α-bromo-β-phenylpropionate yielded the acid [L], which on cyclization gave two acids, one of which was the expected 13-allyl-derivative [LI]. The other acid did not react with bromine and was allotted the structure [LII]; on Curtius degradation it afforded the amine [LIII]. The acid [LII] was recovered mainly unchanged after heating with spongy palladium at 310° C. for one hour [21].



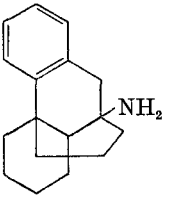
[L]



[LI]

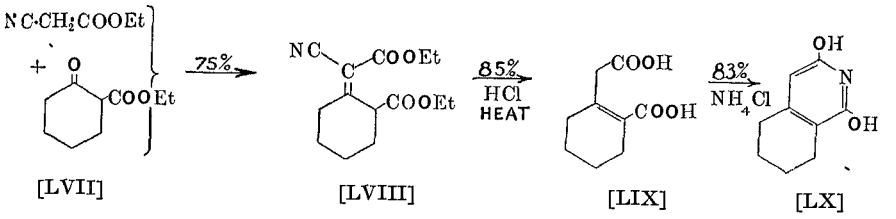


[LII]

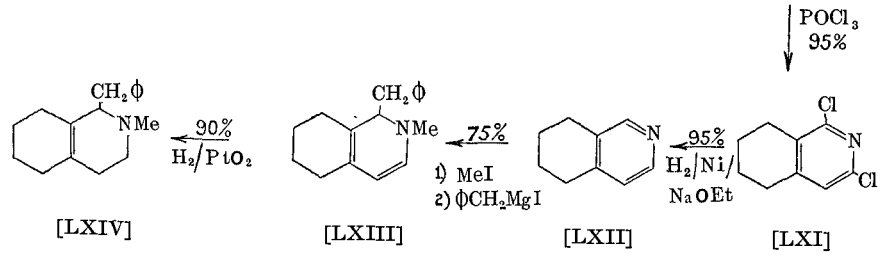


[LIII]

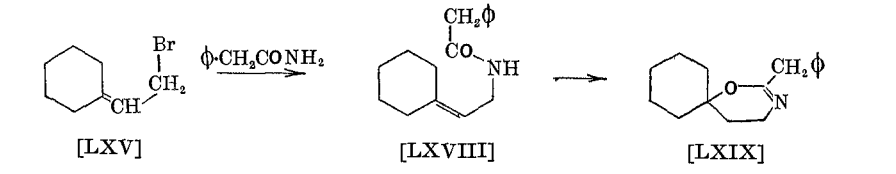
Subsequently the method of obtaining angular-substituted phenanthrenes was extended to the synthesis of the morphine skeleton. 1-Benzyl-2-methyl-1:2:3:4:5:6:7:8-octahydro*iso*quinoline [LIV] was heated with syrupy phosphoric acid at 150° C. for three days, when N-methylmorphinane [LV] was obtained in 50 per cent. yield [16, 22].



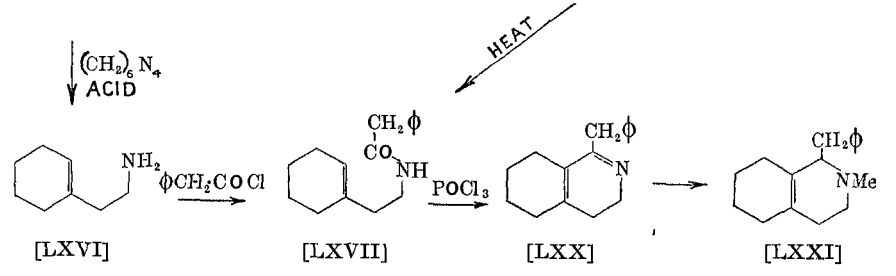
[LVII] [LVIII] [LIX] [LX]



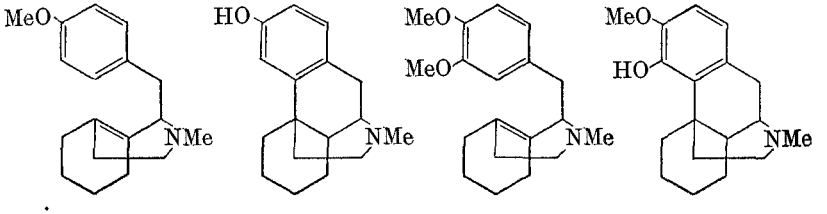
[LXIV] [LXIII] [LXII] [LXI]



[LXV] [LXVIII] [LXIX]

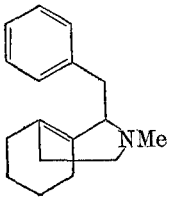


[LXVI] [LXVII] [LXX] [LXXI]

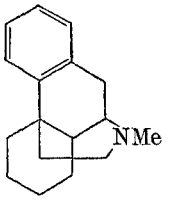


[LXXII] [LXXIII] [LXXIV] [LXXV]

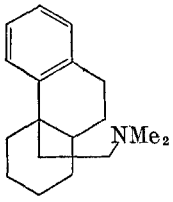
From the mother liquors of the crystallization of this base two isomeric compounds were isolated as picrates [17]. One of these was eventually identified as the C-14 epimer of [LV]. It was subsequently shown that the cyclization of [XLVII], previously reported to give the 8-substituted compound, did in fact give [LVI], identical with the dihydromethine derived from N-methylmorphinane [22].



[LIV]



[LV]



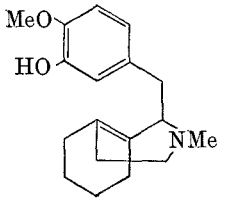
[LVI]

1-Benzyl-2-methyl-1:2:3:4:5:6:7:8-octahydro*iso*quinoline was first synthesized by the route shown [LVII] → [LXIV] [22], but a simpler synthesis [LXV] → [LXXI] [23] has been evolved.

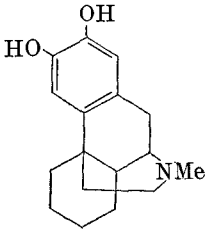
In an analogous manner 3-hydroxy-N-methylmorphinane [LXXIII] was prepared from [LXXII], and when [LXXIV] was heated with hydrochloric acid at 120° C. cyclization and partial demethylation occurred, the product being *dl*-tetrahydrodesoxycodeine [LXXV], identical with the racemate prepared from the separate *d* and *l* isomers obtained from sinomenine and codeine respectively. The racemate was resolved by *d*-tartaric acid [24]. Complete demethylation occurred when the cyclization was effected with hydrobromic acid, the product being *dl*-tetrahydrodesoxymorphine [24].

Schnider and Grüssner in the same way prepared 3- and 2- (or 4) hydroxy-N-methylmorphinane, obtained the same compounds from N-methylmorphinane by way of the nitro and amino compounds, and also synthesized the 3-hydroxy-derivative from [LIV] by nitration, reduction, diazotization, &c., followed by cyclization [25]. They have more recently resolved [LXXIII] and prepared 3-hydroxy-N-allylmorphinane [26]. Schnider and Hellerbach [27] prepared an isomer of [LXXIII] and also synthesized *dl*-tetrahydrodesoxycodeine [LXXV] by the cyclization of [LXXVI], in which reaction a small amount of 2:3-dihydroxy-N-methylmorphinane [LXXVII], isomeric with *dl*-tetrahydrodesoxymorphine, was also obtained. Both [LXXIII] and [LXXVII] exhibit marked analgesic properties to about the same extent, whilst the 2- (or 4) hydroxy-compound is much less active [25, 27].

