platelets, m.p. 266–267°, were obtained in the amount of 4.45 g. (82.8%). A mixed melting point with isolated kinetin gave no depression.

The synthetic product proved indistinguishable from isolated kinetin when examined in the following ways: paper chromatography in various solvent systems as described above, color test with cysteine and sulfuric acid,[19] ultraviolet spectrum in neutral, acidic and alkaline solutions, and infrared spectrum.

Furthermore, in the following biological tests, in which effects of kinetin have been observed, no differences could be detected between the activities of the isolated and synthetic products: Promotion of cell division in tobacco callus and other plant tissue cultures; induction (in combination with auxin, IAA) of cell division and continuous proliferation of tobacco pith tissue *in vitro;* promotion (in combination with adenine) of bud initiation and development in tobacco stem segment cultures; promotion (in combination with IAA) of root initiation and development on cuttings; promotion or inhibition, depending on the concentration, of seedling growth in nutrient solution cultures; stimulation of lettuce seed germination and the inhibition of cell enlargement in pea stem section tests.

Acknowledgments.—The authors gratefully acknowledge the help of R. M. Smith and R. A. Alberty in carrying out electrometric titrations, of N. S. Ling and R. M. Bock for electrometric titrations and ultraviolet spectra, of S. M. Aronovic for infrared spectra, and of K. F. Weinke for a Van Slyke determination. Most of the work of purification of coconut extracts was done by D. A. Buyske and J. R. Mauney. Furfurylamine was kindly provided by F. N. Peters, Quaker Oats Company, and 6-mercaptopurine by G. H. Hitchings, Wellcome Research Laboratories.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF ROCHESTER]

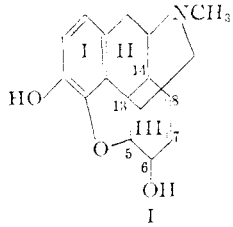
The Synthesis of Morphine

BY MARSHALL GATES AND GILG TSCHUDI

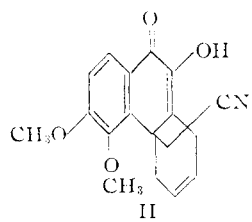
RECEIVED AUGUST 11, 1955

The completion of the first synthesis of morphine is described.

Morphine, the principal alkaloid of opium and the substance primarily responsible for its physiological effect, has attracted the attention of chemists for over one hundred and fifty years. Alkaloid chemistry may correctly be considered to have originated with Sertürner's[1] isolation of morphine from opium and his recognition of its basic character. Early analyses by Liebig, Dumas, Pelletier, Raoult and others serve to illustrate its intimate association with the development of the infant science of chemistry. An equally illustrious group of men contributed to structural studies during a later period, and in our time these structural studies, initiated by Hesse, Vongerichten, Knorr, Pschorr and Freund and carried on brilliantly by Speyer, von Braun, Wieland, Robinson and Schöpf, have culminated in Robinson's[2] proposal in 1925 of the correct structure for morphine (I). In this paper[3] we describe the completion of the first synthesis of morphine and therewith a complete confirmation of the Robinson formula.



I



II

The synthesis and proof of structure of 3,4-dimethoxy - 9,10 - dioxo - 13 - cyanomethyl - 5,8,9,-10,13,14-hexahydrophenanthrene (II) were described in an earlier paper.[4] This adduct on hydrogenation over copper chromite under relatively mild conditions (130°, 27 atm. of hydrogen) undergoes reductive cyclization in the manner observed earlier[5] in a model series to give the keto-lactam III in 50% yield. The weak basicity of this substance and its prominent bands at 5.93 and 6.03 μ in the infrared and at 281 mμ (log ϵ 4.16) in the ultraviolet are consistent with this formulation. The corresponding 6-chloro adduct can likewise be converted into IV, but the poor yields in this reaction and in the preceding Diels–Alder reactions[4] with chloroprene and with 2-ethoxybutadiene discouraged further work with these 6-substituted derivatives, and we were forced to rely on a later introduction of oxygen at C_6. The course of this reductive cyclization, which leads to a tetracyclic carbon–nitrogen skeleton stereoisomeric with that of the morphine alkaloids, is far from clear.[6]

The carbonyl group at C_{10} of III is readily removed by the Wolff–Kishner method. Under the conditions recommended by Huang-Minlon[7] extensive demethylation takes place and the yields of the lactam V after remethylation do not exceed 56%. We find, however, that this reduction

(1) F. W. Sertürner, *Trommsdorf's Journal der Pharmazie*, **13**, 1, 234 (1805); *Ann. chim. phys.*, [2] **5**, 21 (1817).

(2) J. M. Gulland and R. Robinson, *Mem. Proc. Manchester Lit. Phil. Soc.*, **69**, 79 (1925).

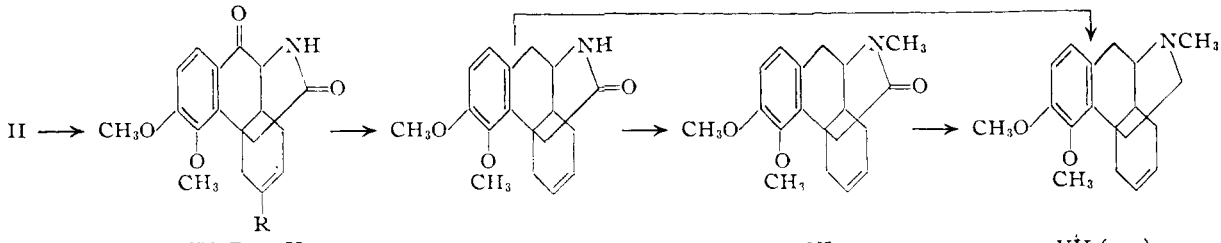
(3) Preliminary accounts of this work have appeared, in THIS JOURNAL, **72**, 4839 (1950), and **74**, 1109 (1952).

(4) M. Gates, *ibid.*, **72**, 228 (1950).

(5) M. Gates, R. B. Woodward, W. F. Newhall and R. Künzli, *ibid.*, **72**, 1141 (1950).

(6) It may be pointed out that if hydrogen is added to the 9,14-double bond of the enolic adduct on the side opposite the cyanomethyl group at C_{13}, the observed *trans* (*vide infra*) ring juncture at C_{13}–C_{14} results. Alkylation of the nitrile group by C_9 would then yield the lactam, either by a process analogous to that observed by Ritter (J. J. Ritter and P. P. Minieri, *ibid.*, **70**, 4045 (1948), and later papers in this series) or by rearrangement of an iminoether formed between the nitrile and the hydroxyl at C_9. It is a pleasure to acknowledge a number of very helpful discussions of this reaction with Professor R. B. Woodward, who first correctly inferred the structure of the keto-lactam resulting from this reductive cyclization in the model series.[5]

(7) Huang-Minlon, *ibid.*, **68**, 2487 (1946).



III, R = H
IV, R = Cl

V VI VII (*rac.*)

proceeds rapidly at temperatures as low as 150–155°[8] and that under these conditions the reaction is extraordinarily clean-cut, no demethylation takes place, and yields above 90% of V are readily obtained. That the carbonyl group conjugated with the aromatic ring has been lost is clearly shown by the loss of the infrared peak associated with this group (5.93 μ in its precursor III) and by the lowered intensity of the ultraviolet max. at 282 mμ, whose log ϵ 3.17 corresponds to the simple veratrole chromophore.[9] The strong band at 6.05 μ in the infrared, associated with the amide carbonyl, is still present.

In our earlier work[3] this lactam was reduced directly with lithium aluminum hydride and the resulting cyclic secondary amine methylated by the formaldehyde–formic acid method to yield *rac*-β-Δ^6-dihydrodesoxycodeine methyl ether (VII). Much more satisfactory is the conversion of the lactam V by means of sodium hydride and methyl iodide to the N-methyl lactam VI followed by reduction of this substance to VII by lithium aluminum hydride.[10] The N-methyl lactam is easily isolated and purified, but it is convenient to carry out the reduction on the crude methylation product, and under these conditions VII is obtained as its picrate in 87.5% yield from V. The infrared spectrum of VII, m.p. 83–84°, in chloroform is indistinguishable from that of natural *d*-β-Δ^6-dihydrodesoxycodeine methyl ether,[11] m.p. 43–44° or 57.5–58° (dimorphic) obtained from β-dihydrothebainone by degradation as described below.

Resolution of VII into its enantiomorphs was easily effected by crystallization with the enantiomorphic dibenzoyltartaric acids. *d*-β-Δ^6-Dihydrodesoxycodeine methyl ether dibenzoyl-L(+)-tartrate and *l*-β-Δ^6-dihydrodesoxycodeine methyl ether dibenzoyl-D(−)-tartrate form an enantiomorphic pair each of which crystallizes beautifully and is of low solubility, whereas the diastereomeric salts of *d*-base D(−)-acid and *l*-base L(+)-acid could not be obtained crystalline. Yields above 80% are readily obtained in the resolution. Recovery of the synthetic *d*-base from its salt gave material exhibiting the same dimorphic melting points (44° and 58°) as natural *d*-β-Δ^6-dihydrodesoxycodeine methyl ether. These melting points were undepressed on mixture with the natural *d*-base and the infrared spectra of the bases are indistinguishable. The identity of synthetic and natural *d*-β-Δ^6-dihydrodesoxycodeine methyl ethers was confirmed by comparison of their methiodides, picrates and dibenzoyl-L(+)-tartrates, whose melting points in each case were the same and showed no depression on mixing. Finally, a very sensitive criterion of identity was provided by the racemization of natural *d*-base and synthetic *l*-base to yield *rac*-β-Δ^6-dihydrodesoxycodeine methyl ether of m.p. 82.5–84°, undepressed by admixture of the purely synthetic racemic base. Similar racemizations were carried out on synthetic *l*- and natural *d*-picrates and dibenzoyl D(−)-tartrate and L(+)-tartrate, and in each case the racemate was identified with the purely synthetic racemate.

This complete identification of synthetic and natural *d*-β-Δ^6-dihydrodesoxycodeine methyl ether provides the first unequivocal proof that the point of attachment of the ethanamine chain in the morphine alkaloids is at C_{13} as postulated by Robinson.[2,12] The identification also provided a welcome relief from the necessity of carrying through the long and arduous synthesis and resolution of this substance, since now material from natural sources could be used in further steps.

The natural β-Δ^6-dihydrodesoxycodeine methyl ether (XIII) required for comparison and for further synthetic steps was prepared from β-thebainone (VIII).[13] Catalytic reduction of β-thebainone as its perchlorate over Adams catalyst produces β-dihydrothebainol[14] (IX) in 60% yield, along with small amounts of β-tetrahydrodesoxycodeine (X),

(8) We suspect that the conditions recommended by Huang-Minlon are too drastic in many cases and that lower temperatures should in general be used.

(9) R. O. Herzog and A. Hillmer, *Ber.*, **64B**, 1288 (1931). See also G. Stork, THIS JOURNAL, **74**, 768 (1952).

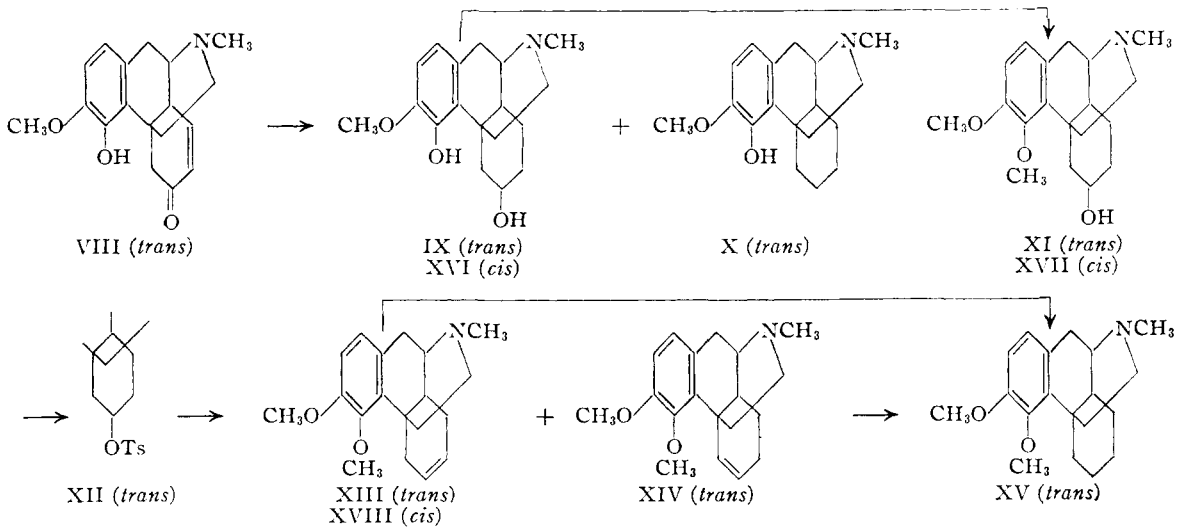
(10) This procedure, which was developed for the preparation of Δ^6-dehydro-N-methylisomorphinane from the corresponding lactam by Dr. Horace Brown of Merck and Co., Inc., to whom we are greatly indebted for its description, is decidedly superior in both yield and quality of product to that first used by us. The lithium aluminum hydride step is much shorter and the reaction mixture is homogeneous throughout, whereas much insoluble complex is present during the reduction of V with lithium aluminum hydride.

(11) This substance is epimeric at C_{14} with morphine and thus has a *trans* fusion of rings II and III. Substances in this stereochemical series have been distinguished from their natural C_{14} epimers by the prefix "β" (L. F. Small and G. L. Browning, Jr., *J. Org. Chem.*, **3**, 618 (1939)) and the prefix "epi" (C. Schöpf and F. Borkowsky, *Ann.*, **458**, 148 (1927); H. Rapoport and J. B. Lavigne, THIS JOURNAL, **75**, 5329 (1953)). We have followed Small's nomenclature. In this paper the use of the terms "trans" and "cis," unless otherwise qualified, refer to the fusion of rings II and III. NOTE ADDED IN PROOF.—A definitive proof of the configuration at C_{13} and C_{14} of the morphine alkaloids as well as their absolute configuration has recently been described by J. Kalvoda, P. Buchschacher and O. Jeger, *Helv. Chim. Acta*, **38**, 1847 (1955).

