Table I gives the yields, melting points and analytical data obtained for the compounds prepared in this study.

TABLE I

Compound	Yield, %	M. p., °C. corr.	Sulfur, % Calcd.	Sulfur, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-$NO_2C_6H_4COSCH_3$	66	96–97	16.26	16.47	7.11	7.17
p-$NO_2C_6H_4COSC_2H_5$	57	67–68	15.15	14.80	6.64	6.79
p-$NO_2C_6H_4COSC_3H_7$	50	30–31	14.24	14.00	6.36	6.32
p-$NO_2C_6H_4COSC_4H_9$	63	13–15	13.35	13.28	5.83	5.89
p-$NH_2C_6H_4COSCH_3$	98	113–114	19.18	18.92	8.39	8.45
p-$NH_2C_6H_4COSC_2H_5$	84	79–79.5	17.60	17.34	7.73	7.72
p-$NH_2C_6H_4COSC_3H_7$	78	60–61	16.25	16.46	7.02	7.25
p-$NH_2C_6H_4COSC_4H_9$	76	37–38	15.10	15.29	6.69	6.50
p-$NO_2C_6H_4COSCH_2CH_2Cl$	70	91–92	13.05	13.31	5.68	5.59
p-$NH_2C_6H_4COSCH_2CH_2Cl$	85	99–101	14.87	14.88	6.46	6.25
p-$NH_2C_6H_4COSC_2H_4N(C_2H_5)_2$	80	52–52.5	12.71	12.98	11.10	11.00
p-$NH_2C_6H_4COSC_2H_4N(C_2H_5)_2$·HCl	100	177.6–178	...	...	9.70	9.64

Summary

Several alkyl esters have been prepared from p-nitrothiobenzoic acid. The amino compounds obtained from them are topical anesthetics.

The thio derivative of novocaine has been prepared and found to have anesthetic properties.

CHICAGO, ILLINOIS

RECEIVED JANUARY 30, 1933
PUBLISHED JULY 6, 1933

[CONTRIBUTION NO. 110 FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Desoxymorphines[1]

BY LYNDON F. SMALL AND DAVID E. MORRIS

Pharmacological studies which have been carried out on the series of desoxycodeines and their hydrogenated derivatives described in previous papers from this Laboratory[1a] make it seem probable that the action of codeine and its isomers in depressing the respiratory reflex may depend to a considerable degree upon the presence of the secondary alcoholic group located in ring III. In view of this hypothesis, an examination of the corresponding series of desoxymorphine derivatives seemed desirable. The desoxymorphines are, however, exceedingly sensitive substances, and the preparation of a complete series has not been possible.

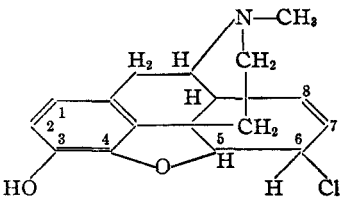
Treatment of α-chloromorphide (I) with zinc dust in boiling alcohol yields only resinous products and unchanged α-chloromorphide instead of

(1) This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc. Presented in part at the New Orleans Meeting of the American Chemical Society, March 30, 1932.

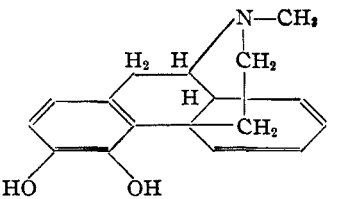
(1a) Small and Cohen, THIS JOURNAL, **53**, 2214, 2227 (1931); Mosettig, Cohen and Small, *ibid.*, **54**, 793 (1932); Small and Cohen, *ibid.*, **54**, 802 (1932).

the expected desoxymorphine analog of desoxycodeine-A. Attempts to prepare desoxymorphine-A by demethylation of desoxycodeine-A were likewise unsuccessful. Reduction of α-chloromorphide with sodium and alcohol led to an uncrystallizable gum, which was still basic in nature, but gave no crystalline salts. In both of these chloromorphide reductions chlorine or hydrogen chloride is removed from the molecule, but the product, which is probably diphenolic in nature, undergoes further changes under the influence of the reagents used.

Desoxymorphine-A.—Electrolytic reduction of α-chloromorphide, on the other hand, results in a satisfactory yield of a crystalline halogen-free reduction product which proved to be the desired desoxymorphine-A (II).



I. α-Chloromorphide



II. Desoxymorphine-A

The reduction is parallel to that in which (the supposed) desoxycodeine-B is formed from α-chlorocodide. Desoxymorphine-A has the empirical formula $C_{17}H_{19}O_2N$, *i. e.*, it contains one less oxygen atom than morphine, $C_{17}H_{19}O_3N$. The change taking place in α-chloromorphide, $C_{17}H_{18}O_2NCl$, through electrolytic reduction is a deeper one than simple replacement of chlorine by hydrogen, for desoxymorphine-A is a diphenol. On treatment with diazomethane it yields a monomethyl ether (identical with desoxycodeine-A) which still contains a phenolic hydroxyl group. The methyl ether dissolves reluctantly in alkali and is precipitated from its alkaline solution by ammonium chloride. The indifference of the hydroxyl group in position 4 toward diazomethane is discussed in a later paragraph.