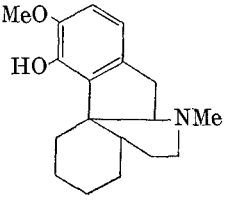
Grewe's synthesis of *dl*-tetrahydrodesoxycodeine, although important as constituting the first synthesis of a morphine derivative, is not entirely unambiguous as cyclization to give [LXXVIII] is not excluded, and although such a structure has been rejected on other grounds (see



[LXXVI]



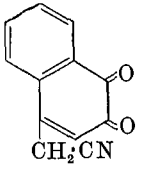
[LXXVII]



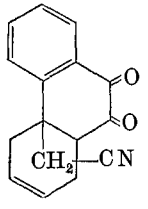
[LXXVIII]

Chap. I), an alternative and unambiguous synthesis was required before the Gulland–Robinson structure could be regarded as being unequivocally verified. Such a series of reactions, culminating in a total synthesis of morphine, has been accomplished by Gates and his co-workers as follows.

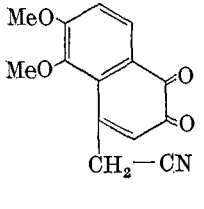
4-Cyanomethyl-1:2-naphthoquinone [LXXIX] underwent Diels–Alder addition of butadiene to give [LXXX] in 56 per cent. yield [28] and the dimethoxyquinone [LXXXI] underwent addition of butadiene, 2-ethoxybutadiene, and chloroprene to give [LXXXII, R = H], [LXXXII, R = OEt], and [LXXXII, R = Cl] respectively [29]. Position 6 was



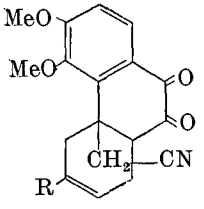
[LXXIX]



[LXXX]



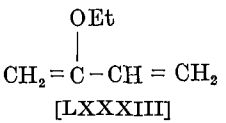
[LXXXI]



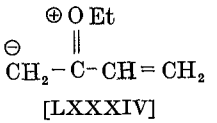
[LXXXII]

assumed for the group R in [LXXXII] on consideration of the forms [LXXXIII], [LXXXIV], [LXXXV], and [LXXXVI], which suggest that in the diene electron-density is greatest at the end nearest the substituent and that the orientation shown in [LXXXII] would result from addition of the diene to [LXXXI], in which position 4 is electron deficient [29].

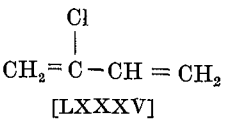
The diketone [LXXX] is soluble in alkali, probably as a result of enolization of the 9-keto group, but on catalytic reduction over copper chromite it yields an alkali-insoluble dihydro-derivative, and this reaction was first assumed to involve reduction of this keto group. The dihydro-derivative on hydrogenation over Raney nickel at room temperature affords a basic hexahydro-compound (giving a neutral diacetyl-derivative) that on further reduction with hydriodic acid and red phosphorus gives a basic desoxy-compound. The latter yields an



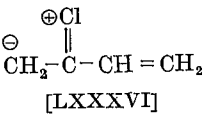
[LXXXIII]



[LXXXIV]

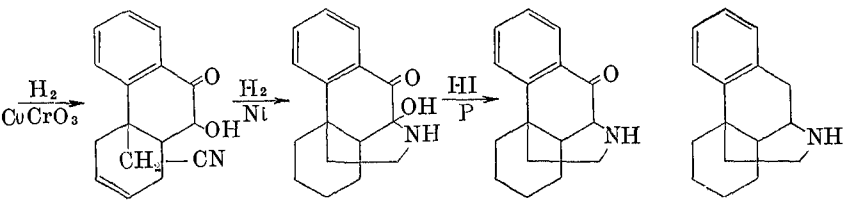


[LXXXV]



[LXXXVI]

oxygen-free base on catalytic hydrogenation. These reactions were first interpreted as shown in formulae [LXXXVII] → [XC] [30].



[LXXXVII] [LXXXVIII] [LXXXIX] [XC]

The reaction path was, however, subsequently reinterpreted in the light of the following observations [31]:

(*a*) The hydrogenation over Raney nickel gives an intermediate tetrahydro-compound.

(*b*) The infra-red absorption spectra of the dihydro-, tetrahydro-, hexahydro-, and desoxy-compounds show bands characteristic of cyclic amides.

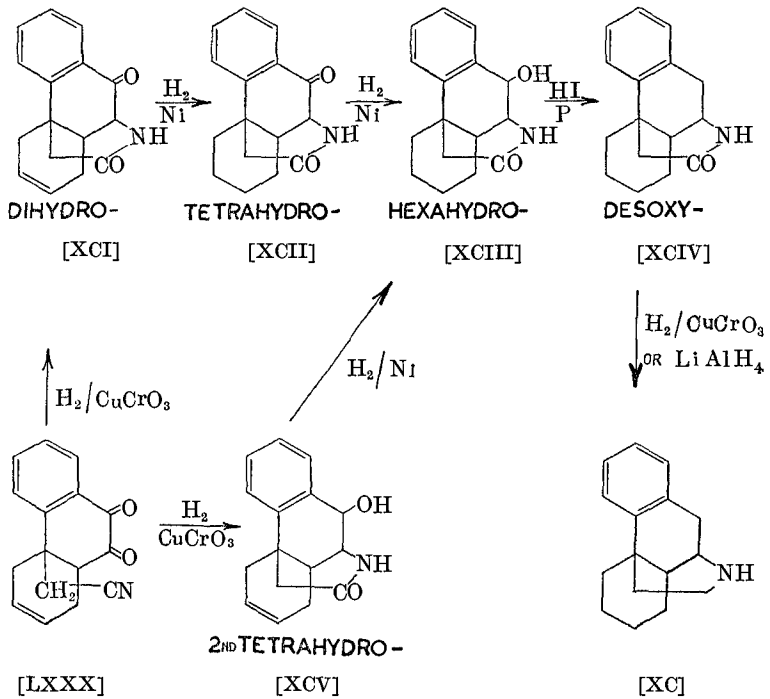
(*c*) A second tetrahydro-compound, possessing the properties of a cyclic amide but not of an aromatic ketone, can be obtained by varying the conditions of the hydrogenation over copper chromite.

(*d*) Only the dihydro- and tetrahydro-compounds are aromatic ketones.

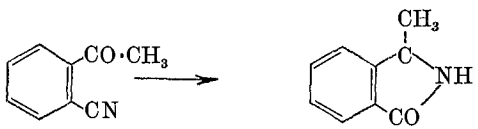
(*e*) The hexahydro-compound is not a carbinolamine.

The reactions are now believed to proceed as follows [31].

The reduction of the desoxy-compound [XCIV] to the oxygen-free base [XC] was effected more conveniently with lithium aluminium hydride than with hydrogen and copper chromite. The ring-closure during the first step was unexpected, but an analogy is to be found in the cyclization of *o*-cyanoacetophenone [XCVI] to [XCVII] under similar conditions [31]. It is clear that cyclization could involve either the 9- or 10-keto group, but ring-closure with the latter is unlikely on steric grounds, and is ruled out by the fact that the di- and tetrahydro-compounds, [XCI] and [XCII], are aromatic ketones [31].



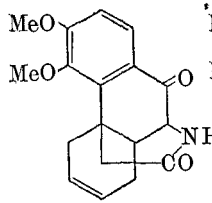
Treatment of the base [LXXX] with formaldehyde resulted in production of N-methyl*iso*morphinane, apparently a C-14 epimer of Grewe's N-methylmorphinane and identical with one of the by-products of the preparation of the latter [30]. Hofmann degradation of N-methyl*iso*-morphinane methiodide leads to a methine base, zinc-dust distillation of which affords 1:2:3:4-tetrahydrophenanthrene. The methine can be reduced to a dihydromethine [30].