(12) Grewe's brilliant synthesis of tetrahydrodesoxycodeine (*Ann.*, **564**, 161 (1949)) does not offer conclusive proof of this point, since the step at which C_{13} is coupled to the aromatic ring is an acid-catalyzed alkylation, a reaction from which the possibility of rearrangement cannot be excluded; *cf.* K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Oxford Press, New York, N. Y., 1954, p. 402.

(13) L. F. Small and G. L. Browning, Jr., *J. Org. Chem.*, **3**, 618 (1939).

(14) The configuration of the hydroxyl at C_6 is presumably axial, *cf.* D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).



readily separated by making use of its insolubility in alkali. Its properties resemble those of its C_{14}-epimer tetrahydroxydesoxycodeine. The phenolic hydroxyl of IX can be methylated in 76% yield without quaternization of the tertiary amino group by the method of Rodionov[15] using trimethylphenylammonium ethoxide. The resulting methyl ether XI also results, along with its C_6-epimer, by reduction of β-dihydrothebainone methyl ether, prepared by methylation of β-dihydrothebainone,[13] with lithium aluminum hydride.

Dehydration of β-dihydrothebainol methyl ether (XI) to a mixture of β-Δ^5- and Δ^6-dihydrodesoxycodeines (XIV and XIII) was carried out in high yield by the action of boiling collidine on the tosylate XII. These olefins are very similar[16] but are readily separated by chromatography. The Δ^6-structure has been assigned to that (m.p. 44° and 58°, dimorphic, 50% from β-dihydrothebainol methyl ether) identical with synthetic *d*-β-Δ^6-dihydrodesoxycodeine methyl ether, the Δ^5-structure to the other, m.p. 78°[17] (27% from β-dihydrothebainol methyl ether). Each of these substances yields β-tetrahydrodesoxycodeine methyl ether (XV), m.p. 36.5–37.5°, on catalytic hydrogenation.

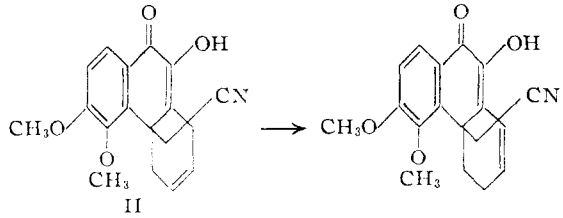
A similar scheme was used to prepare $\Delta^{5(\text{or } 6)}$-dihydrodesoxycodeine methyl ether (XVIII) (rings II/III *cis*) from dihydrothebainol[18] (XVI) for comparison with our synthetic base. In the *cis* series the detosylation appears to proceed largely in a single direction, since the final olefin was obtained in considerably higher yield as its very characteristic salt with fumaric acid, which crystallizes with 2 moles of base to 3 of acid, but we have no information on which to base an assignment of the position of the double bond. The infrared spectrum of this substance is similar to but easily distinguished from that of synthetic *d*-β-Δ^6-dihydrodesoxycodeine methyl ether.

Having established the identity of synthetic and natural β-Δ^6-dihydrodesoxycodeine methyl ether and assured ourselves of an adequate supply of this substance for further work, we turned to the introduction of oxygen at C_6. For this purpose, the double bond produced during the formation of ring III by the Diels–Alder reaction served as a convenient site of operations. A 6,7-epoxide XIX was produced in poor yield by the action of perbenzoic acid, but the action of lithium aluminum hydride on this epoxide gave a hydroxy compound not identical with either epimer (at C_6) of β-dihydrothebainol methyl ether and to which structure XX was accordingly assigned. The action of osmium tetroxide produced a *cis*-glycol XXI in fair yield, but attempts to convert this substance into a known substance bearing oxygen at C_6 by a variety of methods failed, as did similar attempts with the *trans*-glycol XXII, prepared in 71% yield by the action of performic acid on XIII.[19] Hydration with dilute sulfuric acid,

(15) W. Rodionov, *Bull. soc. chim.*, **39**, 305 (1926).

(16) They cannot be separated by crystallization, and mixtures of the bases, their picrates, or their dibenzoyl-L(+)-tartrates show no depression in melting point. Their methiodides, however, are quite dissimilar.

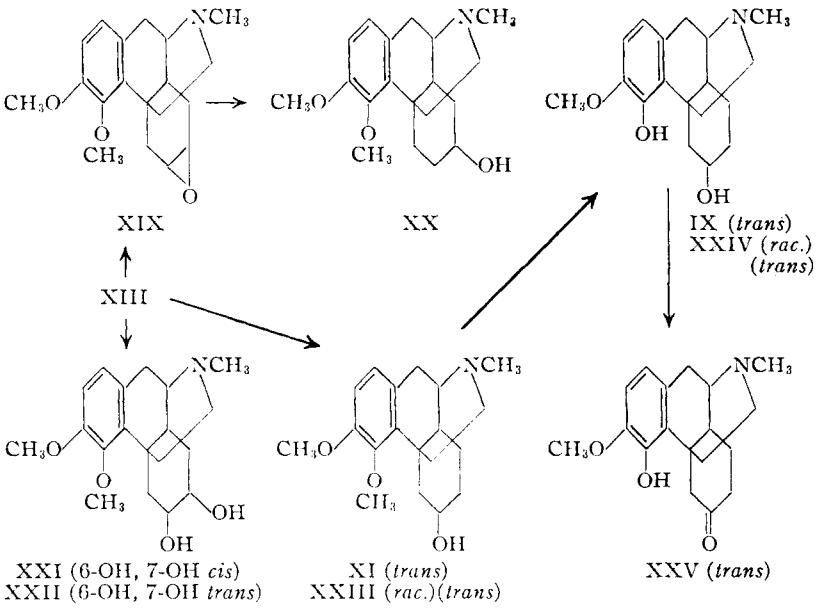
(17) The tosylate of β-dihydrothebainol methyl ether would be expected to give only Δ^5- or Δ^6-β-dihydrodesoxycodeine, whereas the synthetic scheme employed could give only Δ^6- or Δ^7-β-dihydrodesoxycodeine, the latter because of the admittedly unlikely possibility of the transformation



leading to an extension of the conjugated system. Identification of one of the substances from the degradation with the synthetic substance allows at the same time the elimination of the Δ^7-structure for the synthetic material and the correct assignment of the Δ^5- and Δ^6-structures to the degradation products.

(18) A. Skita, *Ber.*, **54**, 1560 (1921). The configuration of the hydroxyl at C_6 is presumably axial; *cf.* Barton, ref. 14.

(19) The action of performic acid according to the directions of D. Swern, *et al.* (THIS JOURNAL, **68**, 1504 (1946)) proceeds much more smoothly than epoxidation with perbenzoic acid, presumably because the higher acidity protects the tertiary amino group more adequately against N-oxide formation.



however, yields β-dihydrothebainol methyl ether[20] (XI) identical in m.p., mixed m.p., infrared spectrum, and m.p. and mixed m.p. of its methiodide with material produced from β-thebainone by hydrogenation and methylation. Yields up to 28% can be obtained if account is taken of recovered XIII. Small amounts of the 7-hydroxy compound XX are also produced. Using *rac*-β-Δ⁶-dihydrodesoxycodeine methyl ether (VII), *rac*-β-dihydrothebainol methyl ether (XXIII), m.p. 148.5–149.5°, whose infrared spectrum in chloroform is indistinguishable from that of natural β-dihydrothebainol methyl ether, is obtained.

Our original intention had been to cleave both ether groups of XI and to attempt a selective remethylation to IX, and some experiments along these lines were carried out. The action of pyridine hydrochloride,[21] however, not only cleaved both phenolic ether groups but also dehydrated ring III to give a substance $C_{17}H_{21}O_2N$, probably demethylated XIII or XIV. The observation (*vide supra*) that demethylation accompanies the Wolff–Kishner reduction of III was put to use, however, and conditions were found which allow the preparation of β-dihydrothebainol (IX) from its methyl ether XI in 54% yield. This cleavage with alkali is quite specific for the methoxyl at C_4, and although some completely cleaved material appears to be formed, we have never observed cleavage of the methoxyl at C_3 alone. The presence of a small amount of hydrazine hydrate serves as an effective antoxidant. Using *rac*-β-dihydrothebainol methyl ether (XXIII), *rac*-β-dihydrothebainol (XXIV) was likewise obtained. The infrared spectrum of this substance (m.p. 185–186°) in chloroform is indistinguishable from that of natural β-dihydrothebainol (m.p. 165.5–166°) in the same solvent. Experiments with racemic material were carried no further than this.

β-Dihydrothebainone (XXV), the first previously known substance to be encountered in this synthesis, is readily produced from IX in high yield (89%) as its perchlorate[13] by oxidation with the potassium *t*-butoxide–benzophenone system.[22]

Of the remaining transformations necessary to convert β-dihydrothebainone (XXV) to morphine, inversion at C_{14} to produce the *cis* fusion of rings II and III loomed large, and we undertook the introduction of α,β-unsaturation in XXV in the hope that equilibration at C_{14} would produce appreciable amounts of an α,β-unsaturated ketone of the *cis* series. When XXV is dibrominated and the resulting crude product treated with 2,4-dinitrophenylhydrazine, a monobromo-α,β-unsaturated ketone dinitrophenylhydrazone (XXVI) (λ_{max}^{chf} 379 mμ, log ε 4.49, $[\alpha]^{27}D$ −1307° (chf.))[23] is produced in 41% yield.[24] This substance also results from β-thebainone (VIII) (*trans*) *or from thebainone* (XXVII) (*cis*) by the action of 2,4-dinitrophenylhydrazine and bromination. Clearly epimerization at C_{14} has taken place in one of these transformations. That the stable dinitrophenylhydrazone has the *cis* configuration was easily shown by cleavage of XXVI with acetone and hydrochloric acid to the previously unknown 1-bromothebainone (XXVIII) (*cis*).[25] The identity of this ketone follows from its formation from thebainone[26] by bromination and from its hydrogenation in good yield over platinum to the known 1-bromodihydrothebainone (XXIX) (*cis*) and over

(20) The predominant production of β-dihydrothebainol methyl ether[14] in this hydration is in no way unexpected. The transition state can only assume the favored four-center planar configuration when the entering groups (H^+, H_2O) are axial–axial *trans*, leading to an axial hydroxyl (*cf.* Barton, ref. 14), and the field effect produced by the charge on the protonated tertiary amino group (in dilute sulfuric acid) clearly favors entry of the nucleophilic group at C_8 rather than C_7. Opening of the epoxide ring of XIX by lithium aluminum hydride is also favored in the axial–axial *trans* configuration of the transition state, suggesting as do the hydration results that XX has the 7-axial configuration of the hydroxyl.

(21) V. Prey, *Ber.*, **74**, 1219 (1941).

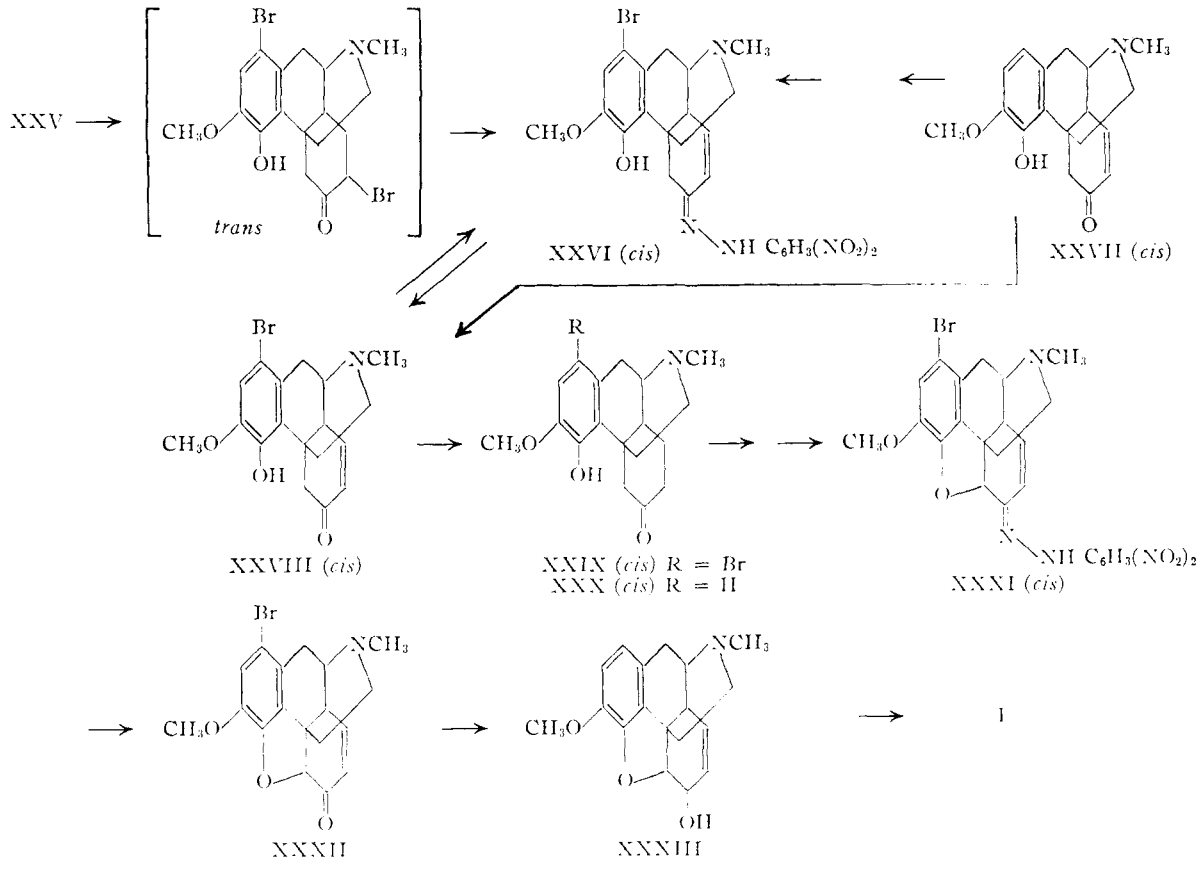
(22) R. B. Woodward, N. L. Wendler and F. V. Brutschy, THIS JOURNAL, **67**, 1425 (1945); H. Rapoport, *et al.*, *J. Org. Chem.*, **15**, 1103 (1950).

