[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, AND THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

THE HALOGENO-MORPHIDES AND -CODIDES, AND THE MECHANISM OF THE MORPHINE-APOMORPHINE TRANSFORMATION[1]

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Received January 6, 1940

The halogenomorphides and halogenocodides are formed when the secondary alcoholic hydroxyl group of morphine or codeine is replaced by a halogen atom. Although the compounds occupy a position of considerable importance in the development of the morphine structural theory, and are the source of the morphine and codeine isomers, there has been no direct proof of structure offered for any single member of the series.

The related pair, α-chloromorphide and α-chlorocodide, are the principal products obtained when morphine and codeine, respectively, are treated with thionyl chloride or phosphorus pentachloride. The halogen atom has tacitly been assumed to take the place of the hydroxyl that is known to occupy the 6-position, although it has been shown (1,2,3) in recent years that replacement of a group at this point in the nucleus often involves an α,γ-shift, as a result of which the new group may appear at position 8. In carrying out numerous kilogram-scale preparations, we have observed that the α compounds are not the only products of the reaction, but are accompanied by the β-halogeno derivatives to the extent of 10% to 15% of the total yield. In the codeine series, α- and β-chlorocodides were obtained in part in the form of a new molecular compound of constant properties, that could not be separated into the components by fractional crystallization, although α- and β-chlorocodides themselves differ considerably in solubility. Separation through salts, a method previously employed successfully for similar molecular compounds in the

[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. Publication authorized by the Surgeon General, U. S. P. H. S.

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morphine series (4), also failed, but the nature of the compound could be shown by preparing it from equal amounts of α- and β-chlorocodides.

The nature of the isomerism between β-chloromorphide or β-chlorocodide and the respective α-chloro derivatives has often been in question (5). It now appears most probable that the β series arises from the α series through an α,γ-shift of halogen, and has the unsaturated center at the 6,7-position. This 8-halogeno structure was postulated several years ago by Schöpf without any experimental evidence (6)[4]. The fact that bromocodide cannot be caused to isomerize in the sense of the α- to β-chlorocodide change (7), indicates that the bromo series may have the same structure as the β-chloro series, although there is no obvious reason why an α-bromo series should not exist. Fluoromorphides have not been prepared, and the iodo compounds have been very little studied.

The present investigation was started in 1933, with the object of establishing definitely the position of the halogen atom in the various known halogeno derivatives mentioned above. Because of difficulties involving rearrangements and anomalous reactions, it has been only partly successful.

It is apparent that halogenation of dihydrocodeine can involve no rearrangement beyond a probable Walden inversion, and that the halogen atom in chlorodihydrocodide must have the same position, although not necessarily the same configuration, as the hydroxyl group in the starting material. There exists, however, no proof of a structural similarity between α-chlorocodide and chlorodihydrocodide, *i.e.*, that no rearrangement takes place in the conversion of codeine to α-chlorocodide. We have now found that by imposition of suitable conditions, namely, hydrogenation of α-chlorocodide hydrochloride in glacial acetic acid, the usual complete reductive elimination of chlorine can be so repressed that a 52% yield of chlorodihydrocodide can be obtained. The remainder of the material is accounted for as tetrahydrodesoxycodeine (40%) and dihydrodesoxycodeine-D (7.5%). This relationship of α-chlorocodide to chlorodihydrocodide leaves no doubt that the halogen atom in the former is actually located on carbon 6.

The evidence for the β-chloro and the bromo series is less satisfactory. Replacement reactions indicate in general that the members of these two series are of the same type. Hydrolysis of β-chlorocodide and of bromocodide yields predominantly isocodeine (8), and reaction of either halogeno compound with secondary amines appears to result exclusively in 6-amino derivatives (1), just as mercaptolysis gives only 6-alkylthio derivatives (2). It is, however, remarkable that in large-scale hydrolysis of bromocodide

[4] The argument of Schöpf, adduced from the work of Small and Cohen on the catalytic reduction of β-chlorocodide, is not very convincing, for α-chlorocodide can likewise be hydrogenated to yield, in part, tetrahydrodesoxycodeine.

we have never observed regeneration of any trace of codeine, which might be expected to appear with its diastereoisomer, isocodeine. These replacement reactions might be interpreted as indicating the 6-position for halogen, but we believe that they favor rather the 8-position, chiefly on the ground, that in the α series, where the structure is known, replacement of halogen involves preferentially the α,γ-shift.

In view of the above cited parallelisms between the β-chloro and bromo compounds, it is somewhat surprising to find, that while α-chloromorphide and bromomorphide in acetic acid react with great ease with hydriodic acid to give the same iodomorphide, β-chloromorphide is quite indifferent, even under more vigorous conditions.

Attempts to locate the halogen of β-chlorocodide by substitution and reduction procedures gave negative results. Whereas dihydrocodeine is transformed smoothly to 6-chlorodihydrocodide by phosphorus pentachloride, dihydroisocodeine yields only a phosphorus-containing compound, probably an ester. Dihydropseudocodeine and dihydroallopseudocodeine both react to give a single 8-chlorodihydrocodide. As a minor product of the same reaction, a non-phenolic base containing two halogen atoms is formed. This may be assumed to be 1,8-dichlorodihydrocodide. Thionyl chloride does not act on the alcoholic hydroxyl of the dihydrocodeine isomers, but chlorinates instead the aromatic nucleus[5], presumably at the 1-position (9). The monochlorodihydrocodeine isomers so obtained are transformed with great ease back to the dihydrocodeine isomers by sodium and alcohol reduction, a reaction quite general for morphine derivatives halogenated in the aromatic ring, but not for those carrying halogen elsewhere in the nucleus.