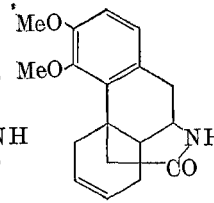
[XCVI] [XCVII]

In a similar way [LXXXII, R = H] was reduced to [XCVIII], which converted by Wolf–Kishner reduction to [XCIX], which in turn was reduced with lithium aluminium hydride and methylated to give *dl*-β-dihydrodesoxycodeine-B methyl ether [C]. The product was compared, by means of the infra-red absorption spectra, with dihydrodesoxycodeine-B methyl ether prepared from dihydrothebainol-B [CI] and with β-dihydrodesoxycodeine-B methyl ether prepared from β-dihydrothebainol-B, which is the C-14 epimer of [CI]. The spectra of

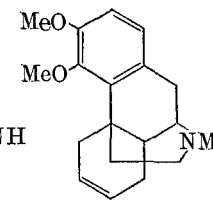
the synthetic racemate and the material derived from β-dihydrothebainol-B were found to be identical, while the spectrum of the base derived from the 'normal' series showed slight but distinct differences [32].



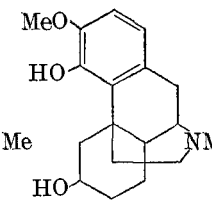
[XCVIII]



[XCIX]



[C]



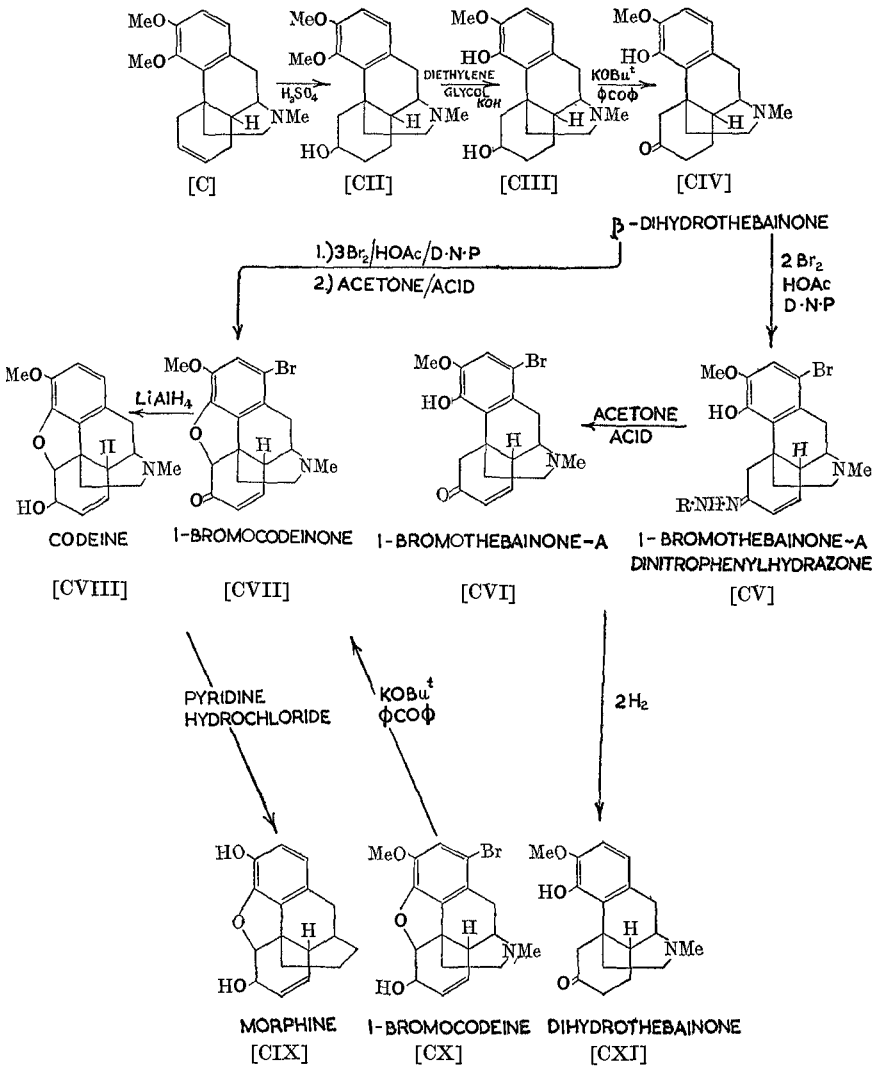
[CI]

Although the method of Gates gives, initially, a series of compounds epimeric at C-14 with those of the normal morphine series, a remarkable epimerization reaction has enabled a total synthesis of morphine to be achieved as follows [33].

The racemic base [C] was resolved by L(+)-dibenzoyltartaric acid and the *d*-isomer hydrated with dilute sulphuric acid, when β-dihydrothebainol-B methyl ether [CII] was obtained, and this underwent partial demethylation on vigorous treatment with potassium hydroxide and diethylene glycol, giving β-dihydrothebainol-B [CIII]. Oxidation of the latter by potassium tertiary butoxide and benzophenone afforded β-dihydrothebainone [CIV]. β-Dihydrothebainone on bromination with two moles of bromine followed by 2:4-dinitrophenylhydrazine gave the dinitrophenylhydrazone of 1-bromothebainone-A [CV], epimerization at C-14 occurring with remarkable ease. Catalytic hydrogenation of 1-bromothebainone-A [CVI], obtained by cleavage of the dinitrophenylhydrazone, afforded dihydrothebainone [CXI].

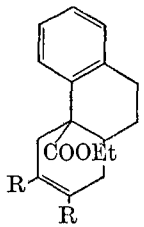
Bromination of β-dihydrothebainone with three moles of bromine, treatment with 2:4-dinitrophenylhydrazine, and cleavage of the resulting dinitrophenylhydrazone yielded 1-bromocodeinone [CVII], identical with an authentic specimen prepared by the Oppenauer oxidation of 1-bromocodeine [CX]. Reduction of 1-bromocodeinone with lithium aluminium hydride gave codeine [CVIII], which was demethylated by the method of Rapoport (who converted codeine-N-methyl-C^{14} to morphine-N-methyl-C^{14} by heating with pyridine hydrochloride [34]) to morphine [CIX]. The compounds at each stage of this elegant synthesis were identified with the authentic material by mixed melting-points and by infra-red spectra [33].

Other workers also have applied the Diels–Alder addition reaction to the preparation of angular-substituted derivatives of phenanthrene possibly obtainable as products of degradation of the morphine alkaloids.

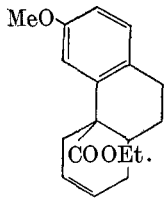


Fieser and Holmes [35], by the addition of butadiene and dimethylbutadiene to ethyl 3:4-dihydro-α-naphthoate, were able to prepare [CXII, R = H] and [CXII, R = Me], and also the methoxy-compounds [CXIII] and [CXIV] in a similar way [36]. Reduction of [CXIV] afforded 3:4-dimethoxy-5:6:7:8:9:10:13:14-octahydrophenanthrene-13-carboxylic acid [CXV], which is theoretically obtainable from [CXVI], a known product of degradation of thebaine [37]. Attempts to convert the carboxyl group of [CXV] to other substituents were made, and in this connexion [CXII, R = Me] was submitted to the Bouveault–Blanc reduction followed by treatment of the product with phosphorus

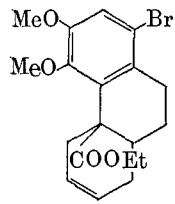
pentachloride and reduction of the resulting 13-chloromethyl compound. Though the product of these reactions [CXVII ?] was not purified and identified, it yielded 2:3-dimethylphenanthrene on dehydrogenation [36]. The corresponding reactions in the dimethoxy series were not carried out.