(23) The very high rotation of this substance was of great value in our work. No exception is yet known to the rule that dinitrophenylhydrazones in the *cis* series of the morphine alkaloids have abnormally high rotations (*cf.* THIS JOURNAL, **74**, 1109 (1952), **75**, 379 (1953)).

(24) This low yield suggests that an appreciable proportion of the bromine enters at C_8, and we have other results which support this supposition.

(25) The position of the bromine atom in 1-bromothebainone (and in 1-bromodihydrothebainone, 1-bromodihydrocodeinone and 1-bromocodeinone and their derivatives) can be assigned with certainty. 1-Bromocodeine,[14] from which 1-bromocodeinone can be obtained, has been degraded to 1-bromo-3,4-dimethoxyphenanthrene which has been synthesized by an unambiguous method (L. Small and S. G. Turnbull, THIS JOURNAL, **59**, 1541 (1937)). 1-Bromodihydrocodeinone and 1-bromodihydrothebainone have been interrelated by Schöpf,[31] and we have related the latter to 1-bromothebainone. The remaining link in this chain of transformations, the conversion of 1-bromocodeinone to 1-bromodihydrocodeinone, is described in the Experimental part of this paper.

(26) C. Schöpf and H. Hirsch, *Ann.*, **489**, 224 (1931).

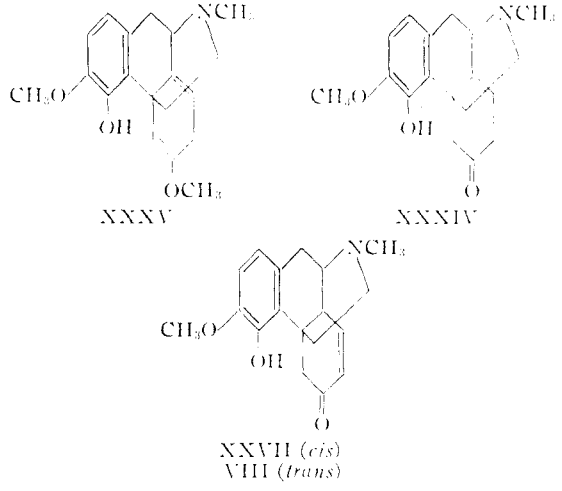


palladium to dihydrothebainone (XXX) (*cis*).[27]

Tribromination of β-dihydrothebainone (XXV) leads in high yield to a crystalline tribromo derivative whose carbonyl absorption in the infrared (5.78 mμ (1727 cm.$^{-1}$)) indicates that two of the bromine atoms occupy the 5- and 7-positions, respectively.[28] All attempts to produce α,β-unsaturation or oxide ring closure with this substance failed, although bromide ion can be removed in a variety of ways.

Closure of the oxide ring between C_4 and C_5 of 1-bromothebainone (XXVIII) would lead to 1-bromocodeinone (XXXII), a substance very closely related to codeine and morphine, and we have studied the bromination of XXVIII with this possibility in mind. A crystalline dibromothebainone probably carrying the second bromine either at C_5 or C_{14}[29] is readily produced, but we have been unable to convert it into XXXII by any of a variety of means. With some reluctance, we therefore turned to the reduction products of XXVIII, 1-bromodihydrothebainone (XXIX) and dihydrothebainone (XXX),[30] as intermediates to XXXII. Dibromination of XXIX (or tribromination of XXX)[31] followed by treatment with 2,4-

(27) The isomerization of *trans*- to *cis*-ketones in this series has been investigated thoroughly in the closely related β-thebainone–thebainone case, and the greater stability of the *cis* system has been demonstrated not only with the 2,4-dinitrophenylhydrazones but also with the free ketones, the latter in both acid and base; *cf.* M. Gates and R. Helg, THIS JOURNAL, **75**, 379 (1953). The three ketones thebainone-B (XXXIV) (K. W. Bentley and A. E. Wain, *J. Chem. Soc.*, 967 (1952)), β-thebainone (VIII) and thebainone (XXVII) form an



interesting series in which the rates of production by acid hydrolysis of phenolic dihydrothebaine (XXXV) are in the order XXXIV > VIII > XXVII, whereas their order of thermodynamic stability is XXVII > VIII > XXXIV.

(28) The parent 1-bromo-β-dihydrothebainone absorbs at 5.86 mμ (1702 cm.$^{-1}$) and the exaltation (25 cm.$^{-1}$) is thus more than once but less than twice that expected of an equatorial bromine (15–20 cm.$^{-1}$); R. N. Jones, *et al.*, THIS JOURNAL, **74**, 2828 (1952); E. J. Corey, *ibid.*, **75**, 2301, 3297 (1953). We interpret this as indicating equatorial bromine at positions 5 and 7, but with that at 5 less nearly coplanar with the carbonyl group than usual because of steric interference.

(29) C. Djerassi, *et al.*, *ibid.*, **72**, 4534 (1950).

(30) A second synthesis of dihydrothebainone has been reported recently by D. Elad and D. Ginsburg (*J. Chem. Soc.*, 3052 (1954)); Coupled with our conversion of dihydrothebainone to morphine, this constitutes a second synthesis of the latter.

(31) These experiments were, of course, suggested by the ring closures effected by C. Schöpf and T. Pfeifer, *Ann.*, **483**, 157 (1930); see also C. Schöpf, T. Pfeifer and H. Hirsch, *ibid.*, **492**, 213 (1932).

dinitrophenylhydrazine produces 1-bromocodeinone 2,4-dinitrophenylhydrazone (XXXI) in 26% yield,[32] and the parent ketone XXXII can be obtained in 27% yield by cleavage of this dinitrophenylhydrazone with acetone and hydrochloric acid. This cleavage is rendered difficult not only by the stability of the hydrazone toward cleavage but by the sensitivity of the resulting unsaturated ketone[33] to acids, and great care must be used to obtain even this yield. The 1-bromocodeinone so obtained is identical in all respects with that obtained from 1-bromocodeine[34] by Oppenauer oxidation.[35]

Energetic treatment of 1-bromocodeinone with lithium aluminum hydride leads, with loss of bromine and stereospecific[36] reduction of the carbonyl group, directly to codeine XXXIII in 65% yield. The cleavage of codeine to morphine has already been described by Rapoport and his coworkers,[37] and we have confirmed their report With this the first synthesis of morphine is complete.

We wish to acknowledge the generous financial help of Merck and Co., Inc., and The Research Corporation, as well as gifts of material through the courtesy of Drs. Karl Pfister and Max Tishler of Merck and Co., Inc., Drs. V. H. Wallingford, A. H. Homeyer and G. B. DeLaMater of the Mallinckrodt Chemical Works, Dr. Lyndon F. Small of the National Institutes of Health and Dr. R. B. Woodward of Harvard University. Stimulating discussions of many phases of this work with the above men and with Drs. Gilbert Stork and R. B. Turner and Professor Clemens Schöpf have aided us immensely.

Experimental

All melting points except those specifically noted are corrected. Analyses for the most part have been carried out by Miss Claire King, Miss Viola Williams and Miss Annette Smith. Most of the infrared spectra were determined by Mr. Carl Whiteman on a Perkin-Elmer model 12c infrared spectrophotometer.

3,4-Dimethoxy-9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (II).—The yield of this Diels–Alder adduct[4] has been raised to 66% by the use of purified dioxane rather than acetic acid as solvent, heating for a longer period (3 days), and using cyanomethylquinone which had been recrystallized from acetone.

The Ketolactam III.—The Diels–Alder adduct, m.p. 238–240°, 1.00 g., was rocked in a high pressure bomb at 124–131° for 4 hours under 27 atm. of hydrogen pressure (cold) with 20 cc. of absolute alcohol and 200 mg. of copper chromite catalyst.[38] The cooled mixture was diluted with benzene, filtered (Celite), extracted several times with 10% sodium hydroxide, then several times with 1% hydrochloric acid and finally once with water. The benzene solution was filtered through anhydrous sodium sulfate and concentrated. The ketolactam, 608 mg., m.p. 256–261°, separated. On recrystallization, 504 mg. (50.1%), m.p. 264–266°, of colorless small prisms, ultraviolet λ_{max} 281 mμ, log ε 4.16; infrared λ_{max} 3.00, 5.93, 6.03 μ, was obtained.

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11. Found: C, 68.62; H, 5.77.

This substance dissolves readily in 12 *N* hydrochloric acid, and on dilution is reprecipitated unchanged.[39]

The 6-chloroketolactam IV was prepared by a similar reduction of 3,4-dimethoxy-6-chloro-9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene.[4] The ketolactam, 83 mg. from 586 mg. of adduct, melted at 268–269°, and depressed the m.p. of a sample of the starting adduct to 217–240°. Unlike the adduct, it is soluble in 12 *N* hydrochloric acid and is precipitated on dilution; infrared λ_{max} 5.93, 6.03 μ.

Anal. Calcd. for $C_{18}H_{18}O_4NCl$: C, 62.16; H, 5.22. Found: C, 61.87; H, 5.16.

The Lactam V.—The ketolactam (801 mg.) was added to a solution of 4.5 g. of potassium hydroxide pellets in 20 cc. of diethylene glycol and 8 cc. of 100% hydrazine hydrate maintained at 155° (bath). A finely divided yellow precipitate separated rapidly, then redissolved over a period of about 30 minutes. The mixture was held at this temperature for 1 hour at which time it was pale yellow, and was then cooled and diluted with 4 volumes of water. A copious colorless crystalline precipitate separated, 703 mg., air-dried (92%), m.p. 208.5–211°. A sample was recrystallized from benzene for analysis as felty needles (cool solutions) or prisms (hot solutions), m.p. 209.5–211°, infrared λ_{max} 3.20, 6.05 μ, ultraviolet λ_{max} 282 mμ, log ε 3.17.

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; OCH_3, 20.73. Found: C, 72.44; H, 7.09; OCH_3, 20.31.

The temperature used in this experiment is considerably below that (190–210°) customarily used in the Huang-Minlon modification of the Wolff–Kishner reduction. If higher temperatures are used (200–210°), the product is extensively demethylated. We have isolated from such reactions a **monomethyl ether**, m.p. 283–286° (uncor.).

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; OCH_3, 10.90. Found: C, 71.27; H, 6.80; OCH_3, 10.41.

This substance is readily remethylated with dimethyl sulfate and alkali to give the lactam V. Otherwise the crude reaction mixture can be remethylated directly to give V in 56% yield.

The N-Methyllactam VI.—A solution of 150 mg. of lactam V in 50 cc. of toluene was concentrated by boiling to 25 cc. and treated with 15 mg. of sodium hydride. The solution was refluxed for 2 hours and 15 minutes and then

(32) K. Goto and I. Yamamoto (*Proc. Japan Acad.*, **30**, 769 (1954)), working in the enantiomorphic sinomenine series, have confirmed and improved our conversion of dihydrothebainone to morphine and with the *d*-codeine and *d*-morphine thus obtained have racemized ordinary codeine and morphine. Their improvement consists of refluxing the crude dinitrophenylhydrazone with pyridine, and we are grateful to them for the details of this work in advance of publication. They have also carried out the same conversion through 1-bromo-(+)-dihydrocodeinone (*cf.* C. Schöpf and T. Pfeifer, ref. 31), although their assignment of the structure 1,7-dibromodihydro-(+)-codeinone 2,4-dinitrophenylhydrazone to the intermediate appears to be incorrect. We have prepared its enantiomorph, m.p. 212–213°, $[\alpha]^{27}D$ −1030° (*c* 0.241, chf.), and find its molecular formula to be $C_{24}H_{24}O_7N_6Br$ (Calcd.: C, 50.18; H, 4.21; Br, 13.91. Found: C, 50.04, 50.06; H, 4.47; 4.39; Br, 13.85) rather than $C_{24}H_{23}O_6N_6Br_2$ as claimed by Goto. Apparently the bromine at C_7 is hydrolyzed during processing. Like its enantiomorph, this substance readily yields the corresponding α,β-unsaturated ketone dinitrophenylhydrazone on boiling with pyridine.

(33) The parent codeinone undergoes a wide variety of rearrangements in acid. For an excellent account of these and an ingenious mechanistic interpretation of them and some related rearrangements see G. Stork in "The Alkaloids," Academic Press, Inc., New York, N. Y., 1952, p. 189.

(34) E. Speyer and H. Rosenfeld, *Ber.*, **58**, 1110 (1925).

(35) A. H. Homeyer and G. B. DeLaMater, U. S. Patent 2,654,756, We are indebted to Dr. Homeyer for details of this method in advance of issue.

(36) M. Gates, THIS JOURNAL, **75**, 4340 (1953).

(37) H. Rapoport, C. H. Lovell and B. M. Tolbert, *ibid.*, **73**, 5900 (1951).

(38) This reaction is notably capricious, and depends to a marked extent on the history of the catalyst. That used in this experiment was prepared according to "Organic Syntheses," Coll. Vol. II, p. 142 (John Wiley and Sons, Inc., New York, N. Y., 1943) on one-tenth the scale, except that, for the precipitation of the complex ammonium chromate, only 13.5 cc. of ammonium hydroxide was used, leaving the filtrate bright yellow (acid), and the final catalyst was *not* leached with 10% acetic acid.

(39) Advantage may be taken of this slight basicity to separate the ketolactam from an isomeric neutral by-product, m.p. 219–222° (Found: C, 69.07; H, 6.36), sometimes obtained in this reductive cyclization. We have not fully identified this by-product, but it appears to be a ketol formed by simple reduction of the diketone system, since oxidation with bismuth trioxide gives the starting Diels–Alder adduct.

treated with 1 cc. of methyl iodide. On bringing the solution to a boil again, the color lightened and sodium iodide precipitated. The mixture was refluxed for 1 hour, cooled, washed three times with water, filtered through anhydrous sodium sulfate and concentrated to yield 168 mg. of colorless needles, m.p. 220–227.5°. Several crystallizations from benzene gave 131 mg., m.p. 227–229°, soluble in 12 *N* hydrochloric acid, reprecipitated unchanged on dilution. Its infrared spectrum shows no absorption in the 2.5–3.4 μ region.