The apparent impossibility of obtaining all four isomeric chlorodihydrocodides effectively blocks direct determination of the structure of β-chlorocodide. After long investigation, it was found that β-chlorocodide could be hydrogenated, as the hydrochloride in alcoholic hydrogen chloride solution, with retention of the halogen atom in a small portion of the product. While the β-chlorodihydrocodide obtained could not be brought to satisfactory analytical purity, it is obviously different from either 6-chlorodihydrocodide or 8-chlorodihydrocodide. This still leaves the alternative configuration at the 6- or 8-position as a possibility, and there seems to be little prospect of proving the β-chlorocodide structure by this method.

8-Chlorodihydrocodide proved to be exceptionally unreactive. Drastic

[5] Späth and Spitzer, *Ber.*, **59**, 1477 (1926), observed nuclear chlorination in the preparation of picolinic acid chloride with impure thionyl chloride, which they remark upon as surprising, since picolinic acid is not an especially easy substance to chlorinate.

sodium and alcohol reduction, and prolonged electrolytic reduction, left it unchanged, while autoclave treatment with sodium methoxide did not remove hydrogen chloride[6], but effected only demethylation at position 3, to give 8-chlorodihydromorphide[7]. Elimination of hydrogen chloride was ultimately accomplished with sodium and cyclohexanol (to give desoxycodeine-D) and is described in the following paper (10).

Attempts to replace the hydroxyl of the dihydrocodeine isomers with bromine met with only partial success. Dihydrocodeine, with phosphorus tribromide, usually yielded phosphorus-containing products, although in one experiment a phosphorus-free phenolic product was obtained that had the composition of a demethylated bromodihydrocodide. As in attempted chlorinations, dihydroisocodeine gave always products that contained phosphorus. From dihydropseudocodeine, 8-bromodihydrocodide was obtained in poor yield, while dihydroallopseudocodeine apparently suffered bromination and loss of hydrogen bromide, together with demethylation at the 3-methoxyl group (10). These reactions contributed little to the solution of the problem, since catalytic hydrogenation of bromocodide under a wide variety of conditions gave principally halogen-free products. The structure of bromomorphide, like that of β-chloromorphide, must rest for the present on speculations and analogy. Experiments now in progress on the reaction of phenylmagnesium bromide with these halogeno compounds may contribute evidence on the question.

POLYHALOGEN DERIVATIVES. THE MECHANISM OF APOMORPHINE FORMATION

In devising a better route to the powerful drug dihydrodesoxymorphine-D ("Desomorphine"), discovered in the Virginia laboratory in 1930[8], Kurt Warnat (Hoffmann-La Roche, Basel) made the interesting discovery that morphine, in warm concentrated hydrochloric acid, adds a molecule of hydrogen chloride at the 4,5-oxide ring, and suffers replace-

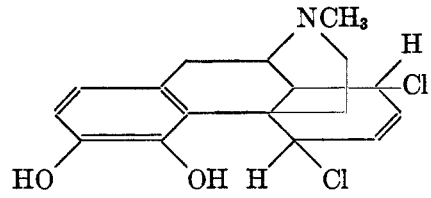
[6] Under parallel conditions, 6-chlorodihydrocodide and 6-chlorodihydromorphide lose hydrogen chloride to give desoxycodeine-C and desoxymorphine-C. Small and Cohen, *J. Am. Chem. Soc.*, **53**, 2214 (1931); Small and Morris, *J. Am. Chem. Soc.*, **55**, 2874 (1933).

[7] The demethylating action of sodium alkoxide in the morphine series has been previously noted by Small, Turnbull, and Fitch, *J. Org. Chem.*, **3**, 212 (1938); Small and Morris, *J. Am. Chem. Soc.*, **55**, 2876 (1933).

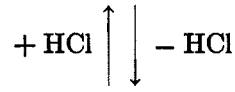
[8] Dihydrodesoxymorphine-D was prepared by Small and Eilers in November 1930 and submitted for pharmacological tests on July 21, 1932. The publications, Small, Yuen, and Eilers, *J. Am. Chem. Soc.*, **55**, 3863 (1933); Small, U. S. Patent, 1,980,972, (Nov. 13, 1934) embody later improvements in the preparation.

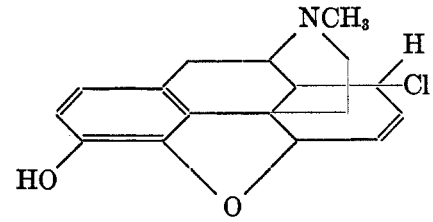
ment of the alcoholic hydroxyl by chlorine in a manner parallel to that involved in the formation of β-chloromorphide (11).

With the kind permission of Dr. Warnat, the unpublished details of the reaction are here communicated. Warnat formulates the dichlorodihydrodesoxymorphine as in formula I, and as proof advances the formation of a diacetyl derivative and the facile conversion of I to β-chloromorphide (II) in the presence of alkali. We observe that this transformation proceeds with such ease that it is not possible to isolate the base,



I. Dichlorodihydrodesoxymorphine





II. β-Chloromorphide

dichlorodihydrodesoxymorphine, from its hydrochloride, for the ring-closure takes place even in the presence of sodium bicarbonate. Indeed, no alkaline agent is necessary, for if the very sparingly soluble hydrochloride is merely boiled with water for ten minutes, it passes completely into solution, and the solution becomes strongly acid. By concentration under diminished pressure, the hitherto unknown β-chloromorphide hydrochloride is obtained in good yield. The ease of ring-closure is remarkable in view of the fact that the 4-hydroxyl is so weakly acidic that it does not react with diazomethane; a monomethyl ether is formed, which is transformed to β-chlorocodide by sodium bicarbonate, and hence must have had the 4-hydroxyl free.