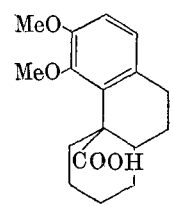
[CXII]



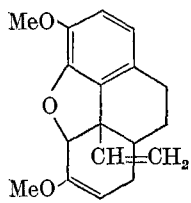
[CXIII]



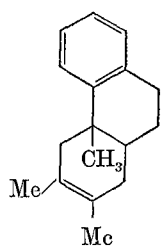
[CXIV]



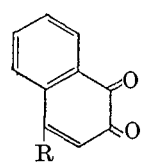
[CXV]



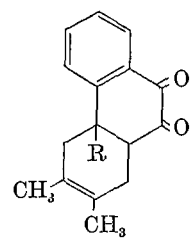
[CXVI]



[CXVII]



[CXVIII]

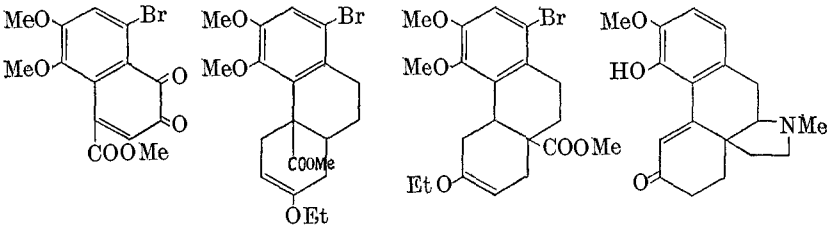


[CXIX]

The 1:2-naphthoquinone derivatives [CXVIII, R = $CH_2\phi$] and [CXVIII, R = $CH(COOEt)_2$] were likewise converted to [CXIX, R = $CH_2\phi$] and [CXIX, R = $CH(COOEt)_2$], but as the yields were poor and the starting materials sensitive and difficult to prepare, these reactions were not investigated further [38].

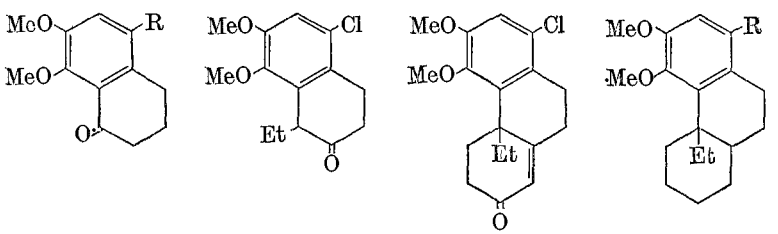
After a preliminary investigation [39] addition of 2-ethoxybutadiene to [CXX] was found to give [CXXI], not the corresponding 6-ethoxy compound. This was proved by submitting the product of interaction of 6-ethoxybutadiene and methyl 3:4-dihydro-α-naphthoate to hydrolysis, treatment with methylmagnesium iodide, and dehydrogenation, when 2-methylphenanthrene was obtained. Presumably the addition of 6-ethoxybutadiene to methyl 3:4-dihydro-7:8-dimethoxy-β-naphthoate would give [CXXII], the hydrolysis of which would afford a compound theoretically accessible by the degradation of metathebainone [CXXIII] [40].

A different approach to the problem of morphine synthesis was made by Ghosh and Robinson [41], who built up the hydrogenated-phenanthrene nucleus from a β-tetralone by the now familiar addition of a Mannich base methiodide. The tetralone [CXXIV, R = Cl] was con-



[CXX] [CXXI] [CXXII] [CXXIII]

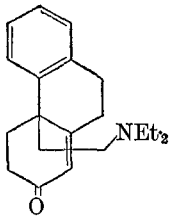
verted to [CXXV] by condensation with ethylmagnesium iodide, dehydration, and oxidation, and the product condensed with the methiodide of diethylaminobutanone to give [CXXVI], catalytic and Clemmensen reduction of which gave [CXXVII, R = Cl]. In the same way [CXXVII, R = H] was prepared as an oil [41], presumably a mixture of isomers, as this compound has recently been obtained as a crystalline solid by the degradation of thebaine [42].



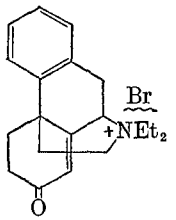
[CXXIV] [CXXV] [CXXVI] [CXXVII]

An attempt has been made to synthesize the morphinane ring-system in this way, and 1-(β-diethylaminoethyl)-2-keto-1:2:3:4-tetrahydronaphthalene was converted to [CXXVIII] by condensation with the appropriate Mannich base methiodide, the product brominated with N-bromosuccinimide, and finally converted to the quaternary salt [CXXIX]. Work on the corresponding N-dimethyl series was abandoned when it was found impossible to obtain the requisite substituted β-tetralone in a state even approaching purity. The synthesis of [CXXX] has been accomplished by the same method, its production being accompanied by the production of [CXXXI] as a result of further ring-extension [43].

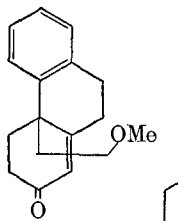
The method of preparing the meta-bridged ring-system in [CXXIX] was earlier discovered by Barltrop [44], who alkylated 2-carbethoxy-*cyclo*hexanone with β-diethylaminoethyl chloride, brominated the resulting [CXXXII] and heated the product, in this way obtaining ethyl 9-keto-2-ethylmorphan-5-carboxylate ethobromide [CXXXIII]. 9-Keto-5-methyl-2-ethyl-6:7-benzomorphan ethobromide [CXXXIV] was prepared in a similar way from [CXXXV].



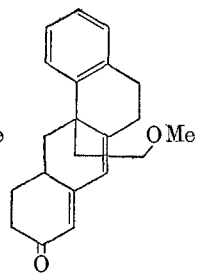
[CXXVIII]



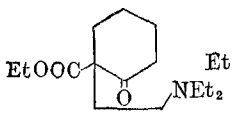
[CXXIX]



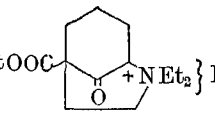
[CXXX]



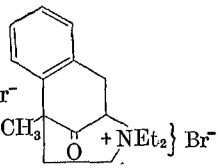
[CXXXI]



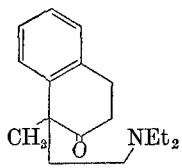
[CXXXII]



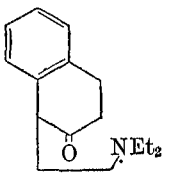
[CXXXIII]



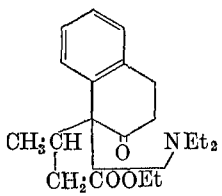
[CXXXIV]



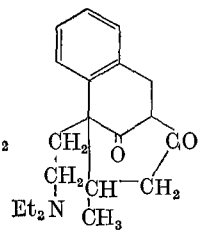
[CXXXV]



[CXXXVI]



[CXXXVII]



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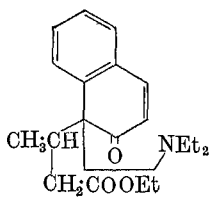
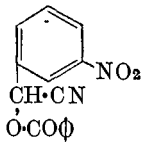


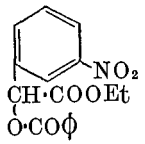
[CXXXIX]

Treatment of [CXXXVI] with ethyl crotonate and sodium afforded a mixture of [CXXXVII] and [CXXXVIII]. When an attempt was made to close the morphan ring in [CXXXVII] by bromination and treatment with alkali, only a small amount of a salt, apparently vinyldiethylamine hydrobromide, was obtained. This presumably arose from loss of hydrogen bromide from the brominated tetralone giving [CXXXIX], in which the tendency to become fully aromatic is so great that extrusion of the side-chain ensues [44]. (Cf. the loss of the side-chain during the degradation of certain derivatives of codeine and thebaine.)