Anal. Calcd. for $C_{19}H_{23}O_3N$: C, 72.82; H, 7.40. Found: C, 72.82; H, 7.70.

Racemic β-Δ⁶-Dihydrodesoxycodeine Methyl Ether (VII).—A solution of 505 mg. of lactam V in 40 cc. of toluene was concentrated by boiling to about half the original volume, treated with 45 mg. of sodium hydride and refluxed for 2 hours. The mixture was cooled, treated with 1 cc. of methyl iodide, refluxed for 1 hour, concentrated to about 10 cc., diluted with 12 cc. of absolute ether and treated with 15 cc. of a 1 *N* solution of lithium aluminum hydride in ether. The mixture was then refluxed for 48 hours and decomposed with ethyl acetate followed by enough dilute hydrochloric acid to dissolve all aluminum salts. The acid layer was separated and the organic layer extracted twice with dilute hydrochloric acid containing a little sodium sulfite. The combined acid layers were slowly run into an excess of strong potassium hydroxide solution containing Rochelle salt (under these conditions no alumina separates), and the oil which separated was taken into ether, dried, concentrated and pumped out at 100° to give 469 mg. of nearly colorless very viscous oil which was taken into a small amount of methanol and treated with a methanolic solution of 425 mg. of picric acid. A nicely crystalline bright yellow **picrate** separated and was collected and washed with methanol, 780 mg. (87.5%), m.p. 199.5–200.5° dec. Further crystallization does not raise its m.p. although picrate prepared from base recovered from its racemic dibenzoyl tartrate (*vide infra*) has m.p. 210–212° dec.

Anal. Calcd. for $C_{25}H_{28}O_9N_4$: C, 56.81; H, 5.34. Found: C, 56.55; H, 5.76.

This picrate is also obtainable from the N-methyllactam in 82% yield by similar reduction with lithium aluminum hydride. A sample of it (280 mg.) was converted to the free base by partition between dilute lithium hydroxide solution and freshly distilled peroxide-free ether. The combined ether extracts were washed with lithium hydroxide solution, then with water, dried, filtered, and concentrated to yield 156 mg. (98% from picrate) of a colorless viscous oil which crystallized on standing, m.p. 72–79°, and which after several crystallizations from methanol melted at 84–85°, sheaves of large colorless plates or leaves.

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42. Found: C, 76.34; H, 8.57.

Its infrared spectrum in chloroform is indistinguishable from that of natural *d*-β-Δ⁶-dihydrodesoxycodeine methyl ether (*vide infra*) and similar to, but not identical with, that of Δ⁵ or ⁶-dihydrodesoxycodeine methyl ether prepared from dihydrothebainol (*vide infra*).

Its dibenzoyl racemic tartrate was prepared from 11 mg. of base and 14 mg. of racemic dibenzoyltartaric acid in methanol, and after three crystallizations from methanol–chloroform melted at 184–184.2°.

Anal. Calcd. for $C_{37}H_{39}O_{10}N$: C, 67.57; H, 5.98. Found: C, 67.37; H, 6.05.

Resolution of *rac*-β-Δ⁶-Dihydrodesoxycodeine Methyl Ether.—A methanol solution of 120 mg. of *rac*-β-Δ⁶-dihydrodesoxycodeine methyl ether was treated with a methanol solution of 159 mg. of dibenzoyl-L(+)-tartaric acid. A first fraction, 88 mg., m.p. 162–163°, and a second fraction, 23 mg., m.p. 159–160°, were obtained; total yield of **d-β-Δ⁶-dihydrodesoxycodeine methyl ether dibenzoyl-L(+)-tartrate**, 111 mg. (82%). A small portion was crystallized from methanol three times and dried in high vacuum at room temperature, m.p. 162–163.5°, colorless prisms, $[\alpha]^{27}D$ +44.5° (*c* 1.53, chf.).

Anal. Calcd. for $C_{37}H_{39}O_{10}N \cdot H_2O$: C, 65.76; H, 6.12. Found: C, 65.60; H, 6.07.

Its m.p. showed no depression on admixture of the dibenzoyl-L(+)-tartrate of natural β-Δ⁶-dihydrodesoxycodeine methyl ether, $[\alpha]^{27}D$ +48° (*c* 1.80, chf.) (*vide infra*) and the infrared spectra of these substances are indistinguishable.

The synthetic *d*-salt (57 mg.) was suspended in water and treated with an excess of dilute ammonia. The precipitated oil solidified on standing, and was collected and dried, 22 mg. (theory 25 mg.), m.p. 41.5–42.5°. Several crystallizations from pentane gave pure **d-β-Δ⁶-dihydrodesoxycodeine methyl ether**, m.p. 43.5–44.5°, $[\alpha]^{27}D$ +80° (*c* 1.24, alc.).

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42. Found: C, 76.40; H, 8.51.

This substance is also obtainable in a modification melting at 57.5–58°, toward which the lower melting form is metastable. Natural *d*-β-Δ⁶-dihydrodesoxycodeine methyl ether (*vide infra*) also occurs in dimorphous forms of these melting points, and mixed melting points of the corresponding forms are not depressed. The infrared spectra of the synthetic and natural *d*-bases are indistinguishable.

***d*-β-Δ⁶-Dihydrodesoxycodeine methyl ether methiodide**, prepared from the synthetic *d*-base and methyl iodide and crystallized from methanol–ethyl acetate, melted at 186.5–188°, and did not depress the melting point of the natural *d*-base methiodide (*vide infra*).

***d*-β-Δ⁶-Dihydrodesoxycodeine methyl ether picrate**, prepared in and crystallized from methanol, melted at 230–231.5° dec., and did not depress the melting point of the natural *d*-base picrate (*vide infra*).

Anal. Calcd. for $C_{25}H_{28}O_9N_4$: C, 56.81; H, 5.34. Found: C, 56.86; H, 5.84.

The methanol filtrates from the crystallization of the *d*-base dibenzoyl-L(+)-tartrate were combined, concentrated to dryness, treated, with dilute ammonia and allowed to stand overnight. The viscous oil which separated was washed with water by decantation twice and dried, 63 mg. It was taken into methanol and treated with 82 mg. of dibenzoyl-D(−)-tartaric acid. Short scratching caused the separation of 70 mg. of crude ***l*-β-Δ⁶-dihydrodesoxycodeine methyl ether dibenzoyl-D(−)-tartrate** as prisms, m.p. 159–159.5°, which after 2 further crystallizations from methanol with the aid of Norite melted at 161.5–162°, 52 mg., $[\alpha]^{27}D$ −44° (*c* 1.94, chf.).

Anal. Calcd. for $C_{37}H_{39}O_{10}N \cdot H_2O$: C, 65.76; H, 6.12. Found: C, 66.09; H, 6.45.

The *l*-base dibenzoyl-D(−)-tartrate from another resolution (116 mg.) was suspended in water, made basic to excess with ammonia and triturated. Crystallization of the precipitated oil occurred after several hours, and the crude ***l*-β-Δ⁶-dihydrodesoxycodeine methyl ether** was collected, 48 mg. (theory 51 mg.), m.p. 49–52°. After two crystallizations from methanol it had m.p. 55.5–57°, $[\alpha]^{27}D$ −79° (*c*, 1.09, alc.).

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42. Found: C, 76.54; H, 8.73.

***l*-β-Δ⁶-Dihydrodesoxycodeine methyl ether picrate**, prepared in and crystallized from methanol, melted at 228.5–230°.

Anal. Calcd. for $C_{25}H_{28}O_9N_4$: C, 56.81; H, 5.34. Found: C, 56.92; H, 5.69.

A mixture of 2.15 mg. of this synthetic *l*-base picrate and 2.15 mg. of natural *d*-base picrate, when crystallized from chloroform–methanol, had m.p. 210–212°, undepressed by admixture of purely synthetic racemic picrate (*vide supra*) of m.p. 210–212°.

β-Dihydrothebainol (IX).—A solution of 50 g. of β-thebainone perchlorate,[13] m.p. 150–153°, evac. tube, in 1.5 l. of alcohol with 500 mg. of Adams catalyst was stirred under approximately 1 atmosphere of hydrogen at room temperature. Absorption of the first mole of hydrogen was rapid, and was complete within 45 minutes. The mixture was then acidified with 20 cc. of concd. hydrochloric acid and hydrogenation was continued for 50 to 60 hours, during which two additional 1-g. portions of catalyst were added. A total of about 95% of the amount calculated for 2 moles of hydrogen was absorbed.

The solution was freed of catalyst by filtration and concentrated to a small volume, when the quite soluble perchlorate of β-dihydrothebainol separated. This material was removed by filtration, and the filtrate concentrated to dryness by blowing on the steam-bath. Both fractions of solid residue were suspended in 10% sodium hydroxide containing some hydrosulfite. The insoluble portion was

collected and washed with water (to dissolve some precipitated sodium salt), and resuspended in 10% sodium hydroxide. The alkali-insoluble portion remaining (about 2.5 g.) consists principally of **β-tetrahydrodesoxycodeine (X)** resulting from hydrogenolysis of the hydroxyl function in ring III. Its hemihydrate, m.p. 140–152°, sintering at 126°, is obtained on crystallization from ethyl acetate or methanol containing a little water; $[\alpha]^{29}D$ −40° (*c* 1.24, chf.).

Anal. Calcd. for $C_{18}H_{25}O_2N \cdot {}^1/_2H_2O$: C, 72.94; H, 8.84. Found: C, 73.04; H, 8.88.

Its hydriodide, crystallized from dilute methanol, melts at 259–261° dec.

Anal. Calcd. for $C_{18}H_{26}O_2NI$: C, 52.05; H, 6.31. Found: C, 52.15; H, 6.57.

Its methiodide, crystallized from methanol–ethyl acetate, melts at 160–164°, softening from 150° (hydrate).

Anal. Calcd. for $C_{19}H_{28}O_2NI \cdot H_2O$: C, 51.01; H, 6.76. Found: C, 50.97; H, 6.97.

Its picrate, crystallized from chloroform–methanol, melts at 233–234° with dec.

Anal. Calcd. for $C_{24}H_{28}O_9N_4$: C, 55.81; H, 5.46. Found: C, 55.78; H, 5.22.

The combined alkaline filtrates were carbonated to excess, then extracted three times with chloroform. The washed and dried chloroform extracts were concentrated and the residue was crystallized from ethyl acetate to give 19.2 g. of **β-dihydrothebainol**, m.p. 163–164.5°. A second crop, 1.5 g., m.p. 161–163°, was obtained from the filtrate, total yield 20.5 g., 60%. Analytically pure β-dihydrothebainol melts at 165.5–166°, $[\alpha]^{30}D$ −23° (*c* 0.920, alc.).

Anal. Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31. Found: C, 71.34; H, 8.36.

Its methiodide, prepared in ethyl acetate and crystallized from methanol–ethyl acetate, melts at 264–265°.

Anal. Calcd. for $C_{19}H_{28}O_3NI$: C, 51.24; H, 6.34. Found: C, 51.15; H, 6.51.

β-Dihydrothebainone methyl ether was prepared by methylation of β-dihydrothebainone essentially as described below for β-dihydrothebainol. When processed as described below, 6.18 g. of β-dihydrothebainone[13] (purified through its perchlorate, m.p. 262–264° dec.) yielded 6.31 g. of alkali-insoluble red-brown glass which was distilled in a short-path molecular still at 10^{-2} mm. (bath 220–230°) to yield 5.55 g. (86%) of straw-yellow glass which slowly crystallized, m.p. 116–120°. After several crystallizations from cyclohexane, it had m.p. 122–123°, $[\alpha]^{27}D$ −51.4° (*c* 2.49, alc.), infrared λ_{max} 5.89 μ.

Anal. Calcd. for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99; OCH_3, 19.68. Found: C, 72.43; H, 8.06; OCH_3, 19.34.

Its very sparingly soluble **picrate**, prepared in methanol and crystallized from chloroform–methanol, melts at 249–250° dec.

Anal. Calcd. for $C_{25}H_{28}O_{10}N_4$: C, 55.14; H, 5.18. Found: C, 55.00; H, 5.45.

Its semicarbazone crystallizes from alcohol as a solvate, m.p. 202.5–204°, gas evol., colorless cottony needles.

Anal. Calcd. for $C_{20}H_{28}O_3N_4 \cdot {}^1/_2C_2H_5OH$: C, 63.77; H, 7.90. Found: C, 63.65; H, 8.35.

Reduction of β-Dihydrothebainone Methyl Ether with Lithium Aluminum Hydride.—A solution of 132 mg. of β-dihydrothebainone methyl ether in 4 cc. of absolute ether was treated with 2 cc. of 0.56 *M* lithium aluminum hydride in ether. The mixture was allowed to stand one hour, then decomposed, first with ethyl acetate, then with excess dilute hydrochloric acid. The clear acid solution was separated and run into an excess of potassium hydroxide solution containing Rochelle salt. The precipitated oily base was taken up in chloroform (several extractions), washed, dried, filtered and concentrated. Crude material prepared this way yields a picrate which melts sharply at 181–183° and which has the expected composition (Found: C, 55.17; H, 5.65) but which is apparently a eutectic of the picrates of β-dihydrothebainol methyl ether and its C_6-epimer.

The crude material was processed as follows: hot cyclohexane was added and the solution was seeded with β-dihydrothebainol methyl ether. Crystallization took place slowly, and from two crops by careful recrystallization from ethyl acetate a total of 45 mg. (34%) of **β-dihydrothebainol methyl ether (XI)**, m.p. 152–154°, prisms, was obtained. Its m.p. was not depressed by admixture with a sample prepared by methylation of β-dihydrothebainol (*vide infra*).

The combined filtrates were concentrated, the solvent replaced by methanol, and 70 mg. of picric acid was added. Several recrystallizations of the resulting picrate from methanol yielded 63 mg. (28%) of the **picrate** of the **C_6-epimer of β-dihydrothebainol methyl ether**, m.p. 224.5–226° dec., prisms.

Anal. Calcd. for $C_{25}H_{30}O_{10}N_4$: C, 54.94; H, 5.53. Found: C, 54.66; H, 5.82.