We find that β-chloromorphide is an intermediate step in the con-

version of morphine to dichlorodihydrodesoxymorphine. This is evident from the fact that β-chloromorphide can be used instead of morphine as the starting material for the reaction, and is demonstrated more convincingly by our observation that if the reaction between morphine and hydrochloric acid is interrupted at the first appearance of crystals of dichlorodihydrodesoxymorphine hydrochloride, the hydrochloric acid solution contains approximately equal amounts of morphine and β-chloromorphide.

β-Chloromorphide has long been recognized as being an intermediate in the transformation of morphine to apomorphine (12). It is, however, only the first step in the process, the second intermediate being dichlorodihydrodesoxymorphine, for experiment shows that the dichloro compound, under the conditions imposed in the morphine-apomorphine reaction, gives a yield of apomorphine quite comparable to that obtained from morphine. The mechanism proposed by Schöpf and Hirsch (13), which involves an improbable series of alternate additions and eliminations of hydrogen chloride, becomes superfluous. The essential steps in the formation of apomorphine have now been realized individually and successively. Morphine is first transformed to β-chloromorphide, through substitution of chlorine for the alcoholic hydroxyl, simultaneous with, or followed by an α,γ-shift of halogen. The cyclic ether group of β-chloromorphide, activated by the 6,7-unsaturation (14), adds a molecule of hydrogen chloride, and the resulting dichlorodihydrodesoxymorphine undergoes rearrangement. The transitory intermediate may be of the metathebainone type (a), analogous to that postulated by Schöpf, but we consider it more probable that the intermediate is formed by loss of hydrogen chloride at 8,14 (b), and that an α,γ-shift of the chain from 13 to 8 is accompanied by loss of the second molecule of hydrogen chloride (aromatization) to yield apomorphine. Dichlorodihydrodesoxymorphine

Morphine

↓

β-Chloromorphide

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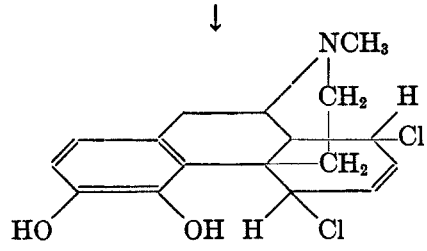

Dichlorodihydrodesoxymorphine

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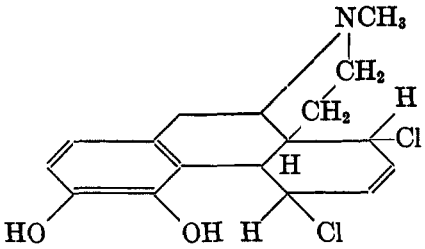
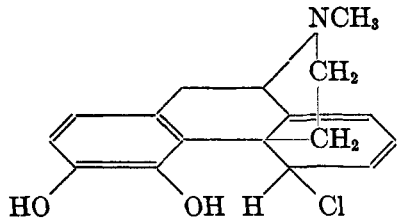


(a)



(b)

Possible intermediates

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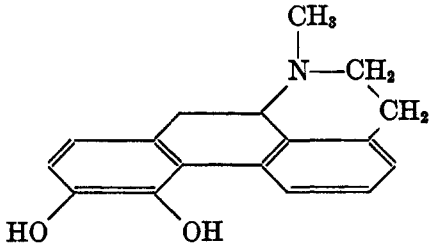

Apomorphine

carries halogen at both C-5 and C-8, and, of these positions, the former is probably the more active; this follows from the extreme ease of ether ring-closure to the 5-position, and the comparative inactivity of β-chloromorphide toward iodination or hydrolysis. That the shift of the ethanamine chain does not proceed toward C-5, an adjacent carbon atom, may be due to the relative difficulty of formation of the 7-membered ring. The only proved examples of a move of the chain to this position also involve breaking the ring structure, between C-9 and nitrogen.

It is reasonable to assume that apocodeine (apomorphine 3-methyl ether, known as pseudoapocodeine in early publications) is formed from codeine by a mechanism similar to that which we propose for apomorphine. This assumption receives some support in Knorr's observation (15) that a better yield of apocodeine is obtained from pseudocodeine (in which the first step, an α,γ-shift, has already taken place) than from codeine. The usual preparative methods have consisted in melting codeine with oxalic acid or zinc chloride. In a recent improvement on the oxalic acid method, Folkers (16) succeeded in obtaining a 12.8% yield of apocodeine. We have observed, in experiments unrelated to the subject of this paper, and in which no attempt was made to find optimum conditions, that fusion

of codeine with glacial phosphoric acid gives yields of apocodeine of about 30%.

Trichloromorphide. Morphine reacts with thionyl chloride to form principally α-chloromorphide (17). The beautifully crystalline product obtained from the reaction has, however, a specific rotation about 100° lower than that of pure α-chloromorphide. By the use of suitable purification methods, we have found that this is due chiefly to the presence of β-chloromorphide, (to the extent of about 3%), but that a second by-product, containing three chlorine atoms, can also be isolated (1.2% yield). This new compound, which we shall call trichloromorphide, is a phenolic base, and reacts with diazomethane to give a monomethyl ether, trichlorocodide, which has no phenolic properties. This result, together with the fact that trichloromorphide is regained unchanged from its solution in alkali, shows that it is not related to Warnat's dichlorodihydrodesoxymorphine. Analysis indicates clearly that the morphine alcoholic hydroxyl and two hydrogen atoms have been replaced by chlorine. The 1- and 6- (or 8-) positions for two of the halogens are therefore probable, but the location of the third is not obvious. Attempts to obtain identifiable halogen-free material by various reductions of trichlorocodide were unsuccessful.