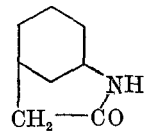
The parent base, morphan, has been synthesized as follows. Condensation of *m*-nitrobenzaldehyde with benzoyl chloride and sodium cyanide yielded [CXL], which was converted to [CXLI] and hydrogenated over Raney nickel at 200° C. to give [CXLII]; the latter was then reduced to morphan [CXLIII] with hydrogen and copper chromite [45]. Morphan may be more simply prepared by the hydrogenation of ethyl *m*-nitrophenylacetate over platinum oxide, followed by reduction of the [CXLII] so formed by lithium aluminium hydride [46].



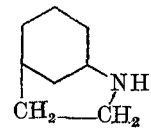
[CXL]



[CXLI]

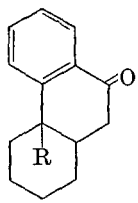


[CXLII]

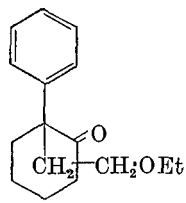


[CXLIII]

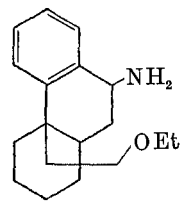
Newman and Farbman [47] submitted 2-phenyl-2-methyl-*cyclo*hexanone to the Reformatsky reaction, dehydration, reduction, and cyclization to obtain [CXLIV, R = Me], and [CXLIV, R = $CH_2 \cdot CH_2 \cdot OEt$] was prepared similarly from [CXLV] [48]. Reduction of the oxime of [CXLIV, R = $CH_2 \cdot CH_2 \cdot OEt$] afforded [CXLVI], the OEt group of which was replaced by Br and the product cyclized to [CXLVII], though the structure of this was not conclusively established [48].



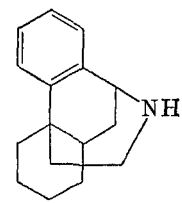
[CXLIV]



[CXLV]



[CXLVI]



[CXLVII]

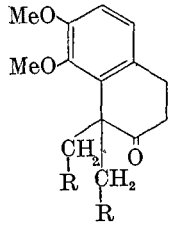
Other attempts at the synthesis of possible degradation products of morphine have been made by Ganguly [49], who prepared 13-methyl-octahydrophenanthrene-10-carboxylic acid, and by Sengupta, Ganguly, and Banerjee [50], who synthesized a hydrogenated phenanthrylene oxide.

Soffer and his co-workers, having developed a method for preparing 2-keto-7:8-dimethoxy-1:2:3:4-tetrahydronaphthalene [51], converted this compound to [CXLVIII, R = COOMe], [CXLVIII, R = $CH_2 \cdot COOMe$], [CXLVIII, R = CN], and [CXLVIII, R = H]. Hydrolysis of [CXLVIII, R = COOMe] gave [CXLVIII, R = COOH] which has only a transient existence as the free acid, being stable only as the ketone hydrate lactone [CXLIX]. The latter is stable to Clemmensen reduction and to condensation with mercaptans, but is reduced to [CL] by the Wolf–Kishner method. These reactions are intended as a basis for a synthesis of the morphine ring-system [52].

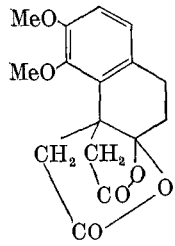
Sargent and Small [42, 53] report the successful degradation of thebaine to an optically active substance, probably [CLI, $R_1 = R_2 = Et$] or [CLI, $R_1 = Me$, $R_2 = Pr$], both of which are being synthesized for comparison.

Barltrop and Nicholson [54] have utilized the fact that Grignard reagents add to ethyl *cyclo*hexylidenecyanoacetate [55] to prepare [CLII, R = H] and [CLII, R = COOEt], the first of which can be con-

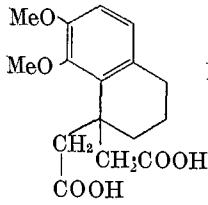
verted to [CLIII], which can be reduced to [CLIV]. Similarly [CLV] has been prepared in poor yield [54].



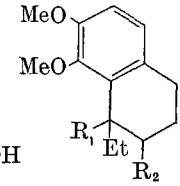
[CXLVIII]



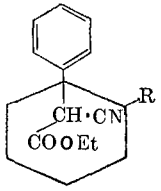
[CXLIX]



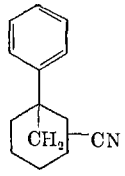
[CL]



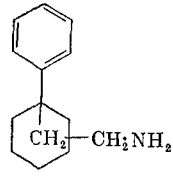
[CLI]



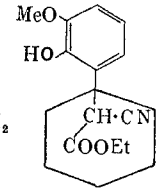
[CLII]



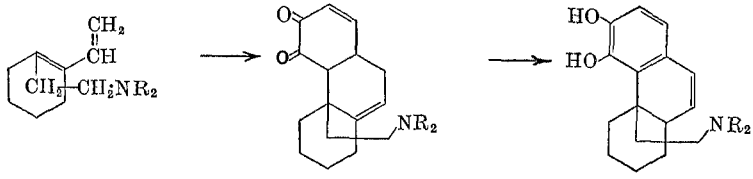
[CLIII]



[CLIV]

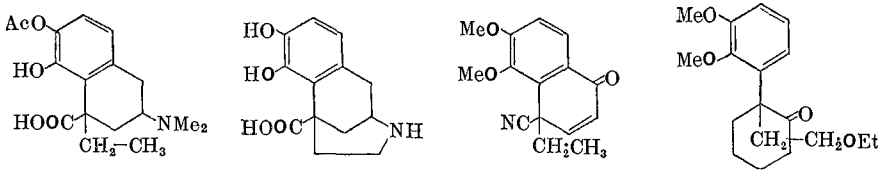


[CLV]



[CLVI] [CLVII] [CLVIII]

Unsuccessful attempts have been made to synthesize the morphine skeleton with the correct orientation of oxygen substituents in the aromatic nucleus by the Diels–Alder addition of a diene such as [CLVI] to *o*-benzoquinone to give [CLVII] and finally [CLVIII]; the requisite dienes have not so far been prepared [56].



[CLIX] [CLX] [CLXI] [CLXII]

Mention must finally be made of the work of Horning and his collaborators [57–61], who have synthesized many compounds, such as [CLIX], [CLX], [CLXI], and [CXLII], that have parts of the morphine

skeleton, and of Koelsch [62–63], who has made unsuccessful attempts to apply the Michael addition reaction to morphine synthesis.

An excellent review on synthetic approaches to the morphine structure has recently been published [64].

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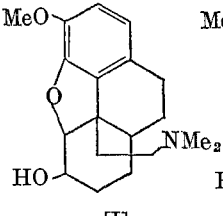
APPENDIX

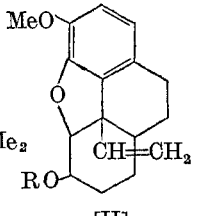
ADDITION TO CHAPTER VI

It was shown in Chapter VI that the degradation of the methohydroxides of dihydrocodeine methine and α-tetrahydrocodeimethine proceeds with the production, in addition to the simple nitrogen-free products, of substances having undergone methylation at the 6—OH group. It has since been shown that the degradation of γ-tetrahydrocodeimethine [I] gives also a nitrogen-free compound in which cyclization has occurred between the 6—OH group and the residue of the C-13 side-chain [1].