The C_6-epimer of β-dihydrothebainol methyl ester was recovered from a similar sample of its picrate (259 mg.) by partition between dilute lithium hydroxide and chloroform. The washed, dried, filtered and concentrated chloroform solution yielded 159 mg. of pale yellow glass (theory 150 mg.) which was distilled in a short path still at 10^{-2} mm. (bath 160–200°). The colorless distillate, $[\alpha]_D^{27}$ −19° (*c* 2.25 alc.), could not be caused to crystallize.

Anal. Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57. Found: C, 71.37; H, 8.53.

Its methiodide, prepared in ethyl acetate and crystallized from ethyl acetate–methanol containing a little water, melts at 146–151° with gas evolution.

Anal. Calcd. for $C_{20}H_{30}O_3NI \cdot H_2O$: C, 50.32; H, 6.76. Found: C, 49.86; H, 6.79.

β-Dihydrothebainol Methyl Ether (XI).—An alcoholic solution of trimethylphenylammonium ethoxide was prepared as follows: To a warm solution of 1.4 g. of sodium in 20 cc. of absolute alcohol was added a warm solution of 17.5 g. of dimethylaniline methyl toluenesulfonate adduct in 40 cc. of absolute alcohol. Sodium *p*-toluenesulfonate precipitated at once and was removed by filtration and washed with absolute alcohol.

To this solution was added 13.0 g. of β-dihydrothebainol. The alcohol was removed under slightly reduced pressure, and the dark residue was heated in an oil-bath for 1.5 hours at 130°. The cooled mixture was dissolved in 15% acetic acid, steam distilled to remove dimethylaniline, made basic with 20% potassium hydroxide and extracted with chloroform three times. The washed, dried, and concentrated chloroform extracts yielded a residue which on crystallization from ethyl acetate gave 10.3 g. (76%) of β-dihydrothebainol methyl ether as heavy prisms, m.p. 149–151°, and a second crop (0.4 g.) melting at 148–150°. Analytically pure β-dihydrothebainol methyl ether melts at 153–155°, $[\alpha]^{27}D$ −22° (*c* 2.50 alc.). This substance also results, along with its C_6-epimer, from the reduction of β-dihydrothebainone methyl ether with either lithium aluminum hydride or sodium borohydride.

Anal. Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57. Found: C, 71.93; H, 8.77.

Its methiodide, prepared in ethyl acetate and crystallized from ethyl acetate–methanol, melted at 243–245° as small colorless prisms.

Anal. Calcd. for $C_{20}H_{30}O_3NI$: C, 52.29; H, 6.58. Found: C, 52.30; H, 6.57.

Its picrate, prepared in and crystallized from methanol, was obtained in two polymorphic forms, m.p. 190–191°, and m.p. 221–222.5°. Solutions of the lower melting form deposit the higher melting form on seeding.

Anal. Calcd. for $C_{25}H_{30}O_{10}N_4$: C, 54.94; H, 5.53. Found (190–191°): C, 55.27; H, 5.85. (221–222.5°): C, 55.30; H, 5.64.

Tosylate of β-Dihydrothebainol Methyl Ether (XII).—A solution of 10.3 g. of β-dihydrothebainol methyl ether of m.p. 149–151° in 95 cc. of freshly distilled dry pyridine was treated with 12.5 g. of tosyl chloride and allowed to stand 5.5 days at room temperature. The mixture, which had become deep red and deposited long needles, was then cooled, diluted with 20 cc. of water, allowed to stand for two hours, then diluted with ice-water, made just alkaline with carbonate solution, and extracted four times with ether. The ether extracts were washed several times with water, once with saturated brine solution, filtered through anhydrous sodium sulfate, and concentrated. During the concentration partial crystallization of the tosylate occurred. A total of 16.4 g. (15.3 calcd.) of partially crystalline

residue, suitable for use in the next step, was obtained. A portion of the crystalline material, m.p. 129–131°, was crystallized several times from ethyl acetate–ether for analysis, m.p. 133–133.5°, colorless needles.

Anal. Calcd. for $C_{26}H_{33}O_5NS$: C, 66.21; H, 7.05. Found: C, 66.19; H, 7.35.

Detosylation.—Crude tosylate of β-dihydrothebainol methyl ether (16.4 g.) was refluxed for two hours in 2,4,6-collidine. The cooled mixture was diluted with ether, washed several times with dilute carbonate, then twice with water and concentrated. The residue was steam distilled to remove collidine, diluted with ether, separated from a small aqueous layer which was extracted with ether, and the combined ether layers were dried over sodium sulfate, concentrated, and finally pumped out to yield 9.8 g. (theory 9.72 g.) of thick colorless oil. This material was chromatographed on 550 g. of alumina (activity I), eluting progressively with benzene, benzene–chloroform (4–1), chloroform and chloroform–methanol (10–1) to give as the two principal components crude β-Δ⁶-dihydrodesoxycodeine methyl ether, 5.30 g., m.p. 54–56°, and crude β-Δ⁵-dihydrodesoxycodeine methyl ether, 4.35 g., partially crystalline, as less and more strongly adsorbed fractions, respectively.

The pooled fractions of each component were purified through their respective picrates to yield a total of 8.55 g. of **β-Δ⁶-dihydrodesoxycodeine methyl ether picrate**, m.p. 230–232° dec. (*Anal.* Calcd. for $C_{25}H_{28}O_9N_4$: C, 56.81; H, 5.34. Found: C, 56.88; H, 5.67) and 4.60 g. of crude **β-Δ⁵-dihydrodesoxycodeine methyl ether picrate**, m.p. 215–217° dec., a small sample of which after several crystallizations from methanol had m.p. 225.5–226.5° dec.

Anal. Calcd. for $C_{25}H_{28}O_9N_4$: C, 56.81; H, 5.34. Found: C, 56.96; H, 5.43.

The first of these picrates, on conversion to the free base by partition between chloroform and dilute lithium hydroxide, yielded **β-Δ⁶-dihydrodesoxycodeine methyl ether (XIII)**, 4.85 g. (50% from β-dihydrothebainol methyl ether), m.p. 52–54°. Several recrystallizations from pentane give either material melting at 43.5–44° or at 57.5–58°,[40] $[\alpha]^{27}D$ +80° (*c* 1.55 alc.), the latter the more stable, both colorless needles.

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42. Found (43.5–44°): C, 76.49; H, 8.61. (57.5–58°): C, 76.39; H, 8.62.

This substance (11 mg., higher-melting form) and 11 mg. of synthetic *l*-β-Δ⁶-dihydrodesoxycodeine methyl ether were combined and crystallized from methanol to give 19 mg. of ***rac*-β-Δ⁶-dihydrodesoxycodeine methyl ether**, m.p. 82.5–84°, undepressed by admixture of purely synthetic racemic base (*vide supra*) of m.p. 83–84°.

β-Δ⁶-Dihydrodesoxycodeine methyl ether methiodide was prepared in ethyl acetate and crystallized from methanol–ethyl acetate, m.p. 188–189°.

Anal. Calcd. for $C_{20}H_{28}O_2NI$: C, 54.42; H, 6.39. Found: C, 54.33; H, 6.51.

β-Δ⁶-Dihydrodesoxycodeine methyl ether dibenzoyl-L(+)-tartrate, prepared in and crystallized from methanol, melted at 163–163.5°, $[\alpha]^{27}D$ +48° (*c* 1.80 chf.).

Anal. Calcd. for $C_{37}H_{39}O_{10}N\cdot H_2O$: C, 65.76; H, 6.12. Found: C, 65.99, 65.68; H, 6.37, 6.07.

This substance, 1.35 mg., and 1.33 mg. of the synthetic dibenzoyl-D(−)-tartrate of *l*-β-Δ⁶-dihydrodesoxycodeine methyl ether were combined and crystallized several times from methanol to give the dibenzoyl racemic tartrate of ***rac*-β-Δ⁶-dihydrodesoxycodeine methyl ether**, m.p. 182°, not depressed by admixture of purely synthetic racemic salt (*vide supra*) of m.p. 184°.

No crystalline salt could be obtained with dibenzoyl-D(−)-tartaric acid.

β-Tetrahydrodesoxycodeine Methyl Ether (XV).—The β-Δ⁶-base (50 mg.), m.p. 57–57.5°, was hydrogenated over Adams catalyst in methanol containing acetic acid until the uptake of hydrogen had ceased. The solution was freed from catalyst, concentrated, diluted with ether, washed with an excess of dilute ammonia, then with water, dried and concentrated. The residue was taken into a little methanol and treated with 40 mg. of picric acid in methanol. A light yellow crystalline **picrate**, 91 mg. (88 mg. theory), m.p. 198–201°, was obtained. After crystallization from chloroform–methanol, this material melted at 204–206°.

Anal. Calcd. for $C_{25}H_{30}O_9N_4$: C, 56.60; H, 5.70. Found: C, 56.52; H, 5.77.

This picrate (61 mg.) was converted to the free base by partition between ether and dilute lithium hydroxide. Removal of the ether after processing left 35 mg. of colorless oil (34.5 mg. theory) which could be crystallized from pentane, m.p. 36.5–37.5°, $[\alpha]^{27}D$ −18° (*c* 1.92, alc.).

Anal. Calcd. for $C_{19}H_{27}O_2N$: C, 75.71; H, 9.03. Found: C, 75.46; H, 8.96.

Its methiodide, prepared in ethyl acetate and crystallized from ethyl acetate–methanol, had m.p. 236–237°.

Anal. Calcd. for $C_{20}H_{30}O_2NI$: C, 54.18; H, 6.82. Found: C, 54.54; H, 6.75.

The second of the picrates from the chromatographed bases described above, on conversion to the free base as in the isomeric case, yielded 2.60 g. (27% from β-dihydrothebainol methyl ether) of **β-Δ⁶-dihydrodesoxycodeine methyl ether (XIV)**, m.p. 77–78°, which after several crystallizations from pentane had m.p. 78.5–79°, colorless prisms or plates.

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42. Found: C, 76.39; H, 8.54.

β-Δ⁵-Dihydrodesoxycodeine methyl ether methiodide, prepared in ethyl acetate and crystallized from methanol–ethyl acetate, had m.p. 227.5–229°, colorless plates or prisms.

Anal. Calcd. for $C_{20}H_{28}O_2NI$: C, 54.42; H, 6.39. Found: C, 54.80; H, 6.52.

β-Δ⁵-Dihydrodesoxycodeine methyl ether dibenzoyl-L(+)-tartrate, prepared in and crystallized from methanol, had m.p. 166–166.5°.

Anal. Calcd. for $C_{37}H_{39}O_{10}N\cdot H_2O$: C, 65.76; H, 6.12. Found: C, 65.76; H, 6.23.

No crystalline salt could be obtained with dibenzoyl-D(−)-tartaric acid.

It is noteworthy that β-Δ⁵- and β-Δ⁶-dihydrodesoxycodeine methyl esters, their dibenzoyl-L(+)-tartrates and picrates as pairs melt close to one another and do not give melting point depressions on mixing. The methiodides, however, differ considerably in melting point. These two bases cannot be separated by direct crystallization, or by crystallization of their picrates or dibenzoyl-L(+)-tartrates, although they are readily separable by chromatography.

The hydrogenation of β-Δ⁵-dihydrodesoxycodeine methyl ether as described above for the Δ⁶-base leads also to **β-tetrahydrodesoxycodeine methyl ether**, m.p. 36.5–37.5°, **picrate** m.p. 201–202°, **methiodide** m.p. 235–236°. These melting points are undepressed by mixture with the corresponding substances from the Δ⁶-base.

Dihydrothebainol Methyl Ether (XVII).—A solution of 2.11 g. of dihydrothebainol,[18,41] m.p. 163–166°, in 25 cc. of absolute alcohol was treated with the diazomethane solution (distilled) from 9.0 g. of nitrosomethylurea. The mixture was allowed to stand at room temperature for 23 hours, then concentrated, eventually by blowing, to dryness. The residue was taken into a 50% benzene–hexane solution, extracted four times with Claisen alkali, washed twice with water, filtered through anhydrous sodium sulfate and concentrated. Final removal of solvents at the pump yielded an orange viscous oil or glass, 1.66 g. This material is suitable for use in subsequent reactions. It may be purified through its **hydrobromide**, prepared in acetone by the addition of hydrobromic acid and crystallized from acetone–methanol, m.p. 254.5–255°, $[\alpha]^{28}D$ +34° (*c* 0.44, alc.).

Anal. Calcd. for $C_{19}H_{28}O_3NBr$: C, 57.29; H, 7.08. Found: C, 57.21; H, 7.29.

A small sample of the free base, recovered from this hydrobromide by partition between aqueous carbonate and ether and pumped free of solvent, failed to crystallize, $[\alpha]^{27}D$ −28.4° (*c* 1.52, alc.).

Anal. Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57; OCH_3, 19.55. Found: C, 71.42; H, 8.73; OCH_3, 18.88.

Its methiodide, prepared in ethyl acetate and crystallized from methanol, melted at 279–281°, colorless fine needles.

(40) We originally reported this substance as an oil, *cf.* ref. 3.

(41) Our sample was prepared by reduction of dihydrothebainone in dilute hydrochloric acid over Adams catalyst.

Anal. Calcd. for $C_{20}H_{30}O_3NI$: C, 52.29; H, 6.58. Found: C, 52.35; H, 6.48.

$\Delta^{5(or\ 6)}$-Dihydrodesoxycodeine Methyl Ether (XVIII).—A solution of 0.69 g. of dihydrothebainol methyl ether in 8 cc. of freshly distilled anhydrous pyridine was treated with 1.00 g. of purified tosyl chloride and allowed to stand at room temperature for 4.5 days. The mixture was cooled, diluted with water, allowed to stand three hours, then diluted with ether, made just alkaline with carbonate and extracted three times with ether. The ether layers were washed with carbonate, water, saturated brine solution, and then filtered through anhydrous sodium sulfate and concentrated. The light brown very viscous oily residue weighed 0.95 g. after pumping out. No attempt was made to purify it, although a crystalline **tosylate methiodide**, m.p. 165–166°, sheaves of prismatic needles from acetone–ethyl acetate, was readily obtained.

Anal. Calcd. for $C_{27}H_{36}O_5NSI$: C, 52.85; H, 5.91. Found: C, 52.45; H, 6.04.