Pentachloroxycodide. Codeine, dihydropseudocodeine, β-chlorocodide, and α-chloromorphide are converted to resinous products by cold sulfuryl chloride. Morphine, which is ordinarily more sensitive than codeine to acidic agents, is unaffected. α-Chlorocodide reacts very rapidly at 0° with sulfuryl chloride to give a good yield of crystalline base having the composition $C_{18}H_{20}Cl_5NO_3$, *i.e.*, containing one oxygen and four chlorine atoms more than the starting material. Its solubility in organic media shows that it is not perchlorinated at nitrogen. From the analytical results, it is apparent that the new constituents have been added, not substituted, but no suggestion can be offered concerning the mode of addition. Neither hydrolysis nor reduction yielded any identifiable products.

EXPERIMENTAL

Hydrogenation of α-chlorocodide. A suspension of 10.0 g. of α-chlorocodide (of m.p. 151°, $[\alpha]_D^{26}$ −383.0°) in 25 cc. of absolute ether was treated with an excess of ethereal hydrogen chloride, and the pasty mass was stirred vigorously until evolution of heat ceased. The powdery, amorphous salt was filtered, washed well with absolute ether, and dried in a vacuum; yield 11.7 g. The entire product was dissolved in 40 cc. of glacial acetic acid (distilled from chromic anhydride) and subjected to hydrogenation in the presence of 100 mg. of platinum oxide. The absorption, corrected to standard conditions, was 1282 cc., or 1.73 moles, and stopped completely in one hour. After dilution with an equal volume of water, the solution was filtered, layered with 300 cc. of ether, and made alkaline with ammonia. The

precipitate extracted readily into the ether, from which large, glassy, six-sided crystals rapidly separated. These crystals, and the residue from distillation of the ether, were treated with 5.0 g. of *d*-tartaric acid. The first crop of tartrate, which separated at room temperature, had the m.p. 191–192° (foaming). It was converted to the base, and yielded 5.2 g. of chlorodihydrocodide, m.p. after crystallization from alcohol, 172.5–174°, no depression in mixture with an authentic sample.

Anal. Calc'd for $C_{18}H_{22}ClNO_2$: C, 67.58; H, 6.94; Cl, 11.10.
Found: C, 67.46; H, 7.05; Cl, 11.22, 11.23.

Chlorodihydrocodide hydrochloride melts in an evacuated tube at 203–205°, solidifies, and remelts at 226°. In water it shows $[\alpha]_D^{26}$ −129.5° (c = 1.17). The base has $[\alpha]_D^{27}$ −177.8° (chloroform, c = 1.57).

The mother liquors from the precipitation of chlorodihydrocodide tartrate gave 1.1 g. of dihydrodesoxycodeine-D acid tartrate (equivalent to 0.72 g. of base) after standing several days in the ice-box. The salt melted at 125–128° (gas evol.) and did not depress the melting point of a known sample. The separation of the tartrates is possible only because of the marked tendency of dihydrodesoxycodeine-D tartrate toward delayed crystallization. The end mother liquors from preparation of the tartrate gave 3.8 g. of tetrahydrodesoxycodeine hemihydrate when converted to base in the usual way. These products account for 9.9 g. of the 10 g. of starting material.

Hydrogenation of β-chlorocodide. Numerous attempts to reduce β-chlorocodide without dehalogenation, as described for the α-isomer, resulted only in dihydrodesoxycodeine-D and tetrahydrodesoxycodeine, accompanied by unreduced β-chlorocodide when catalyst of low activity was used. Reduction in alcoholic hydrogen chloride solution was occasionally successful; the cause of the variations could not be ascertained. Ten grams of β-chlorocodide, $[\alpha]_D$ −10°, in 120 cc. of absolute alcohol with 80 cc. of saturated alcoholic hydrogen chloride and 100 mg. of platinum oxide absorbed 1825 cc. (2.3 moles) of hydrogen rapidly. After removal of the catalyst, solvent and excess acid were taken off under diminished pressure at 40°, the salt was dissolved in water, and the base liberated by ammonia and brought into ether. The ether solution was extracted with the calculated amount of 0.2 *N* hydrochloric acid in seven fractions. The first two fractions yielded only tetrahydrodesoxycodeine; fractions 3 to 5 contained this base together with halogen-containing material. Fraction 6 gave nearly pure β-chlorodihydrocodide (fraction 7, negative). After purification from alcohol, the base melted unsharp at about 145°. In alcohol it showed $[\alpha]_D^{25}$ +37.5° (c = 1.0). Although analytical results were unsatisfactory, the *dextro* rotation value makes it probable that the product is as claimed, for all the other possible reduction-products are *levo*rotatory.

Anal. Calc'd for $C_{18}H_{22}ClNO_2$: C, 67.58; H, 6.94; Cl, 11.10.
Found: C, 67.41; H, 7.83; Cl, 11.18.

Reduction of bromocodide hydrobromide in glacial acetic acid, with excess hydrogen bromide and various catalysts resulted in absorption of about 2.5 moles of hydrogen. The principal product was always tetrahydrodesoxycodeine. Some bromine-containing product could be isolated by exhaustive fractional extraction, but the basicity differences involved were too small to permit complete separation.

Iodomorphide. The halogen atom in α-chloromorphide and bromomorphide enters into exchange reactions so readily that the hydriodides cannot be prepared in the usual way. Even under the gentlest conditions, either base gives exclusively iodomorphide hydriodide. Three grams of α-chloromorphide in 24 cc. of 10% acetic acid was brought into solution by addition of 40 cc. of boiling water, and treated with 4.9 g. of potassium iodide in 5 cc. of water. The clear solution was allowed to

cool very slowly, and finally kept overnight in the ice-box. The yield of long, white crystals was nearly quantitative. A similar result was obtained by working with cold solutions, or using bromomorphide. Iodomorphide hydriodide can be recrystallized from water (70°) in an atmosphere of carbon dioxide, with addition of a trace of sodium hydrosulfite to prevent oxidation. The white crystals turn yellow unless dried in an inert atmosphere. In water, the salt shows $[\alpha]_D^{25}$ +114.5° (c = 0.23).