Desoxymorphine-A absorbs two molecules of hydrogen in the presence of platinum or palladium, giving tetrahydrodesoxymorphine, the demethylated analog of tetrahydrodesoxycodeine. The presence of the two double linkages predicated by the empirical formula is thus demonstrated.[2]

Desoxymorphine-C.—The preparation of the second of the desoxymorphines has its starting point in chlorodihydromorphide (III). This substance, which is most conveniently prepared by the action of thionyl chloride on dihydromorphine,[3] proved to be unexpectedly resistant to electrolytic reduction. It was recovered unchanged from prolonged

(2) Attempts were made to hydrogenate desoxymorphine-A with addition of but 1 mole of hydrogen under the conditions developed in this Laboratory for pseudocodeine types, in the original belief that the compound still contained the oxide ring. These were unsuccessful; in every case two molecules of hydrogen were absorbed. Compare the behavior of desoxymorphine-C and desoxycodeine-C.

(3) The only preparation of chlorodihydromorphide recorded in the literature is that by demethylation of chlorodihydrocodide, Mannich and Löwenheim, *Arch. Pharm.*, **258**, 295 (1920).

treatment in the electrolytic cell, a process which in the case of the methyl ether, chlorodihydrocodide, gave good yields of dihydrodesoxycodeine-C.[4] Chlorodihydromorphide, like chlorodihydrocodide, is indifferent toward catalytic hydrogen. When, however, chlorodihydromorphide is treated with sodium methylate in the autoclave at 140°, it suffers loss of hydrogen chloride, probably between carbon atoms 6 and 7, and gives an excellent yield of a new base having the formula $C_{17}H_{19}O_2N$. This is an isomer of the desoxymorphine-A described above and has received the name desoxymorphine-C (Formula IV) because of its relationship to desoxycodeine-C. In desoxymorphine-C the ether bridge is still intact, for the compound contains but one phenolic hydroxyl group. On treatment with diazomethane it yields a monomethyl ether, the known desoxycodeine-C, which has no phenolic properties. The desoxy derivatives in which the ether bridge is unopened are relatively stable, hence desoxymorphine-C can also be prepared by demethylation of desoxycodeine-C with sodium methylate, but not with acidic reagents as hydrochloric or hydriodic acids.[5] This demethylation accounts for the appearance of desoxymorphine-C in small amounts during the preparation of desoxycodeine-C from chlorodihydrocodide and sodium methylate.[6] Desoxymorphine-C, which melts at 189–190°, is probably identical with the substance designated by Knoll and Co.[7] as dihydrodesoxymorphine and described only as having the melting point 183°.

While the empirical formula and the indubitable presence of the ether bridge in desoxymorphine-C show that the compound can contain but one alicyclic double linkage, two molecules of hydrogen are taken up on hydrogenation in the presence of palladium or platinum. One molecule of hydrogen is used in opening the 4,5 ether bridge, and the second in satisfying the unsaturation in ring III. The product which results is tetrahydrodesoxymorphine (V). This extraordinary tendency toward reductive scission of the ether ring on hydrogenation is characteristic of morphine derivatives having a double linkage in the 6,7-position,[8] and desoxymorphine-C, like desoxycodeine-C, must be of the pseudocodeine or γ-isomorphine type. Such structures are amenable to partial hydrogenation under the special conditions already described for pseudocodeine,[8d] whereby the addition of hydrogen can be limited mainly to the alicyclic double bond. When desoxymorphine-C hydrochloride in glacial acetic acid was hydrogenated in the presence of platinum oxide, the absorption amounted to but 1.5 moles of hydrogen. The product consisted of approximately

(4) Small and Cohen, THIS JOURNAL, **53**, 2235 (1931).