A portion of the crude tosylate (0.90 g.) was refluxed for 2.5 hours in 10 cc. of collidine, then cooled, diluted with ether, washed twice with carbonate, and then steam distilled to remove collidine. The residue was taken into 1% hydrochloric acid, the acid solution was washed once with ether, made basic with carbonate, and the organic base taken into chloroform (three extractions). The chloroform solutions were washed, dried, filtered, and concentrated, and the residue was distilled at 10^{-3} mm. (bath 140–180°). The distillate (0.47 g., theory 0.57 g.) was a nearly colorless viscous oil.

A sample of this oil (48 mg.) was treated in a very small amount of methanol with 35 mg. of fumaric acid and diluted with absolute ether. A total of 74 mg. of crude **fumarate** (2 moles of base to 3 of acid) of m.p. 226–229° was obtained in two crops. Recrystallization from methanol–ether raised the m.p. to 233–235°, gas evol.

Anal. Calcd. for $C_{23}H_{29}O_8N$ (1 to 1): C, 66.49; H, 7.04. Calcd. for $C_{25}H_{31}O_8N$ (2 to 3): C, 63.41; H, 6.60. Found: C, 63.41, 63.53; H, 6.58, 6.91.

A sample of the fumarate (92 mg.) was partitioned between aqueous carbonate and freshly distilled ether. The ether extracts were washed with water, then brine, filtered through anhydrous sodium sulfate, concentrated and pumped out to leave a residue of 57 mg. (58 mg. theory for salt composed of 2 moles of base, 3 of acid) of colorless very viscous oil. Its infrared spectrum in chloroform is similar to, but demonstrably different from, that of synthetic *rac*-β-Δ^6-dihydrodesoxycodeine methyl ether.

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42. Found: C, 75.83; H, 8.44.

Its methiodide (38 mg. of material melting at 247–249° or higher from 27 mg. of crude distilled base), prepared in ethyl acetate and crystallized from acetone–ethyl acetate, melts at 251.5–252.5° when pure.

Anal. Calcd. for $C_{20}H_{28}O_2NI$: C, 54.42; H, 6.39. Found: C, 54.28; H, 6.83.

Epoxide of β-Δ^6-Dihydrodesoxycodeine Methyl Ether (XIX).—A solution of 598 mg. of β-Δ^6-dihydrodesoxycodeine methyl ether and 244 mg. of benzoic acid in 14 cc. of chloroform was treated with 10.6 cc. of 0.583 *M* perbenzoic acid in chloroform. After 3 hours over 95% of the perbenzoic acid had been used up, and the reaction mixture was then extracted with carbonate and then twice with sodium hydrosulfite in an attempt to reduce any N-oxide back to the tertiary amine. The chloroform solution was dried, filtered and concentrated. The partially crystalline residue was triturated with cyclohexane, leaving an insoluble amorphous residue of 503 mg., m.p. 80–170°.

Concentration of the cyclohexane filtrate yielded 180 mg. of yellow glass which readily yielded a crystalline **picrate**, m.p. 190–193°, which after several crystallizations from chloroform–methanol gave 128 mg. of small bright yellow prisms, m.p. 198.5–200°.

Anal. Calcd. for $C_{25}H_{28}O_{10}N_4$: C, 55.14; H, 5.18. Found: C, 54.79; H, 5.22.

A sample of this picrate (100 mg.) was converted to the free base by partition between chloroform and dilute lithium hydroxide to yield 57 mg. of pale yellow glass which crystallized readily, m.p. 89–92°. After several crystallizations it melted at 92–93.4°. Its infrared spectrum shows no absorption in the hydroxyl region.

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 72.35; H, 7.99. Found: C, 72.08; H, 7.97.

The crude amorphous material, insoluble in cyclohexane, can be converted into the epoxide picrate in 34% yield by catalytic hydrogenation, and thus probably contains the corresponding N-oxide.

7-Hydroxy-β-tetrahydrodesoxycodeine Methyl Ether (XX).—The crude total epoxidation product of an epoxidation conducted as above on 200 mg. of β-Δ^6-dihydrodesoxycodeine methyl ether was dissolved in anhydrous ether and treated with 4 cc. of 0.95 *M* lithium aluminum hydride in ether. The mixture was allowed to stand for two days, then cautiously decomposed with dilute hydrochloric acid, using enough to dissolve aluminum salts completely. The separated dilute acid layer was run dropwise into an excess of strong potassium hydroxide solution containing Rochelle salt, and the resulting mixture (no inorganic precipitate) was extracted several times with chloroform. The washed, dried, filtered, and concentrated chloroform solution yielded a residue of 120 mg. of oil, which was chromatographed on 30 g. of alumina in chloroform. Development with chloroform caused 55 mg. of weakly adsorbed material to pass through the column. This material on treatment with 42 mg. of picric acid in methanol, readily yielded 51 mg. of a crystalline picrate, m.p. 198–200° dec., which was not purified, but was reconverted to the free base (34 mg.) by partition between dilute lithium hydroxide and ether. This base crystallized readily from ethyl acetate as heavy prisms and after two such crystallizations melted at 141–142° (14.5 mg.).

Anal. Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57. Found: C, 72.13; H, 8.64.

Its methiodide, prepared in ethyl acetate and crystallized from ethyl acetate–methanol, melts at 262–263.5°.

Anal. Calcd. for $C_{20}H_{30}O_3NI$: C, 52.29; H, 6.58. Found: C, 51.86; H, 6.50.

Its picrate, prepared from a pure sample of the base and crystallized from methanol, melts at 218–219° dec.

Anal. Calcd. for $C_{25}H_{30}O_{10}N_4$: C, 54.94; H, 5.53. Found: C, 55.43; H, 5.73.

This compound is also obtained as a minor product of the hydration of β-Δ^6-dihydrodesoxycodeine with acid (*vide infra*).

***cis*-6,7-Dihydroxy-β-tetrahydrodesoxycodeine Methyl Ether (XXI).**—A solution of 89 mg. of β-Δ^6-dihydrodesoxycodeine methyl ether in 1 cc. of benzene was treated with 1.6 cc. of a 0.198 *M* solution of osmium tetroxide in benzene. The solution immediately became deep brown or black and a brown-black precipitate separated. After 1.5 hours at room temperature, the precipitate of osmate ester was separated by centrifugation, washed with benzene and hydrolyzed by warming on the steam-bath with a solution of sodium sulfite and disodium phosphate. The black precipitate was removed by filtration, washed with methanol, and the filtrates were made basic with ammonia and extracted four times with chloroform. The chloroform extracts were washed, dried, filtered, and concentrated to yield a very pale yellow glass, 71 mg., which was treated in methanol with 50 mg. of picric acid to yield 54 mg. of bright yellow needles, m.p. 222–224° dec., which after crystallization from methanol–chloroform melted at 226–227° dec.

Anal. Calcd. for $C_{25}H_{30}O_{11}N_4$: C, 53.38; H, 5.38. Found: C, 53.39; H, 5.48.

A total of 63 mg. of picrate prepared in this way was converted to the free base by partition between lithium hydroxide and chloroform to yield 39 mg. (37 mg. theory) a nearly colorless glass which crystallized readily, m.p. 135–143°. After two crystallizations from ethyl acetate 21 mg. of colorless plates, m.p. 151–152°, was obtained.

Anal. Calcd. for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.16. Found: C, 68.13; H, 8.38.

***trans*-6,7-Dihydroxy-β-tetrahydrodesoxycodeine Methyl Ether (XXII).**—A solution of 382 mg. of β-Δ^6-dihydrodesoxycodeine methyl ether in 6 cc. of 98% formic acid was treated with 0.20 cc. of 30% hydrogen peroxide, and the mixture was allowed to stand at room temperature for 40 hours. The solution was diluted with water, made basic with 10%

sodium hydroxide solution, and extracted four times with chloroform. The washed, dried and filtered chloroform solution was concentrated, and the residue was taken into methanolic sodium hydroxide solution and allowed to stand overnight. The methanol was largely removed by blowing, and the residue was distributed between chloroform and water (four extractions). The washed, dried, filtered and concentrated chloroform layers yielded a residue of 339 mg. from which a total of 302 mg. (71%) of needles, m.p. 198–199.5°, was obtained by crystallizations from methanol–ethyl acetate. A small sample recrystallized for analysis melted at 201–202°, colorless needles.

Anal. Calcd. for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.16; OCH_3, 18.62. Found: C, 68.52; H, 8.19; OCH_3, 18.36.

Its picrate, prepared in and crystallized from methanol, melted at 245–246.5° dec.

Anal. Calcd. for $C_{25}H_{30}O_{11}N_4$: C, 53.38; H, 5.38. Found: C, 53.99; H, 5.48.

What appears to be a **monomethyl ether** of this substance was obtained as a by-product of the hydrogenation, in methanol, of the epoxide XIX, m.p. 174.5–175.5° (large prisms from ethyl acetate).

Anal. Calcd. for $C_{20}H_{29}O_4N$: C, 69.13; H, 8.41; OCH_3, 26.80. Found: C, 68.72; H, 8.32; OCH_3, 25.97.

β-Dihydrothebainol methyl ether (XI).—A solution of 208 mg. of β-Δ⁶-dihydrodesoxycodeine methyl ether in 18 cc. of 18% sulfuric acid was heated under nitrogen on the steam-bath for 5 days. The resulting straw-yellow solution was diluted with ice-water, made basic with potassium hydroxide solution, and extracted four times with chloroform. The extracts were washed, dried, filtered, concentrated and pumped out to leave an almost colorless residue of very viscous oil or glass, 228 mg. This material was chromatographed on 13 g. of alumina in alcohol-free chloroform. Development with alcohol-free chloroform caused the elution of a total of 110 mg. of crude recovered starting material which was converted to its sparingly soluble dibenzoyl-L(+)-tartrate, 216 mg., m.p. 163.5–165° (corresponding to 97 mg. of starting base). Development with increasing proportions of acetone in alcohol-free chloroform produced an intermediate fraction, which after careful rechromatography and processing through its picrate (21 mg., m.p. 214–216.5° dec.) yielded 7 mg. of **7-hydroxy-β-tetrahydrodesoxycodeine methyl ether**, m.p. 140–141°, undepressed on admixture of a sample prepared from the epoxide (*vide supra*), **methiodide**, m.p. 262–263.5°, and finally a fraction (58 mg., m.p. 144–151°) of crude **β-dihydrothebainol methyl ether** which on crystallization from ethyl acetate yielded 34 mg. (28% based on starting material not recovered) of stout colorless prisms, $[\alpha]^{28}D$ −23° (*c* 2.78 alc.), m.p. 151–153.5°, undepressed on admixture with material produced by the methylation of β-dihydrothebainol (*vide supra*). The infrared spectra of these substances are indistinguishable. Its **methiodide** melted at 243–244° and did not depress the m.p. of a sample prepared from β-dihydrothebainol through its methyl ether.

In some runs, small amounts of the **C₆-epimer of β-dihydrothebainol methyl ether** (*vide supra*) were recovered from intermediate fractions as its **picrate**, m.p. 216–222°.

***rac*-Dihydrothebainol methyl ether (XXIII)**, prepared in 28% yield from 98.5 mg. of *rac*-β-Δ⁶-dihydrodesoxycodeine methyl ether by the same method, melts at 149–150.5° (colorless small prisms). Its infrared spectrum in chloroform solution is indistinguishable from that of natural β-dihydrothebainol methyl ether in the same solvent.

Anal. Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57. Found: C, 72.00; H, 8.36.

What is probably ***rac*-7-hydroxy-β-tetrahydrodesoxycodeine methyl ether** also results in small amounts from the hydration of *rac*-β-Δ⁶-dihydrodesoxycodeine methyl ether. Its infrared spectrum in solution has not been compared with the active form (*vide supra*), but its position on the chromatogram corresponds to that of the active form in the preceding hydration; fine colorless prismatic needles or blades, m.p. 172.5–173.5°.

Anal. Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.58. Found: C, 71.75; H, 8.75.

β-Dihydrothebainol (IX).—A mixture of 300 mg. of β-dihydrothebainol methyl ether, m.p. 153–154°, 10 cc. of diethylene glycol, 12 pellets of potassium hydroxide and 0.2 cc. of hydrazine hydrate (which exerts an important antoxidant effect) was heated under nitrogen for 1.25 hours at 221–227° (bath). During the first five minutes of heating the mixture was blown with nitrogen to remove water. The mixture was cooled, diluted with water containing a little hydrosulfite, carbonated to excess with a stream of carbon dioxide, and extracted four times with chloroform. The washed, dried, filtered and concentrated chloroform solution yielded a residue of 186 mg. which slowly crystallized. The aqueous layer still contains material, probably completely demethylated, not extractable by chloroform and was extracted four times with butanol. The butanol extracts were filtered through anhydrous sodium sulfate, concentrated to a sirup under diminished pressure, and remethylated in methanol solution by treatment overnight with the ethereal diazomethane solution from 1 g. of nitrosomethylurea. The resulting mixture was freed of solvents by blowing and partitioned between chloroform and dilute ammonia. The washed, dried, filtered and concentrated chloroform extracts yielded a residue of 90 mg. which solidified slowly. The two solid fractions, totalling 276 mg., were chromatographed on 15 g. of alumina in alcohol-free chloroform. Development with alcohol-free chloroform–acetone (15%) eluted a fraction composed largely of unchanged β-dihydrothebainol methyl ether which after crystallization from ethyl acetate melted at 152.5–154° (97 mg.). Further development with acetone–methanol (10%) yielded 105 mg. (54% based on starting material used) of β-dihydrothebainol, m.p. 159–164°, which after crystallization from ethyl acetate melted at 165.5–166°, undepressed by admixture of β-dihydrothebainol prepared by the reduction of β-thebainone (*vide supra*), $[\alpha]^{28}D$ −25° (*c* 1.06 alc.). It is soluble in alkali and reprecipitated by carbonation.

Its methiodide melted at 266–268° and did not depress the m.p. of authentic β-dihydrothebainol methiodide.

***rac*-β-Dihydrothebainol (XXIV)**, prepared in approximately the same yield by cleavage of *rac*-β-dihydrothebainol methyl ether (125 mg.), melts at 185–186°, colorless leaves. Its infrared spectrum in chloroform is indistinguishable from that of natural β-dihydrothebainol in the same solvent. It is soluble in alkali and reprecipitated on carbonation.