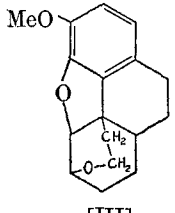
The products of dry-distillation of γ-tetrahydrocodeimethine methohydroxide were separated into the following: 6-γ-hydroxy-13-vinyloctahydromethylmorphenol [II, R = H]; 6-γ-methoxy-13-vinyloctahydromethylmorphenol [II, R = CH_3] and, after removal of olefinic matter by osmium tetroxide oxidation, 6-codiran [III]. No such cyclic ether could be isolated from the degradation products obtained from α-tetrahydrocodeimethine and the formation of such a compound during the degradation of γ-tetrahydrocodeimethine allegedly shows that in isocodeine the ethanamine chain at C-14 and the hydroxyl group at C-6 are arranged on the same side of ring C [1]. Hydrogenation of [II, R = CH_3] gave the 13-ethyl compound.



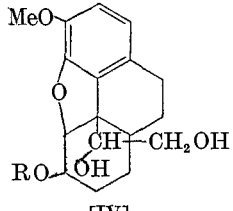
[I]



[II]



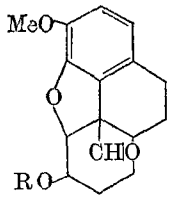
[III]



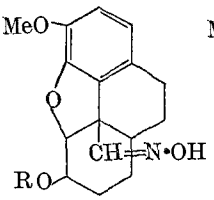
[IV]

Further degradation of [II, R = H and R = CH_3] has been achieved as follows. Oxidation of [II, R = H] with osmium tetroxide afforded 6-γ-hydroxy-13-(α:β-dihydroxyethyl)-octahydromethylmorphenol [IV, R = H] which was converted to 6-γ-hydroxy-13-aldehydooctahydromethylmorphenol [V, R = H], which resisted all attempts at direct oxidation to the acid. However the oxime [VI, R = H] was dehydrated to 6-γ-acetoxy-13-cyano-octahydromethylmorphenol [VII, R = Ac] hydrolysis of which afforded 6-γ-hydroxy-13-carboxyoctahydromethylmorphenol [VIII, R = H]. This sequence of reactions was repeated with [II, R = CH_3] giving [IV, R = CH_3]–[VI, R = CH_3] and with 6-α-hydroxy- and 6-α-methoxy-13-vinyloctahydromethylmorphenol obtained from α-tetrahydrocodeimethine. [VIII, R = H] could not be lactonized.

The preparation of 6-γ-hydroxy-13-vinyloctahydromethylmorphenol [II, R = H] was effected very conveniently from dihydrothebaine dihydromethine [IX] as follows. Hofmann degradation afforded [X] hydrolysis of which gave [XI] and the latter gave a mixture of α and γ [II, R = H] containing 52 per



[V]



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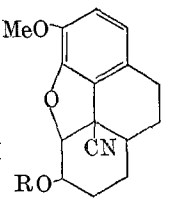
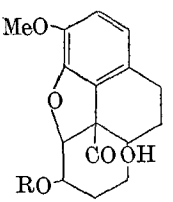
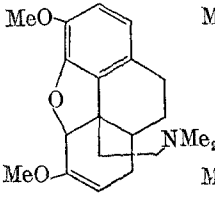


[VII]



[VIII]

cent. γ on reduction with aluminium *iso*propoxide. As dihydrocodeine can be readily oxidized by benzophenone and potassium *tert.* butoxide whilst dihydroisocodeine is resistant to oxidation under such conditions the α isomer of [II, R = H] was removed from the reaction mixture by oxidation back to [XI] [1].



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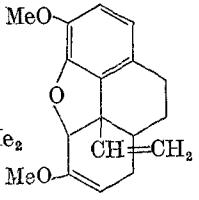
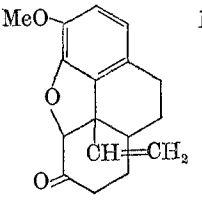
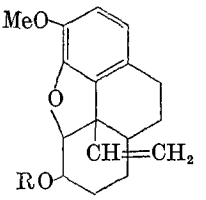


[X]

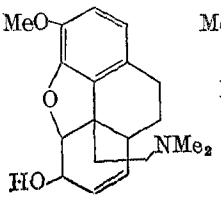


[XI]



[II]

Codeine dihydromethine [XII] has now been prepared by the sodium-ammonia reduction of codeine methiodide, together with dihydrodesoxy-codeine-C dihydromethine [XIII]. Both [XII] and [XIII] result from the sodium and liquid ammonia reduction of α-codeimethine [XIV] [2] (cf. p. 106). The sodium and liquid ammonia reduction of dihydrocodeine methiodide affords α-tetrahydrocodeimethine, and the reduction of β-codeimethine [XV] yields neopine dihydromethine [XVI]. When the methiodide of the latter is heated with sodium *cyclo*hexyloxide in *cyclo*hexanol a mixture of methyl-morphenol [XVII] and (+)-6-hydroxy-3-methoxy-5:6:7:8:9:10-hexahydro-phenanthrylene-4:5-oxide [XVIII] is obtained. The latter structure is assigned to the product on account of the close resemblance of its ultra-violet absorption spectrum to that of α-codeimethine. This represents a new type of degradation with hydrolytic scission of the side-chain [2]. Metathebainone methine has also been degraded in this way [2].



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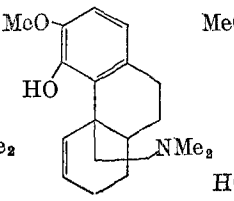

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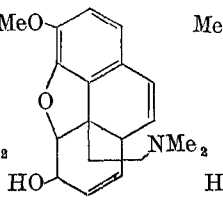

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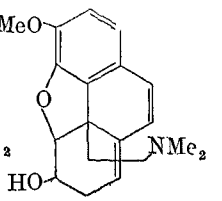

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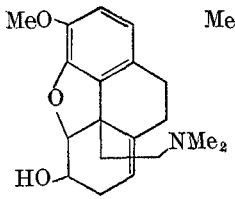

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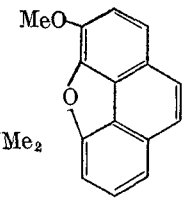
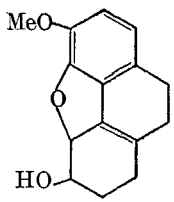


[XVII]



[XVIII]