Anal. Calc'd for $C_{17}H_{19}I_2NO_2$: I, 48.54. Found: I, 48.74.

Iodomorphide base is a vitreous solid having $[\alpha]_D^{27}$ +123.2° (methanol, c = 1.10). The liberation of the base from the salt involved appreciable hydrolysis, as indicated by the analysis.

Anal. Calc'd for $C_{17}H_{18}INO_2$: I, 32.13. Found: I, 30.25.

The acid tartrate crystallized best from 50% alcohol. In water, $[\alpha]_D^{25}$ +120.3° (c = 0.20).

Anal. Calc'd for $C_{21}H_{24}INO_8$: I, 23.28. Found: I, 22.76.

The salicylate was prepared with alcoholic salicylic acid, and was purified from alcohol. It had the m.p. 161° (decomp.) and $[\alpha]_D^{26}$ +113.4° (alcohol, c = 0.88).

Anal. Calc'd for $C_{24}H_{24}INO_5$: I, 23.81. Found: I, 23.66.

The benzoate, prepared like the salicylate, had the m.p. 159–160° (decomp.) and $[\alpha]_D^{26}$ +115.5° (alcohol, c = 1.13).

Anal. Calc'd for $C_{24}H_{24}INO_4$: I, 24.54. Found: I, 24.35.

The methiodide was prepared by treating the amorphous base with cold methyl iodide. It could be crystallized in small portions from 50% alcohol without hydrolysis. In 50% alcohol it showed $[\alpha]_D^{26}$ +90° (c = 0.21), but after the solution stood for 36 hours the value dropped to +54°.

Anal. Calc'd for $C_{18}H_{21}I_2NO_2$: I, 47.27. Found: I, 47.35.

Iodomorphide was further identified by conversion to iodocodide. An excess of diazomethane was distilled into a suspension of iodomorphide benzoate in absolute ether containing a little methanol. After 48 hours the solution was shaken with dilute hydrochloric acid, and the ether and methyl benzoate discarded. From the acid layer, a good yield of iodocodide was obtained; identification by melting point and rotation.

On catalytic hydrogenation, iodomorphide absorbed one mole of hydrogen, giving a halogen-free, amorphous base that could not be identified. It resisted sublimation in a high vacuum at 200°, and is therefore probably dimolecular.

β-Chloromorphide hydriodide. When a hot solution of β-chloromorphide in 10% acetic acid was treated with potassium iodide, β-chloromorphide hydriodide was obtained in 92% yield. The salt crystallized from water in large white needles, and had $[\alpha]_D^{26}$ 0° (water, c = 0.2). No substitution by iodine took place, as was shown by analysis, and by the fact that β-chloromorphide could be regained from the salt.

Anal. Calc'd for $C_{17}H_{19}ClINO_2$: I, 29.41.
Found, (ionic halogen): I, 29.75.
Calc'd, mixed silver halides from 117.8 mg. sample: 102.1 mg.
Found: 103.8 mg.

Molecular compound of α- and β-chlorocodides. The alcohol mother liquors from the purification of α-chlorocodide were freed as far as possible from α- and β- chlorocodides by successive concentrations and crystallizations, and finally diluted with water. The crystalline precipitate that separated had the melting point 112–113°, and after purification from alcohol melted at 114–116°. This melting point did not change on fractional crystallization of the product. The compound sublimed in a high vacuum at 110°; the sublimate melted at 115–117°, $[\alpha]_D^{25}$ −150.4° (absolute

alcohol, $c = 1.077$). When equal amounts of α- and β- chlorocodide were crystallized together from alcohol, the product was identical in physical properties with that described above, and gave no depression in mixed melting point. In view of the fact that the main portion of the α and β isomers can be separated without difficulty, the appearance of the molecular compound in the end-fraction is remarkable.

8-Chlorodihydrocodide. Five grams of dihydropseudocodeine was added slowly to 10 g. of phosphorus pentachloride in 15 cc. of dry chloroform, and the mixture was boiled under reflux for 8 hours. The solution was poured on ice, and chloroform was removed under diminished pressure. The water solution was made ammoniacal, and the base was extracted into ether, from which 4.5 g. of dark oil was obtained. This yielded a crystalline tartrate, which was purified from water, decolorizing with Norit; the yields averaged 3 to 4 grams. The tartrate melted at 230–232° (evac. tube). The base was regenerated from the tartrate and recrystallized from 75% acetone. It had the m.p. 123–124°, $[\alpha]_D^{25}$ −42.7° (absol. alcohol, $c = 1.05$).

Anal. Calc'd for $C_{18}H_{22}ClNO_2$: C, 67.58; H, 6.94; N, 4.38; Cl, 11.10.
Found: C, 67.80, 67.79, 67.81; H, 6.30, 6.58, 6.57; N, 4.37; Cl, 11.28.

The parallel reaction of dihydroallopseudocodeine with phosphorus pentachloride gave the same product, but in somewhat lower yield.

8-Chlorodihydromorphide. 8-Chlorodihydrocodide was regained from prolonged vigorous reduction with sodium in ethanol or from drastic electrolytic reduction. The action of sodium in cyclohexanol is discussed in a following communication (Desoxycodeine-D). Sodium methoxide caused demethylation. Three grams of 8-chlorodihydrocodide in 240 cc. of methanol containing 6 g. of sodium was heated in an autoclave at 140° for 24 hours. The solution was diluted with water, and methanol was removed under diminished pressure. A crystalline precipitate (0.7 g.) of starting material separated. Carbon dioxide was passed into the alkaline solution, whereby 1.4 g. of lustrous platelike crystals was precipitated. The compound was very sparingly soluble in organic media, and was recrystallized from 850 cc. of boiling acetone. Analytical values and the strongly phenolic nature show it to be 8-chlorodihydromorphide; m.p. 257–258° (evac. tube, decomp.).