Anal. Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31. Found: C, 70.98; H, 8.58.

Demethylation of β-Dihydrothebainol Methyl Ether with Pyridine Hydrochloride.—A mixture of 204 mg. of β-dihydrothebainol methyl ether and 247 mg. of freshly fused pyridine hydrochloride was heated for four hours at 195–200° (bath). The cooled brownish residue was dissolved in water, made basic with potassium hydroxide containing hydrosulfite, and extracted several times with chloroform. The chloroform, after processing, was found to contain only a trace of non-volatile residue. The aqueous alkaline layer was then carbonated to excess and extracted several times with butanol. The butanol extracts were washed, filtered through anhydrous sodium sulfate, and concentrated under nitrogen. Crystallization occurred during the concentration, and the residue melted at 239–242° dec. (162 mg.). Several crystallizations from butanol gave 72 mg. of small prisms, m.p. 258–262° dec., $[\alpha]^{28}D$ +46° (*c* 1.32, diox.).

Anal. Calcd. for $C_{17}H_{21}O_2N$: C, 75.24; H, 7.80. Found: C, 75.03, 75.20; H, 8.08, 8.01.

This substance has apparently not only lost both methoxyl groups (insolubility in chloroform) but has also suffered dehydration of the hydroxyl at C_6.

β-Dihydrothebainone (XXV).—A solution of 380 mg. of freshly cut metallic potassium in 7 cc. of absolute *t*-butyl alcohol (distilled from sodium) and 20 cc. of dry benzene was distilled with the addition of more benzene until the boiling point reached that of pure benzene, and an additional ten minutes. β-Dihydrothebainol (400 mg., m.p. 162–164°) and benzophenone (3 g.) were then added in dry benzene. A transient deep greenish-brown color rapidly lightening to pale yellow was produced. The mixture was heated under reflux for 2.5 hours, cooled and extracted three times with dilute hydrochloric acid. The acid extracts were washed with benzene, made basic with ammonia, and extracted six times with chloroform. The chloroform extracts were washed, dried, filtered and concentrated to yield 399 mg. of light tan glassy residue which was taken into

alcohol and treated with an excess of 25% perchloric acid to yield 450 mg. of **β-dihydrothebainone perchlorate**, m.p. 262–264°, dec., infrared λ_{max} 5.88 μ. An additional 25 mg., m.p. 261–263°, total yield 457 mg. (89.6%), was obtained by careful processing of the filtrate.

Recrystallization of a small sample from alcohol gave material of m.p. 264–266° dec., not depressed by admixture of authentic β-dihydrothebainone perchlorate[42] of m.p. 264–267° dec. (reported 254–255°). A small amount of the perchlorate, m.p. 262–264°, was converted to the free base by partition between chloroform and dilute ammonia to yield a glass which crystallized readily when seeded with authentic β-dihydrothebainone[42] and then had m.p. 115–118°. Recrystallization from dilute methanol raised the m.p. to 120.5–122° (reported 116–118°), undepressed by admixture with the authentic sample, $[\alpha]^{26}D$ −47° (*c* 1.53, alc.) (reported $[\alpha]^{27}D$ −48.1°,[13] −50.9°[42]).

Its oxime melted at 223–226° dec., undepressed by admixture with authentic β-dihydrothebainone oxime of m.p. 223–225° dec. (reported[13] 225–226°).

1,x,x-Tribromo-β-dihydrothebainone was prepared by treating 301 mg. of β-dihydrothebainone (recovered from its perchlorate by partition between chloroform and dilute ammonia) dissolved in 30 cc. of acetic acid–absolute ether (1:1) containing a few drops of 4 *N* hydrobromic acid in acetic acid, with 3 cc. of a solution of 1.60 g. of bromine in 10 cc. of glacial acetic acid. Decoloration of the bromine was rapid. The mixture was allowed to stand at room temperature for 22 hours, then diluted with water, made just basic with ammonia, and extracted four times with chloroform. The residue from the washed, dried, filtered, and concentrated chloroform extracts (520 mg. after pumping out) crystallized when triturated under ethyl acetate, m.p. 212–214° dec. Several crystallizations from chloroform–alcohol gave small prisms melting at 219–221° with profound decomposition, $[\alpha]^{25}D$ −53.2° (*c* 3.18, chf.), infrared λ_{max} 5.78 μ (1727 cm.$^{-1}$) (*Anal.* Calcd. for $C_{18}H_{20}O_3NBr_3$: C, 40.17; H, 3.75; OCH_3, 5.77. Found: C, 40.53; H, 3.89; OCH_3, 5.76.) All attempts to convert this substance into an α,β-unsaturated ketone or into a substance in which the oxide ring is closed (action of 2,4-dinitrophenylhydrazine, 2,4,6-collidine, sodium iodide in acetone, lithium chloride in dimethylformamide, sodium ethoxide and the like) failed.

Hydrogenation of this substance (134 mg.) over Adams catalyst in acetic acid yielded **1-bromo-β-dihydrothebainone**, m.p. 172.5–174°, $[\alpha]^{26}D$ −32° (*c* 2.03, alc.), infrared λ_{max} 5.88 μ, after crystallization from alcohol and drying at 132°, identical with a sample prepared by the monobromination of β-dihydrothebainone.

Anal. Calcd. for $C_{18}H_{22}O_3NBr$: C, 56.85; H, 5.83. Found: C, 57.21; H, 6.08.

Its perchlorate melts at 272–276° dec., $[\alpha]^{25}D$ −12° (*c* 1.25, alcohol-water 1:1).

Anal. Calcd. for $C_{18}H_{23}O_7NBrCl$: C, 44.97; H, 4.82. Found: C, 45.18; H, 4.76.

Its 2,4-dinitrophenylhydrazone melts (solvated) at 144–148° with gas evolution, when crystallized from ethyl acetate–chloroform. For analysis it was dried at 100° and reduced pressure.

Anal. Calcd. for $C_{24}H_{26}O_6N_5Br$: C, 51.43; H, 4.68. Found: C, 52.00; H, 5.15.

1-Bromothebainone 2,4-Dinitrophenylhydrazone (XXVI). (a) **From β-Dihydrothebainone (XXV).**—The free base recovered from 402 mg. of β-dihydrothebainone perchlorate by partition between ammonia and chloroform was taken into 10 cc. of glacial acetic acid and brominated by dropwise addition of a solution of 2 millimoles of bromine in 8 cc. of glacial acetic acid. Decoloration of the bromine was rapid. The solution was allowed to stand 24 hours at room temperature to effect equilibration of bromine between positions 5 and 7, then treated with 220 mg. of 2,4-dinitrophenylhydrazine, and refluxed for five minutes. The cooled solution was made basic with ammonia, extracted four times with chloroform and the chloroform extracts washed twice with ammonia, once with water, dried, filtered and concentrated to yield an orange-red residue (704 mg.) which was chromatographed in alcohol-free chloroform on 15 g. of alumina. Elution with this solvent gave 439 mg. of crude crystalline dinitrophenylhydrazone which after recrystallization from ethyl acetate yielded a total of 229 mg. (41%) of 1-bromothebainone 2,4-dinitrophenylhydrazone, m.p. 203–205°. An analytical sample, crystallized several more times from ethyl acetate, melted at 207–208°, $[\alpha]^{27}D$ −1307° (*c* 1.63, chf.); −1090° (*c* 0.800, acetone), $\lambda_{max}^{chf.}$ 379 mμ, log ε 4.49. The substance exhibits a solid phase transition at about 165° during the m.p. determination. (*Anal.* Calcd. for $C_{24}H_{24}O_6N_5Br$: C, 51.62; H, 4.33. Found: C, 51.69; H, 4.45.)

(b) **From Thebainone (XXVII).**—A solution of 103 mg. of thebainone half-hydrate[26,43] and 70 mg. of 2,4-dinitrophenylhydrazine in 3 cc. of glacial acetic acid was heated on the steam-bath for 20 minutes, cooled, treated with 100 mg. of anhydrous sodium acetate, and brominated by the addition of 3.33 cc. of a solution of 1.60 g. of bromine in 100 cc. of acetic acid. A transient perbromide separated. After 5 minutes the mixture was diluted with water, made basic with ammonia and extracted several times with chloroform. The chloroform extracts were washed twice with dilute ammonia, once with water, dried, filtered and concentrated. The residue was crystallized three times from ethyl acetate to give 88 mg. of orange plates or prisms, m.p. 207–208°, undepressed by admixture with the material described above resulting from the action of two moles of bromine followed by 2,4-dinitrophenylhydrazine on β-dihydrothebainone. Their infrared spectra are indistinguishable.

(c) **From β-Thebainone (VIII).**—A sample of β-thebainone perchlorate was converted to its 2,4-dinitrophenylhydrazone,[44] m.p. 224–225°, and a solution of 63 mg. of this substance in 1 cc. of glacial acetic acid containing 15 mg. of anhydrous sodium acetate was brominated with 1.32 cc. of a solution of 1.60 g. of bromine in 100 cc. of acetic acid. A transient perbromide separated. After five minutes, processing of the mixture as described in the preceding example yielded 74 mg. of amorphous orange-red **1-bromo-β-thebainone 2,4-dinitrophenylhydrazone** which crystallized as an alcohol solvate from ethyl acetate–alcohol, 45 mg. of ruby red prisms, m.p. 157–165°, with vigorous gas evolution, $[\alpha]^{27}D$ −76.4° (*c* 1.57, chf.).

Anal. Calcd. for $C_{24}H_{24}O_6N_5Br \cdot C_2H_5OH$: C, 51.66; H, 5.00; C_2H_5OH, 7.62. Found: C, 52.47; H, 5.22; C_2H_5OH, 7.89.

This substance (34 mg.) was heated for 2.5 hours in 1 cc. of glacial acetic acid on the steam-bath. The mixture was diluted, made basic with ammonia, extracted several times with chloroform, and the chloroform extracts were washed, dried, filtered and concentrated. Several crystallizations of the residue from ethyl acetate gave orange-yellow plates of **1-bromothebainone 2,4-dinitrophenylhydrazone**, m.p. 206–207°, undepressed by admixture with the samples described above. Its infrared spectrum is indistinguishable from those of the two samples described above.

This substance can also be obtained more directly from β-thebainone by brominating the crude product (largely thebainone 2,4-dinitrophenylhydrazone) of the action of 2,4-dinitrophenylhydrazine on β-thebainone base in hot acetic acid.

1-Bromothebainone (XXVIII).—A solution of 200 mg. of 1-bromothebainone 2,4-dinitrophenylhydrazone in 20 cc. of acetone and 8 cc. of 12 *N* hydrochloric acid was refluxed for 20 minutes, cooled, diluted strongly with water, and extracted four times with chloroform. The chloroform extracts were washed with dilute ammonia, dried, filtered and concentrated to 25 cc. with chloroform. The rotation of this solution (−0.88°) corresponds to a content of unchanged dinitrophenylhydrazone of 17 mg. and, after removal of solvent, the residue, on partition between 30% acetic acid and 1:1 benzene–cyclohexane, yielded 13 mg. of recrystallized starting material, m.p. 203.5–205°, $[\alpha]^{25}D$ −1360° (*c* 0.0472, chf.).

The colorless acid raffinate solution was made basic with ammonia and extracted four times with chloroform. The chloroform extracts were washed, dried, filtered and concen-

(42) H. Rapoport and J. B. Lavigne, THIS JOURNAL, **75**, 5329 (1953). We are indebted to Professor Rapoport for a sample of crystalline β-dihydrothebainone. It was originally reported as an oil and in our hands had never crystallized, even though highly purified through its very sparingly soluble perchlorate.

(43) Our sample was prepared by acid hydrolysis of phenolic dihydrothebaine; *cf.* M. Gates and R. Helg, THIS JOURNAL, **75**, 379 (1953).

(44) M. Gates and R. Helg, ref. 43.

trated to leave 106 mg. of crude 1-bromothebainone, m.p. 185–191°, which after crystallization from ethyl acetate gave 76 mg. (60% on basis of starting material not recovered) of small colorless needles, m.p. 196.5–198°. An analytical sample melted at 198.5–199.5°, $[\alpha]^{27}D$ −85° (*c* 1.54, chf.). (*Anal.* Calcd. for $C_{18}H_{20}O_3NBr$: C, 57.15; H, 5.33. Found: C, 57.45; H, 5.31.) Like thebainone, this substance is readily soluble in dilute alkalies with a yellow color. Its m.p. is undepressed by admixture with the substance, m.p. 197–198°, $[\alpha]^{27}D$ −86.8° (*c* 1.67, chf.), prepared by monobromination of thebainone half-hydrate (1 cc. of a solution of 1.60 g. bromine in 100 cc. of acetic acid, 31 mg. of thebainone in 1 cc. of acetic acid, processed as usual and recrystallized three times from ethyl acetate). Their infrared spectra are indistinguishable (infrared λ_{max} 5.97 μ). A small sample was reconverted to its 2,4-dinitrophenylhydrazone, m.p. 204–205.5°.

Cleavage with lower concentrations of hydrochloric acid carried out for longer periods of time gave poorer results.

1,x-Dibromothebainone was prepared by bromination of 1-bromothebainone (298 mg.), m.p. 195–197°, in 10 cc. of acetic acid with 3 cc. of acetic acid containing 0.79 millimole of bromine. Hydrobromic acid in acetic acid (4 *N*) was added dropwise until the initial precipitate of perbromide began to redissolve. After 20 minutes the completely homogeneous decolorized solution was diluted with water, made just basic with ammonia, and extracted four times with chloroform. The residue from the washed, dried, filtered and concentrated chloroform extracts crystallized readily when covered with acetone to yield 177 mg. of small tan prisms, m.p. 210-214° with profound decomposition and foaming. Recrystallization from chloroform–acetone (very sparingly soluble in acetone alone) gave material of m.p. 215–218°, profound decomposition, infrared λ_{max} 5.90 μ (1690 cm.$^{-1}$).

Anal. Calcd. for $C_{18}H_{19}O_3NBr_2$: C, 47.29; H, 4.19. Found: C, 47.43; H, 4.36.

The substance gives no precipitate with alcoholic silver nitrate, and is unaltered by short boiling with collidine. It is slowly soluble in cold 15% potassium hydroxide solution, and on warming this solution deposits an amorphous solid from which no 1-bromocodeinone could be isolated.