Compound	*m.p. °C.*	*Solvent for recrystn.*	*Crystal form*	*Specific rotation*	*Temp.*	*Solvent*	*Refs.*
6-α-hydroxy-13-vinyloctahydromethylmorphenol	..	..	oil	+2·6	25	EtOH	1
6-α-methoxy-13-vinyloctahydromethylmorphenol	57–59	50% EtOH	..	+19·2	25	EtOH	1
6-γ-hydroxy-13-vinyloctahydromethylmorphenol	..	..	oil	..	..	..	..
— *p*-phenylbenzoate	117–119	EtOH	..	−171·0	20	dioxane	1
6-γ-methoxy-13-vinyloctahydromethylmorphenol	73·5–75	H_2O+ EtOH	..	+14·1	21	dioxane	1
6-codiran	88–90	pentane	..	+17·0	25	EtOH	1
6-γ-methoxy-13-ethyloctahydromethylmorphenol	..	..	oil	..	..	..	1
6-α-hydroxy-13-(α:β-dihydroxyethyl)-octahydromethylmorphenol	212–214	EtOH	..	−70·2	25	dioxane	1
6-γ-hydroxy-13-(α:β-dihydroxyethyl)-octahydromethylmorphenol	151–153	$CHCl_3$	..	−63·0	19	EtOH	1
6-α-methoxy-13-(α:β-dihydroxyethyl)-octahydromethylmorphenol	..	not analysed			..	..	1
6-γ-methoxy-13-(α:β-dihydroxyethyl)-octahydromethylmorphenol	155–157	H_2O	..	−53·5	21	dioxane	1
6-α-hydroxy-13-aldehydoöctahydromethylmorphenol oxime	131–132	benzene+ pentane	..	+13·9	26	EtOH	1
6-γ-hydroxy-13-aldehydoöctahydromethylmorphenol oxime	152–153	benzene	..	−2·6	25	EtOH	1
6-α-methoxy-13-aldehydoöctahydromethylmorphenol oxime	118–120	benzene+ pentane	..	+8·7	25	EtOH	1
6-γ-methoxy-13-aldehydoöctahydromethylmorphenol	105–107	60% EtOH	..	−9 9	26	EtOH	1
— oxime	148–149	EtOH	..	+25·4	25	EtOH	1
— semicarbazone	193–195	*n*-propanol	..	+28·6	26	EtOH	1
6-α-acetoxy-13-cyanoöctahydromethylmorphenol	131–133	H_2O+ EtOH	..	+49·6	26	EtOH	1
6-γ-acetoxy-13-cyanoöctahydromethylmorphenol	120–122	H_2O+ EtOH	..	+37·5	26	EtOH	1
6-α-methoxy-13-cyanoöctahydromethylmorphenol	115–117	Benzene+ pentane	..	..	.	..	1
6-α-hydroxy-13-carboxyoctahydromethylmorphenol	194–195	H_2O	..	+33·6	26	EtOH	1
6-γ-hydroxy-13-carboxyoctahydromethylmorphenol	194–196	benzene+ EtOH	..	+33·6	25	EtOH	1
6-α-methoxy-13-carboxyoctahydromethylmorphenol	129–131	benzene+ hexane	..	+107·0	25	benzene	1
γ-tetrahydrocodeimethine methyl ether	..	..	oil	−15·3	21	EtOH	1
— perchlorate	229–231	EtOH	..	−19·0	21	acetone	1
— methiodide	261·5–263	EtOH	..	−35·8	21	H_2O	1
p-phenylbenzoyl-γ-tetrahydrocodeimethine	c. 80 and 127–128	..	..	−132·7	20	dioxane	1
6-keto-13-vinyloctahydromethylmorphenol	125–127	..	..	−23·8	25	EtOH	1
(+)-6-hydroxy-3-methoxy-5:6:7:8:9:10-hexahydrophenanthrylene-4:5-oxide	..	..	oil	Strongly dextrorotatory	.	$CHCl_3$	2

ADDITION TO CHAPTER VII

TREATMENT of neopine hydrobromide in aqueous formic acid with hydrogen peroxide affords 1-bromoneopine, which can be degraded to 1-bromo-β-codeimethine [2].

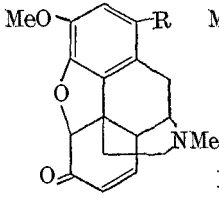
Compound	m.p. °C.	Solvent for recrystn.	Crystal form	Specific rotation	Temp.	Solvent	Refs.
1-bromoneopine	174	60% EtOH	prisms	−42·1	18	EtOH	2
— acid tartrate	243d.	96% EtOH	prisms	0	18	H_2O	2
— methiodide	225	65% EtOH	prisms	0	18	H_2O	2
1-bromo-β-codeimethine	180	60% EtOH	plates	+193	18	$CHCl_3$	2

ADDITION TO CHAPTER IX

DIHYDRODESOXYCODEINE-C dihydromethine [XIII] has been prepared by the sodium and liquid ammonia reduction of α-codeimethine [XIV] [2].

ADDITION TO CHAPTER X

CODEINONE and 1-bromocodeinone [XIX, R = H] and [XIX, R = Br] have been prepared by the Oppenauer oxidation of codeine [XX, R = H] and 1-bromocodeine [XX, R = Br] respectively using potassium *t*-butoxide and benzophenone. On reduction with lithium aluminium hydride these two ketones are converted into codeine [3].



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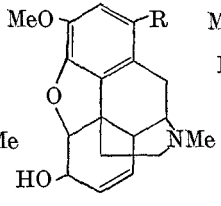
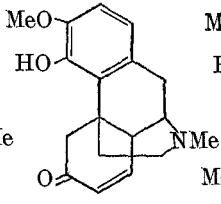
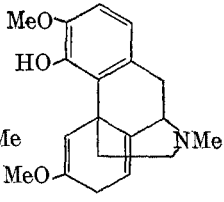


[XX]



[XXI]



[XXII]

ADDITION TO CHAPTER XV

FOLLOWING the epimerization (at C-14) of 1-bromo-β-thebainone-A 2:4-dinitrophenylhydrazone to 1-bromothebainone-A 2:4-dinitrophenylhydrazone [3] (see Chap. XXVIII), it has been shown that in acetic acid or sodium ethoxide solution β-thebainone-A is converted into an equilibrium mixture of β-thebainone-A and thebainone-A [XXI], the equilibrium favouring the latter ketone. Utilizing this reaction a method has been developed for the preparation of thebainone-A in good yield from dihydrothebaine-φ [XXII] [4].

Compound	m.p. °C.	Specific rotation	Temp.	Solvent	Refs.
1-bromothebainone-A	198·5–199·5	−74·0	32	$CHCl_3$	3
— 2:4-dinitrophenylhydrazone	207–208	−1307·0	27	$CHCl_3$	3
β-dihydrothebainol	165·5–166·5	..	..	..	3
— methiodide	266–268	..	..	..	3
— 4-methyl ether	152–153	..	..	..	3
— 4-methyl ether methiodide	243–244	..	..	..	3
d-β-dihydrodesoxycodeine-B methyl ether 2 forms	43·5–44 / 57·5–58	+80·0	27	EtOH	3
— L(+)-dibenzoyltartrate	162·5–163	+44·5	27	$CHCl_3$	3
— picrate	230–231	..	..	..	3
l-β-dihydrodesoxycodeine-B methyl ether D(−)-dibenzoyltartrate	161·5–162	−44·0	..	..	3
dl-β-dihydrodesoxycodeine-B methyl other dibenzoylracemate	182	..	..	..	3
1-bromocodeinone	202·5–203·5	−164·0	32	$CHCl_3$	3
— 2:4-dinitrophenylhydrazone	224–225	−1940·0	27	$CHCl_3$	3

ADDITION TO CHAPTER XXI

THE 'tetrahydro-thebaine-quinone' reported on p. 291 has been shown to be in fact dihydro-thebaine-quinone in which the unsaturated ketone system has suffered saturation. It is also clear from infra-red spectral measurements that ethyl thebaine-maleate suffers no reduction on hydrogenation, contrary to the statement on p. 290 [2].

ADDITION TO CHAPTER XXVII

ELIMINATION of the side-chain in the morphine series has now been accomplished without the production of a fully-aromatic phenanthrene derivative. The degradation of neopine dihydromethine [XVI] by heating the methiodide with sodium *cyclo*hexyloxide in boiling *cyclo*hexanol affords [XVIII] [2] (see above addition to Chap. VI).