Anal. Calc'd for $C_{17}H_{20}ClNO_2$: C, 66.75; H, 6.60; N, 4.58; Cl, 11.60.
Found: C, 66.69; H, 6.40; N, 4.54; Cl, 11.50.

1,8-Dichlorodihydrocodide. The mother liquor from the preparation of 8-chlorodihydrocodide tartrate was concentrated to one-fourth its volume, and a small crop of tartrate was removed. The remaining solution yielded a new base, which was purified by several crystallizations from alcohol; the m.p. was 190.5–191.5°.

Anal. Calc'd for $C_{18}H_{21}Cl_2NO_2$: Cl, 20.08. Found: Cl, 20.29.

Dihydrocodeine isomers with thionyl chloride. Dihydrocodeine reacts with cold thionyl chloride to give a good yield of a chlorinated base of m.p. 187–190°. Its nature as 1-chlorodihydrocodeine is evident from the result of reduction with sodium in alcohol, which gave pure dihydrocodeine, m.p. 85–87°.

Dihydroisocodeine under the same conditions gave a chlorinated base that was isolated as the tartrate (Calc'd: Cl, 7.3. Found: Cl, 7.9). The base liberated from the tartrate was difficult to crystallize; m.p. 103–105°. On reduction with sodium and alcohol it gave a quantitative yield of dihydroisocodeine, m.p. 189–194°.

Dihydropseudocodeine yielded a chlorinated base of m.p. 108–112°, which gave dihydropseudocodeine, m.p. 151–152°, on sodium-alcohol reduction. The chlorination product from dihydroallopseudocodeine and thionyl chloride was isolated as the oxalate, from which chlorodihydroallopseudocodeine, m.p. 189–191° was obtained.

Bromination of the dihydrocodeine isomers. Bromination of the dihydrocodeine

isomers was attempted, using 15 cc. of phosphorus tribromide with 5 g. of alkaloid, in sealed tubes at 105–115° for 5 hours. From dihydrocodeine, phosphorus-containing products were usually obtained. In one experiment only, a phosphorus-free product was isolated, phenolic in nature, m.p. 260–262°, that appears to be 6-bromodihydromorphide; Calc'd for $C_{17}H_{20}BrNO_2$: Br, 22.8. Found: Br, 23.1. Dihydroisocodeine gave an unidentified halogen-free base, isolated only as the salicylate. Dihydroallopseudocodeine gave a small yield of desoxymorphine-D. From dihydropseudocodeine a crystalline base of m.p. 230–232° was obtained, which may be the expected 8-bromodihydrocodide.

Anal. Calc'd for $C_{18}H_{22}BrNO_2$: Br, 21.9. Found: Br, 22.2.

Trichloromorphide. The reaction of anhydrous morphine with thionyl chloride is claimed to result in a yield of 70–90% of α-chloromorphide (17). Under the most scrupulous observation of the conditions of Wieland and Kappelmeier, we were never able to attain these yields of pure product. The crystalline chloromorphide (from ether) obtained from reaction of a total of 1450 g. of anhydrous morphine weighed 1300 g. It showed the specific rotation −269°, whereas pure α-chloromorphide has $[\alpha]_D$ −375°. One hundred-gram portions were each shaken vigorously with 200 cc. of alcohol, and filtered, whereby the specific rotation was raised to −340°. A second, similar, treatment gave a product having $[\alpha]_D$ −360°; total yield 1000 g., or about 65% of the calculated. This material was sufficiently pure for most experimental purposes; one crystallization from methanol resulted in α-chloromorphide of specific rotation −372.5°, but large quantities of methanol were required.

The alcohol washings, 5800 cc., were diluted with water until no further precipitation took place. The powdery, amorphous material weighed 447 g., but contained 147 g. of water, which was subsequently found in the benzene treatment. Fifty grams of the powder was dissolved in 250 cc. of cold benzene, and a small amount of brown flocculent material was removed by filtration through paper pulp. The benzene solution was separated from water (16.5 cc.), diluted with benzene to 1.5 liters, and again filtered through pulp. The benzene solution was extracted with 0.2 *N* hydrochloric acid, the base was liberated with ammonia, and brought into ether. The ether was concentrated to about 30 cc. and decanted from a viscous oil. From the ether, β-chloromorphide crystallized, and the oil, rubbed with ethyl acetate, gave another crop. Total β-chloromorphide, 4.3 g. The ethyl acetate mother liquors, on concentration and dilution with a little benzene, gave 3.1 g. of α-chloromorphide. When the benzene filtrate was diluted with more benzene, a flocculent precipitate formed, which was removed. The total, unidentified amorphous material from the several filtrations involved was 10 g. The benzene was extracted 3 times with 33 cc. of 0.1 *N* hydrochloric acid and 9 times with 33 cc. of 0.2 *N* acid. Fractions 1 to 3 yielded 1 g. of β-chloromorphide; fractions 4 and 5, 0.7 g. of a mixture of α- and β- chloromorphides; fractions 6 and 7, 0.9 g. of α-chloromorphide. Fraction 8 solidified as the hydrochloride, and with 9, 10, and 11, gave 2.5 g. of trichloromorphide. Fraction 12 contained no alkaloid. The yield of trichloromorphide, based on morphine, was about 1.2% of the possible amount.