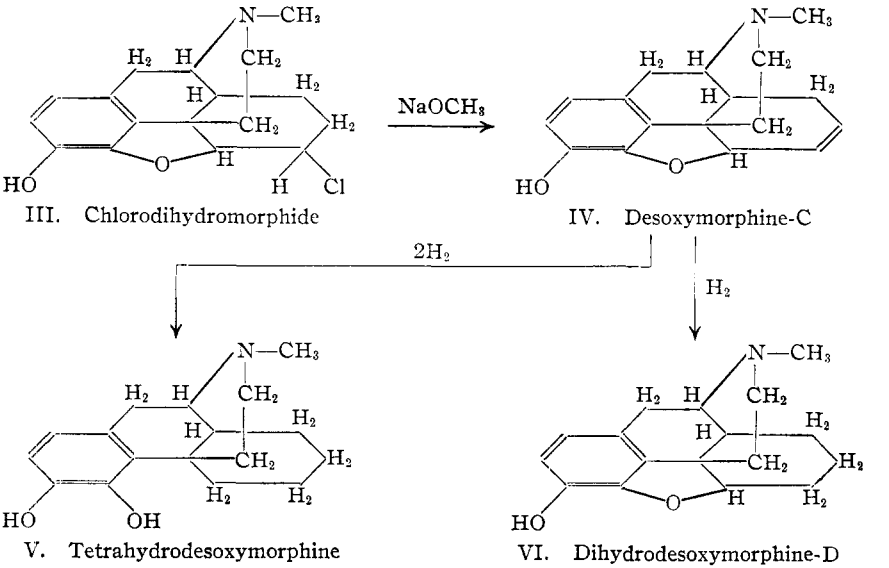
(5) Demethylation with hydriodic acid is practicable in the case of those desoxycodeines in which ring III is saturated, as will be shown by other examples.

(6) Small and Cohen, THIS JOURNAL, **53**, 2225 (1931).

(7) German Patent 414,598 (1922); Friedländer, **15**, 1518; *Jahresb. Chem. Tech.*, **71**, 123 (1925).

(8) (a) Schöpf and Winterhalder, *Ann.*, **452**, 237 (1927); (b) Schöpf and Hirsch, *ibid.*, **489**, 235, Note 1 (1931); (c) Small and Cohen, THIS JOURNAL, **53**, 2221 (1931); (d) Lutz and Small, ibid., **54**, 4715 (1932).

equal amounts of tetrahydrodesoxymorphine and of the (mono)phenolic dihydrodesoxymorphine-D (Formula VI), the latter of which has already been prepared in this Laboratory from other sources and will be further described in another communication. By separation of the sparingly soluble tetrahydrodesoxymorphine from the reduction mixture, and methylation of the remaining crude material with diazomethane, the non-phenolic dihydrodesoxycodeine-D was obtained.



III. Chlorodihydromorphide IV. Desoxymorphine-C

V. Tetrahydrodesoxymorphine VI. Dihydrodesoxymorphine-D

In view of the close chemical relationship between desoxymorphine-C and desoxycodeine-C it is surprising to find that the former is unaffected by electrolytic reduction, which in the case of the latter resulted in a clean scission of the 4,5 ether ring to give the phenolic dihydrodesoxycodeine-B.[9]

Tetrahydrodesoxymorphine.—The tetrahydrodesoxymorphine which is obtained as the end-product from hydrogenation of desoxymorphines-A and -C under ordinary conditions may also be prepared by catalytic hydrogenation of the halogenomorphides.[10] Its structure is quite certain, for on treatment with diazomethane it is converted to tetrahydrodesoxycodeine. Conversely, tetrahydrodesoxymorphine is formed when tetrahydrodesoxycodeine is demethylated with hydriodic acid, this being the most convenient preparative method. Attention has already been called to the peculiar weakly-phenolic character of the hydroxyl group which is attached at the 4 position in the aromatic ring of tetrahydrodesoxy-

(9) Theoretical considerations based on reductions in the pseudocodeine series raise a question as to whether dihydrodesoxycodeine-B actually exists as a chemical individual. The point will be discussed in a later paper. There is, however, no doubt concerning the reality of a reduction of desoxycodeine-C by electrolysis.

(10) Unpublished results, L. F. Small, L. K. Eilers and K. C. Yuen.

codeine.[11] The fact that tetrahydrodesoxymorphine (and desoxymorphine-A) can be methylated only on the 3-hydroxyl is evidently to be attributed to this lack of acidity in the 4-hydroxyl in the desoxy (and certain other) series.

Repeated attempts to prepare the desoxymorphine mentioned by Schryver and Lees[12] have failed. Schryver's desoxymorphine was described only as the hydrochloride; the specific rotation given for this salt is in the same direction, but considerably higher than that of any of the desoxymorphine-A salts. We were unable to prepare a crystalline hydrochloride of desoxymorphine-A. The desoxymorphine which Wright[13] claimed to have obtained from the action of concentrated hydrobromic acid on bromocodide is not described beyond the analysis of its hydrochloride.