ADDITION TO CHAPTER XXVIII

AN oxidation theory of the biogenesis of thebaine was briefly advanced by Robinson in 1948 and reference was made to the formation of bis-nor-laudanosine alkaloids such as oxyacanthine as affording 'some help in regard to the nuclear oxidations required for the above hypothesis'. Robinson added, 'The formation of such diphenyl ethers is clearly an oxidative process; it can of course be imitated in the laboratory in various ways on much simpler substances' [5]. This discussion of the problem pre-dates the more elaborate theory outlined by Schöpf.

Fig. 1 shows a synthetic approach to the morphine structure made by Ginsburg, the correct stereo-chemical arrangement of the rings being obtained. The same synthesis is being carried out in the 3:4-dimethoxy series, the goal being the synthesis of dihydrothebainone.

STEREO-CHEMISTRY

Rapoport has recently completed the study of the arrangement of groups at the asymmetric centres in the morphine group. Having already settled the arrangement at C-5 and C-6 (see the ozonolysis of codeine and isocodeine, Chapter IV) and at C-6 and C-13 (see above addition to Chapter VI) recent work has shown the arrangement of the side-chain at C-13 and the hydrogen atom at C-14 as being *cis* relative to rings B and C in the normal series and *trans* in the β- (or epi) series, (see Fig. 2).

In the normal series a cyclic imide was obtained as final product, but in the β- (or epi) series no such cyclic imide could be obtained.

The arrangement in morphine can thus possibly be represented as follows:

O—C-5 and C-6—OH; *cis* in codeine, *trans* in isocodeine;

C-6—OH and C-13—side-chain; *trans* in codeine, *cis* in isocodeine;

C-13—side-chain and C-14—H; *cis* in normal series, *trans* in β-series.

It will be noted that the formulae shown in Fig. 2, used by Rapoport, interpret thebenone as a six-membered ether, not as a five-membered ether as elsewhere formulated in this monograph.

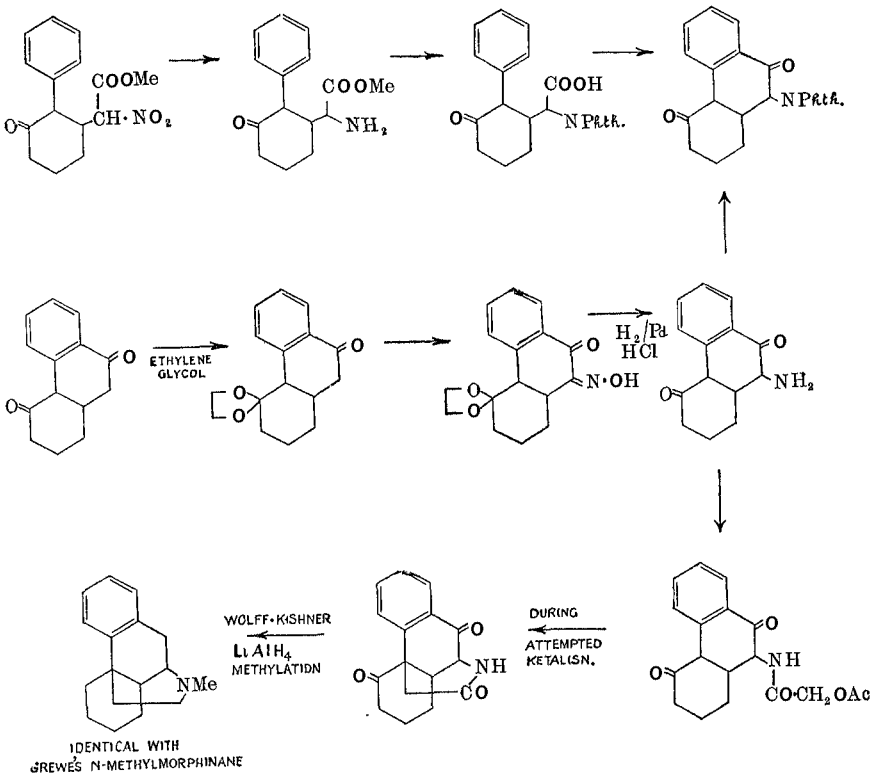

COOMe
CH·NO₂
COOMe
NH₂
COOH
NPhth.
NPhth.
O
ETHYLENE GLYCOL
H₂/Pd
HCl
N·OH
NH₂
NMe
WOLFF-KISHNER
LiAlH₄
METHYLATION
NH
CO
DURING
ATTEMPTED
KETALSN.
NH
CO·CH₂OAc
IDENTICAL WITH
GREWE'S N-METHYLMORPHINANE

FIG. 1.

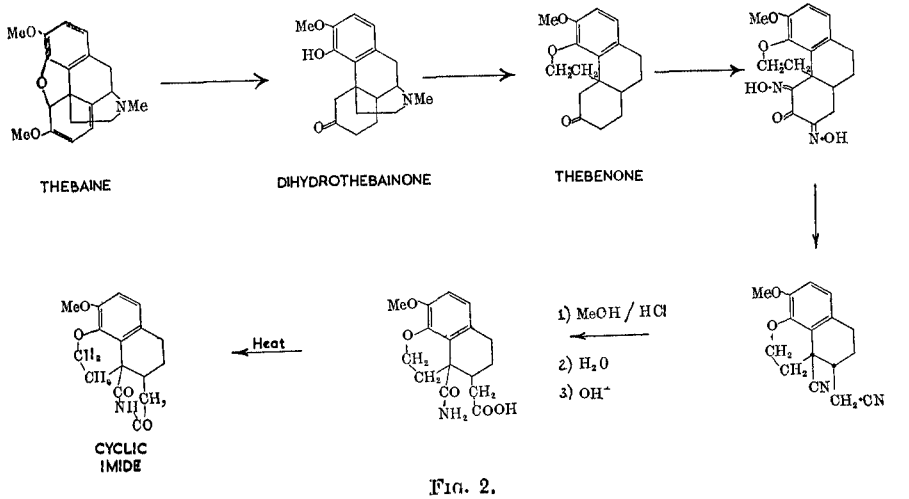

MeO
NMe
THEBAINE
HO
DIHYDROTHEBAINONE
CH₂CH₂
THEBENONE
HO·N
N·OH
Heat
CYCLIC
IMIDE
1) MeOH / HCl
2) H₂O
3) OH⁻
CH₂·CN

FIG. 2.

The five-membered structure, first suggested by Cahn (*J.C.S.*, 1926, 2562), appeared to be generally accepted at the outset of this work (e.g. Small, though interpreting thebenone as being a six-membered ether in 1939, [Small and Browning, *J. Org. Chem.*, 1939, **3**, 618] in 1947 was using a five-membered ether structure for this type of compound, Small, Sargent, and Bralley, *J. Org. Chem.*, 1947, **12**, 847). Accordingly, in the absence of evidence in favour of either structure the one commonly in use in 1950 was used throughout this monograph. It may be of interest to note that thebenol is generally assumed to have suffered cyclization at the carbon atom in the β-position relative to the eliminated nitrogen (see Chapter XXV).

It appears now that the six-membered ring structure has been revived and should it prove correct the thebenone type of formulae in this monograph will have to be read as six-membered ether structures. The necessity for this revision however remains to be demonstrated.

BIBLIOGRAPHY TO APPENDIX

1. Rapoport and Payne, *J.A.C.S.*, 1952, **74**, 2630.
2. Bentley and Thomas, Unpublished work.
3. Gates and Tschudi, *J.A.C.S.*, 1952, **74**, 1109.
4. —— and Helg, ibid. 1953, **75**, 379.
5. Robinson, *Journal of The Royal Society of Arts*, 1948, **96**, 795.

INDEX

Italics refer to physical properties given in tables. Heavy type refers to the principal discussion of a compound.