Trichloromorphide crystallizes best from ethyl acetate, m.p. (decomp.) about 195°. In methanol it has $[\alpha]_D^{21}$ −285° (c = 0.410).

Anal. Calc'd for $C_{17}H_{16}Cl_3NO_2$: C, 54.77; H, 4.33; Cl, 28.55.
Found: C, 54.85; H, 4.32; Cl, 28.43.

The hydrochloride crystallizes when the base is treated with 3 *N* hydrochloric acid, and may be purified from water. It has $[\alpha]_D^{20}$ −245.6° (water, c = 0.721).

Anal. Calc'd for $C_{17}H_{17}Cl_4NO_2$: Cl, 34.68. Found: Cl, 34.57.

Trichlorocodide. Methylation was accomplished in ether containing a little

methanol, with diazomethane. The ethereal solution was washed with sodium hydroxide, concentrated, and the new base was purified from ethyl acetate and from absolute ethanol; m.p. 143–143.5°. It shows in ethyl acetate $[\alpha]_D^{25}$ −302° (c = 1.11).

Anal. Calc'd for $C_{18}H_{18}Cl_3NO_2$: C, 55.88; H, 4.69; Cl, 27.52.
Found: C, 55.80; H, 4.70; Cl, 27.74.

The hydrochloride, prepared with 3 *N* hydrochloric acid and purified from water, has $[\alpha]_D^{25}$ −218° (water, c = 0.840).

Anal. Calc'd for $C_{18}H_{19}Cl_4NO_2$: Cl, 33.53. Found: Cl, 33.71.

Trichlorocodide hydrochloride in aqueous solution with palladium-barium sulfate took up two moles of hydrogen. The product was a liquid from which no crystalline salts could be obtained. Hydrogenation of the base in the presence of piperidine as hydrogen halide acceptor (absorption 3 moles) was not more successful, nor were reductions with zinc and alcohol or sodium and alcohol.

Dichlorodihydrodesoxymorphine. This compound was prepared in the form of hydrochloride, according to Example 1 of the Warnat patent (11). Thirty grams of morphine hydrate yielded 28.6 g. of dichlorodihydrodesoxymorphine hydrochloride, or 73% of the calculated amount. The melting point was 230–235° [reported m.p. 270–272° (Warnat, 18)]. We were not able to find any purification method that would raise the melting point to Warnat's value.

Anal. Calc'd for $C_{17}H_{20}Cl_3NO_2$: C, 54.17; H, 5.37; N, 3.72; Cl, 28.24.
Found: C, 53.87, H, 5.53, N, 3.79, Cl, 28.07. (By Warnat, 18).

The dichlorodihydrodesoxymorphine from our preparation showed $[\alpha]_D^{27}$ +276° (c = 0.104, 50% alcohol); Warnat's value, +263° (11).

When 0.501 g. of dichlorodihydrodesoxymorphine hydrochloride was dissolved in dilute potassium hydroxide, acidified with hydrochloric acid, and made up to 20 cc., the optical rotation, based on the calculated formation of 0.404 g. of β-chloromorphide was $[\alpha]_D$ −10.9° (experiment by K. Warnat).

Diacetyldichlorodihydrodesoxymorphine (18). The hydrochloride of dichlorodihydrodesoxymorphine was boiled for 3 hours with acetic anhydride, to complete solution. The product was precipitated by addition of ether, and the oily precipitate was dissolved in water. The solution was treated with sodium bicarbonate and extracted with ether. The residue from distillation of the ether was dissolved in methanol, and the diacetyl derivative was precipitated by addition of water.

Anal. (18) Calc'd for $C_{21}H_{23}Cl_2NO_4$: C, 59.42; H, 5.47; N, 3.30; Cl, 16.72.
Found: C, 59.89; H, 5.40; N, 3.34, Cl; 16.06.
(Experiment and analysis by K. Warnat.)

We were unable to isolate dichlorodihydrodesoxymorphine base. If the hydrochloride is brought into solution in a large volume of boiling water and treated with sodium bicarbonate, the product is β-chloromorphide. It is probable that the β-chloromorphide is already formed before addition of the precipitating agent. This is evident from the following experiment. Five grams of dichlorodihydrodesoxymorphine was suspended in 100 cc. of water, and boiled until solution was complete (8 minutes). The initially neutral solution became strongly acid. It was evaporated to dryness at 25°, and the frothy product was taken up in 6 cc. of water and seeded with β-chloromorphide hydrochloride (obtained from β-chloromorphide with 3 *N* hydrochloric acid). The first crop of crystals weighed 2.6 g. It was recrystallized twice from water; $[\alpha]_D^{25}$ 0° (c = 2.05).

Anal. Calc'd for $C_{17}H_{19}Cl_2NO_2 + H_2O$: Cl, 19.81; H_2O, 5.0.
Found: Cl, 19.63, 19.86; H_2O, 3.9.

Dichlorodihydrodesoxymorphine hydrochloride can be recrystallized in poor

yield by dissolving 1 g. in 300 cc. of 50% alcohol at room temperature and concentrating to 100 cc. at 25° under diminished pressure; yield 0.2 g. The ring-closure apparently proceeds with facility also with dichlorodihydrodesoxycodeine. Two grams of dichlorodihydrodesoxymorphine hydrochloride was suspended in ether containing methanol and treated with 1 g. of diazomethane during two days. The 4-hydroxyl evidently did not undergo methylation and must be very weakly acidic. The ether was extracted with dilute acetic acid and excess sodium bicarbonate was added. The only product was β-chlorocodide.