This substance can be prepared in better yield (355 mg. from 308 mg.) by dibromination of thebainone half-hydrate, essentially as above but without added hydrogen bromide in acetic acid.

1-Bromodihydrothebainone (XXIX).—A solution of 174 mg. of 1-bromothebainone (from cleavage of its dinitrophenylhydrazone) in 15 cc. of alcohol was hydrogenated over 21 mg. of Adams catalyst. After the theoretical amount (11.9 cc.) of hydrogen had been absorbed (11 min.), the hydrogenation was interrupted. The filtered solution was diluted with water, made basic with ammonia, and extracted four times with chloroform. The washed, dried, filtered and concentrated chloroform extracts yielded 191 mg. (hydrated) of colorless residue which crystallized readily on scratching under ethyl acetate, m.p. 99–115°, foaming, resolidifying, remelting at 154–162°, infrared λ_{max} 5.87 μ (reported[45] foaming 120–127°, melting 167°). The substance was purified through its **hydriodide**, 187 mg. (80%), m.p. 204–206° dec. Further crystallization from water raised the m.p. to 206.5–208.5° dec., beautiful colorless needles which crumble on drying at 100°. Melting points, yields and analysis refer to material so dried.

Anal. Calcd. for $C_{18}H_{23}O_3NBrI$: C, 42.54; H, 4.56. Found: C, 42.42; H, 4.52.

This substance was reported by Schöpf[45] but not analyzed. **1-Bromodihydrothebainone**, $[\alpha]^{25}D$ −81.7° (*c* 0.930, alc.), m.p. 95–120°, foaming, resolidification, remelting 165.5–167.5° undepressed by admixture of an authentic sample,[45] can be recovered from the hydriodide. The infrared spectra of the bases are indistinguishable.

For use in the following experiment, it is convenient to convert the crude hydrogenation product to its **hydrobromide** (66.5%), m.p. 202–206°, foaming 210–212°, loss of hydrate water 140–160°, although this salt is of little value for characterization because of its unsharp melting point; $[\alpha]^{26}D$ −48.6° (*c* 1.07, alc.)

Anal. Calcd. for $C_{18}H_{23}O_3NBr_2 \cdot 2H_2O$: C, 43.48; H, 5.47; H_2O, 7.25. Found: C, 43.82; H, 5.69; H_2O, 7.96.

(45) C. Schöpf and T. Pfeifer, *Ann.*, **483**, 157 (1930).

This salt was also reported by Schöpf[45] but not analyzed.

Hydrogenation of 1-bromothebainone (96 mg.) over palladium-on-barium carbonate (200 mg.) in alcohol led to 74 mg. (theory 76 mg.) of crude dihydrothebainone half-hydrate XXX, m.p. 123–136°, which was purified through its **hydriodide**, m.p. 277–278.5°, mixed m.p. with a sample prepared from authentic dihydrothebainone undepressed.

Anal. Calcd. for $C_{18}H_{24}O_3NI$: C, 50.36; H, 5.63. Found: C, 50.33; H, 5.76.

The hydriodide was converted to **dihydrothebainone** with dilute ammonia and recrystallized from aqueous alcohol, as heavy colorless prisms, m.p. 123–152°.[46] Its infrared spectrum is indistinguishable from that of an authentic sample, infrared λ_{max} 5.90 μ). **Its oxime**, m.p. 252–253.5°, did not depress the m.p. of an authentic sample.

1-Bromocodeinone (XXXII). (a) **From 1-Bromodihydrothebainone (XXIX).**[47]—1-Bromodihydrothebainone hydrobromide dihydrate (497 mg.) in 10 cc. of glacial acetic acid was treated dropwise with swirling with 7 cc. of glacial acetic acid containing 2 millimoles of bromine. Decolorization was rapid. The solution was allowed to stand for 15 minutes after decolorization was complete, treated with 220 mg. of 2,4-dinitrophenylhydrazine, allowed to stand another hour, treated with 164 mg. of anhydrous sodium acetate, and finally allowed to stand 23 hours. The reaction mixture was concentrated to dryness under diminished pressure and the residue taken into 10 cc. of purified pyridine and refluxed for 30 minutes. The pyridine was removed under diminished pressure, and the residue, in chloroform, was extracted five times with 10% sodium hydroxide, washed, dried, filtered, concentrated and chromatographed on 25 g. of alumina. Development with alcohol-free chloroform eluted a total of 276 mg. of crystalline dinitrophenylhydrazone, m.p. 203–208°, which after two crystallizations from ethyl acetate gave 144 mg. (26%) of **1-bromocodeinone-2,4-dinitrophenylhydrazone (XXXI)** as orange prismatic needles, m.p. 222–224°, undepressed by admixture with an authentic sample prepared from 1-bromocodeinone (*vide infra*). An analytical sample melted at 224–225°, $[\alpha]^{27}D$ −1968° (*c* 0.064, chf.), λ_{max}^{chf} 377 mμ, log ϵ 4.51. Its infrared spectrum is indistinguishable from that of the sample from 1-bromocodeinone.

Anal. Calcd. for $C_{24}H_{22}O_6N_5Br$: C, 51.81; H, 3.99. Found: C, 52.07; H, 4.23.

Cleavage of this dinitrophenylhydrazone (200 mg.) was accomplished by refluxing in a mixture of 20 cc. of acetone and 12 cc. of 12 *N* hydrochloric acid for 20 minutes. The cooled mixture was diluted with water and extracted 4 times with chloroform. The quantitative removal of dinitrophenylhydrazone hydrochlorides of this series from aqueous solutions by chloroform is quite general. The chloroform extracts were washed with dilute ammonia, dried, filtered, concentrated and adjusted to 25 cc. The rotation of this solution (−3.58°) corresponded to a content of unchanged dinitrophenylhydrazone of 46 mg., and after partition of the residue from this solution between 50% aqueous acetic acid and 1:1 benzene–cyclohexane, the acid layers yielded by appropriate processing 32 mg. of recrystallized unchanged 1-bromocodeinone dinitrophenylhydrazone, m.p. 219–222°.

The colorless acid solution was cooled with ice, treated with excess 10% sodium hydroxide and extracted 4 times with peroxide-free ether. The ether extracts were washed with dilute alkali, then with saturated brine, filtered through anhydrous sodium sulfate, and concentrated. The residue (48 mg.) crystallized spontaneously (in other runs the crystallizate at this point melted at about 90–92°, but on moistening with ethyl acetate altered form and then melted at 185–195°. The low-melting form, possibly a solvate, has not been characterized). and was recrystallized from ethyl acetate to yield in two crops a total of 30 mg. (27% on the basis of starting material not recovered) of colorless needles, m.p. 197.5–199° dec. One further crystallization raised the m.p. to 201–202° dec. (turning deep red, as does codeinone), undepressed by admixture of an authentic sample

(46) In our hands this substance has always melted unsharply with loss of hydrate water, even though carefully purified through its hydriodide. In our opinion its m.p. is not a good criterion of either purity or identity; *cf.* T. D. Perrine and L. F. Small, *J. Org. Chem.*, **17**, 1543 (1952).

(47) This procedure is essentially Goto and Yamamoto's (ref. 32) modification of our original method.

(*vide infra*); $[\alpha]^{26}D$ −182.7° (*c* 1.42, chf.). Its infrared spectrum is indistinguishable from that of the sample from 1-bromocodeine.

(b) **From 1-Bromocodeine.**—The oxidation procedure of Homeyer and DeLaMater,[35] when applied to 1-bromocodeine[34] (1.54 g., m.p. 158–161°) yielded 1.00 g. (68.5%) of pure **1-bromocodeinone**, m.p. 202.5–203.5°, $[\alpha]^{25}D$ −180.6° (*c* 1.30, chf.), λ_{max}^{alc} 288 mμ, log ε 3.33, infrared λ_{max} 5.97 μ.

Anal. Calcd. for $C_{18}H_{18}O_3NBr$: C, 57.46; H, 4.82. Found: C, 57.55; H, 5.22.

Its 2,4-dinitrophenylhydrazone, crystallized from ethyl acetate, melted at 224–224.5° and did not depress the m.p. of the sample prepared from 1-bromodihydrothebainone.

Catalytic hydrogenation of 1-bromocodeinone (XXXII) (86.4 mg.) in 5 cc. of alcohol over 15 mg. of Adams catalyst, yielded crude **1-bromodihydrocodeinone** (19 mg., m.p. 174–191°) which after three crystallizations from ethyl acetate had m.p. 207.5–208.5°, undepressed by admixture of authentic 1-bromodihydrocodeinone of m.p. 206.5–208.5°, prepared by bromination of dihydrocodeinone.[29] Its melting point was depressed on admixture with the starting 1-bromocodeinone. This hydrogenation was interrupted after 1 mole of hydrogen had been absorbed, although the uptake showed no sign of slackening at this point. The dihydro base was isolated by chromatography on alumina (3.0 g.) in alcohol-free chloroform and appeared as the most weakly adsorbed fraction.

Codeine (XXXIII).—A mixture of 200 mg. of 1-bromocodeinone, m.p. 202.5–203.5°, 0.5 g. of lithium aluminum hydride and 30 cc. of carefully purified tetrahydrofuran was refluxed for 46 hours. After destruction of the excess reagent with ethyl acetate, the mixture was acidified with 2 *N* hydrochloric acid and extracted with ether. The acid layer was added slowly to a strong potassium hydroxide solution containing Rochelle salt. The resulting alkaline suspension was extracted three times with chloroform, and the chloroform layers were washed, dried, filtered, and concentrated to give 146 mg. (159 mg. theory) of colorless glass which was converted to its **hydrobromide**,[36] 131 mg., m.p. 148–150°, resolidifying, remelting 273–278°. Recrystallization of this hydrobromide gave 110 mg., properties essentially unchanged.

This hydrobromide, dissolved in warm water, on treatment with ammonia gave an oil which rapidly crystallized, 70 mg., m.p. 153–156°. Recrystallization from dilute methanol gave 59 mg., m.p. 156.5–158°, large prisms, hydrated, $[\alpha]^{27}D$ −137° (*c* 1.15, alc.) (reported[48] −135.9°). Its m.p. was undepressed on admixture with authentic codeine of m.p. 157–158.4°,[49] crystallized as above, but was strongly depressed by admixture of 1-bromocodeine of m.p. 161–163°. Its infrared spectrum was indistinguishable from that of an authentic sample.

Morphine (I).—Codeine was demethylated essentially as described by Rapoport and his co-workers,[37] but the processing was rendered simpler (no chromatography or sublimination was necessary) and the yield improved by using hydrosulfite in all alkaline solutions. Morphine was obtained in 34% yield as colorless needles, m.p. 254–256.4°, $[\alpha]^{27}D$ −126° (*c* 2.32, methanol) (reported[49] m.p. 253–254°).

(48) O. Hesse, *Ann.*, **176**, 189 (1875).

(49) R. Kempf, *J. prakt. Chem.*, [2], **78**, 201 (1908), has reported the melting point of anhydrous codeine to be 157°. Various other authors report values in the neighborhood of 155° for either hydrated or anhydrous codeine.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND THE INSTITUTE FOR ENZYME RESEARCH, UNIVERSITY OF WISCONSIN]

Phosphoric Esters of Biological Importance. VI. The Synthesis of D-Glucosamine 6-Phosphate and N-Acetyl-D-glucosamine 6-Phosphate[1]

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RECEIVED OCTOBER 24, 1955

Procedures for the synthesis of glucosamine 6-phosphate and N-acetylglucosamine 6-phosphate have been developed. N-Anisylidene glucosamine in pyridine is treated with diphenyl phosphorochloridate and the product is acetylated before isolation. The anisylidene group is removed by hydrolysis and the 1,3,4-tri-*O*-acetyl-6-diphenylphosphoroglucosamine hydrochloride is converted to glucosamine 6-phosphate by reductive cleavage of the phenyl groups followed by hydrolysis of the acetyl groups. Barium hydrogen glucosamine 6-phosphate is isolated at *p*H 4.0. The barium salt may be separated at *p*H 8 but this treatment results in the conversion of part of the glucosamine 6-phosphate to a more acid-labile compound. Another procedure is described for the conversion of the tri-*O*-acetyl intermediate to N-acetylglucosamine 6-phosphate which is isolated as the crystalline monoammonium salt.

The possible involvement of the phosphoric esters of glucosamine and N-acetylglucosamine in the biosynthesis of the mucopolysaccharides encouraged us to seek a definitive chemical synthesis for these compounds. During the course of this work, Glaser and Brown[3] obtained very good experimental evidence for such involvement and extension of this work should be facilitated by the availability of these synthetic phosphoric esters. Glucosamine 6-phosphate has previously been prepared[4] by the enzymatic phosphorylation of glucosamine using ATP. A chemical synthesis has also been reported[5] but the product was of unknown purity. N-Acetylglucosamine 6-phosphate has been synthesized by the chemical[6] and enzymatic[7] acetylation of glucosamine 6-phosphate.

The synthesis of glucosamine 6-phosphate described in this paper is accomplished by the sequence of reactions shown in Fig. 1. In early experiments, the product was isolated, as the barium salt, at *p*H 8.0 to 8.5. Although the elementary analysis, optical rotation and periodate oxidation, indicated that the compound was pure, the acid-lability of part of the phosphorus indicated the presence of a contaminant. Even after repeated precipitations of the compound, the phosphorus liberated by hydrolysis in 1 *N* HCl at 100° for 30 min-

(1) Presented at the 128th National meeting of the American Chemical Society, Minneapolis, 1955. Supported in part by a research grant from the University Research Committee and in part by a research grant (A-531) from The National Institute of Arthritis and Metabolic Diseases, of the National Institutes of Health, Public Health Service.

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(3) L. Glaser and D. H. Brown, *Proc. Nat. Acad. Sci.*, **41**, 253 (1955).

(4) D. H. Brown, *Biochim. Biophys. Acta*, **7**, 487 (1951).

(5) J. M. Anderson and E. Percival, *Chem. and Ind.*, **33**, 1018 (1954).

(6) S. Roseman, *Federation Proc.*, **13**, 283 (1954).

(7) D. H. Brown, *Biochim. Biophys. Acta*, **16**, 429 (1955).