β-Chloromorphide as intermediate. Twenty grams of anhydrous morphine in 210 g. of conc'd hydrochloric acid was held at 60° for 42 hours, with occasional saturation of the solution with hydrochloric acid gas. The first fine crystals of dichlorodihydrodesoxymorphine hydrochloride had begun to form, and were filtered out. The acid solution was evaporated to dryness at 35° under diminished pressure, and the residue, in 15 cc. of water, was seeded with morphine hydrochloride. The crystals weighed 8.6 g., and were practically pure morphine hydrochloride, $[\alpha]_D^{21}$ −103.3°; lit. value −111.5°. The mother liquor was diluted with water, layered with a liter of ether, made ammoniacal, and extracted. A trace of morphine stayed between the layers. The ether solution was extracted with successive portions of 0.2 *N* hydrochloric acid, each portion equivalent to 2 g. of alkaloid, and each fraction was converted back to base and brought into ether. The first three fractions yielded residues that formed dark, semi-crystalline hydrochlorides with 3 *N* hydrochloric acid. Fractions 4 to 6 gave 5.9 g. of β-chloromorphide hydrochloride, $[\alpha]_D^{26}$ 0°. The extremely low solubility of dichlorodihydrodesoxymorphine hydrochloride in acid or water makes it impossible that the β-chloromorphide could have been formed from it.

β-Chloromorphide to dichlorodihydrodesoxymorphine. Nine grams of pure β-chloromorphide in 75 cc. of conc'd hydrochloric acid was held at 65° for 72 hours. At this time 2.9 g. of crystals of dichlorodihydrodesoxymorphine hydrochloride had separated, and the experiment was stopped. The salt showed $[\alpha]_D^{27}$ +272° (*c* = 0.107, 50% alcohol).

Dichlorodihydrodesoxymorphine to apomorphine. In parallel experiments, 5 g. of anhydrous morphine, and 5 g. of dichlorodihydrodesoxymorphine hydrochloride, in sealed tubes with 50 cc. of conc'd hydrochloric acid, were heated at 130–140° for 3 hours. From the morphine, (a) 1.8 g. (33.8% yield) of apomorphine hydrochloride was obtained; from the dichlorodihydrodesoxymorphine (b), 1.5 g. (37.3% yield). The products were identified by rotation, respectively $[\alpha]_D^{25}$ −47.8° (a), and −47.8° (b) (water, *c* = 1.13, 1.21). For further identification, the samples were converted to the diacetyl derivatives. Tiffeneau and Porcher (19) reported complex mixtures in their acetylation of apomorphine. The samples in question were therefore acetylated as hydrochloride, 0.5 g. in 5 cc. of anhydrous pyridine with 2 cc. of acetic anhydride at room temperature for 24 hours. We obtained: from apomorphine (a), 0.30 g. of diacetylapomorphine, m.p. 127–128°, $[\alpha]_D^{24}$ −87.5° (0.1 *N* hydrochloric acid, *c* = 1.12); from apomorphine (b), 0.37 g. of diacetylapomorphine, m.p. 127–128°, $[\alpha]_D^{25}$ −87.5° (0.1 *N* hydrochloric acid, *c* = 1.12); no depression in mixed melting point.

Apocodeine. Twenty grams of glacial phosphoric acid was heated (oil-bath) to the point where it could be stirred, and 4 g. of codeine was added. The mixture was held at 175° with stirring for 12 minutes, where a test showed complete alkali-solubility. The glassy mass was dissolved in 60 cc. of hot water, made alkaline with addition of a little sodium hydrosulfite, and filtered from a trace of amorphous material. The alkaline solution was extracted four times with benzene, from which

a yellow oil was obtained. With 3 *N* hydrochloric acid, this gave 1.3 g. (30%) of white crystalline apocodeine hydrochloride. From this 1.15 g. of apocodeine base was obtained. It crystallized from methanol in small prisms, which appeared to lose solvent at about 96°, and melted at 121–121.5°; $[\alpha]_D^{24}$ −97° (absolute alcohol, c = 0.449). The alkaline solution above, with ammonium chloride and chloroform, gave only dark oils.

Pentachloroxycodide. The action of cold sulfuryl chloride on codeine, β-chlorocodide, α-chloromorphide, or dihydropseudocodeine gave only dark resinous products; morphine was unaffected. One gram of α-chlorocodide was added slowly to 10 cc. of sulfuryl chloride cooled in ice-salt mixture. The cold, yellow solution was poured immediately on ice, and the mixture was made ammoniacal and extracted with ether. One gram of acicular crystals was obtained; they became black without melting at 180–200°. The compound was recrystallized to constant rotation from acetone; $[\alpha]_D^{25}$ −298.8° (acetone, c = 0.36).

Anal. Calc'd for $C_{18}H_{20}Cl_5NO_3$: C, 45.43; H, 4.24; Cl, 37.29.
Found: C, 45.72; H, 4.22; Cl, 37.19.

Qualitative tests for nitrogen were positive, for sulfur negative; the iodide-starch test was negative. The compound decomposed when warmed with dilute acids. Catalytic reduction in acetic acid caused absorption of 2.9 moles, in alcohol 5 moles absorption; the products were colored and resinous; aluminum amalgam reduction also caused decomposition.

SUMMARY

The halogen atom in α-chlorocodide has been proved to occupy the 6-position. New halogenated derivatives of the morphine series and of the isomeric dihydrocodeines have been prepared, but proof of structure for β-chlorocodide and bromocodide was unsuccessful. The reaction of morphine with thionyl chloride gives not only α-chloromorphide, but also β-chloromorphide, and a trichloromorphide, of unknown structure. α-Chlorocodide with sulfuryl chloride gives pentachloroxycodide.

Controlled treatment of morphine with concentrated hydrochloric acid results first in β-chloromorphide, which is then transformed to dichlorodihydrodesoxymorphine. Both of these compounds are intermediates in the conversion of morphine to apomorphine, for which a simple mechanism is offered.

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