Desoxycodeine-C.—In order to demonstrate further the applicability of partial hydrogenation in acid solution to the pseudocodeine type represented by desoxymorphine-C, the hydrogenation of desoxycodeine-C was reinvestigated. Under the conditions usually imposed, Small and Cohen[14] were not able to reduce desoxycodeine-C to a dihydro derivative, and in all such attempts observed absorption of two moles of hydrogen with quantitative formation of tetrahydrodesoxycodeine. Employing the technique mentioned above, we find that when desoxycodeine-C hydrochloride in glacial acetic acid, or desoxycodeine-C base dissolved in an excess of 10% sulfuric acid, is hydrogenated in the presence of platinum oxide, an absorption of considerably less than two moles is observed, and the product consists of a mixture of tetrahydrodesoxycodeine and dihydrodesoxycodeine-D (Formulas V and VI, respectively, OCH_3 in place of OH). This result is in complete accord with observations made in the acid hydrogenation of pseudocodeine, ϵ-methylmorphimethine,[8d] allopseudocodeine, and γ-isomorphine,[15] and further substantiates the pseudocodeine type structure proposed by Small and Cohen for desoxycodeine-C. The purely formal relationship of desoxycodeine-C to dihydrodesoxycodeine-D which was pointed out by these investigators is realized by the partial reduction described.

The So-Called Desoxycodeine-B.—Desoxycodeine-B as described by Freund ("dihydrodesoxycodeine")[16] and by Small and Cohen[17] is prepared by electrolytic reduction of α-chlorocodide. In the present study we have been able to show beyond question that a parallel reduction of α-chloromorphide (of which α-chlorocodide is the methyl ether) results in desoxymorphine-A, whose methyl ether is desoxycodeine-A. Moreover, desoxy-

(11) Freund, *J. prakt. Chem.*, **101**, 29 (1921); Mannich and Löwenheim, *Arch. Pharm.*, **258**, 304 (1920); Kondo, *Ber.*, **63**, 646 (1930); Small and Cohen, THIS JOURNAL, **54**, 802 (1932).

(12) Schryver and Lees, *J. Chem. Soc.*, **77**, 1024 (1900).

(13) Wright, *Chem. News*, **23**, 302 (1871).

(14) Small and Cohen, THIS JOURNAL, **53**, 2220 (1931).

(15) Unpublished results, L. F. Small and R. E. Lutz.

(16) Freund, *J. prakt. Chem.*, **101**, 23 (1921).

(17) Small and Cohen, THIS JOURNAL, **53**, 2214 (1931).

codeines-A and -B are represented as differing in the arrangement of conjugated double bonds in ring III, yet both are reduced by sodium and alcohol (presumably a 1,4-mechanism) to the same dihydrodesoxycodeine-A. These facts led us to believe that desoxycodeine-A and the so-called desoxycodeine-B must be identical, a belief which has been substantiated by experiment. The so-called desoxycodeine-B consists mainly of desoxycodeine-A, with an uncertain amount of extraordinarily persistent impurity. The presence of this (crystalline) impurity, which has the m. p. 115° (unsharp) and specific rotation $[\alpha]_D^{26}$ +6.6°, accounts for the lower melting point and rotation of the so-called desoxycodeine-B in comparison with pure desoxycodeine-A. The impurity described could be isolated only in minute quantity because of the extreme difficulty involved in its separation from desoxycodeine-A. We believe that it may represent the true desoxycodeine-B, for it can be hydrogenated to tetrahydrodesoxycodeine; in favor of this hypothesis may be advanced the fact that the so-called desoxycodeine-B, in large scale catalytic hydrogenations, was always found to absorb exactly two moles of hydrogen. Desoxycodeine-A is known, however, to reduce further electrolytically to dihydrodesoxycodeine-A, and the identity of the impurity under discussion with this base is not excluded.

We have found desoxycodeine-A to exist in two distinct hemihydrated forms and an anhydrous form.

The physiological action of the desoxymorphines and of tetrahydrodesoxymorphine has been investigated at the University of Michigan by Dr. N. B. Eddy. Desoxymorphine-C in particular proves to be a very toxic but exceedingly active substance, especially in regard to respiratory and gastro-intestinal action. In tetrahydrodesoxymorphine the toxicity and other physiological effects are much less pronounced.

Experimental

Reduction of α-Chloromorphide: Desoxymorphine-A.—A solution of 20 g. of pure α-chloromorphide (having $[\alpha]_D^{27}$ −372.4° in methanol, c = 0.529) in 300 cc. of 20% sulfuric acid was electrolyzed at 10–20° for fourteen hours, using a 60 sq. cm. lead cathode and a current of 12 amp. At the end of the reduction the solution in the cathode chamber was nearly neutralized with concd. ammonia under strong cooling, filtered, and divided into two portions to facilitate rapid extraction. To each portion about 1 g. of sodium hydrosulfite was added to protect against oxidation, and the alkaloid was thrown out by addition of the minimum amount of satd. sodium carbonate necessary for complete precipitation. The slightly pink precipitate was extracted as rapidly as possible into 1500 cc. of ether, and the aqueous layer shaken out once more with 300 cc. of ether. The combined ether from both portions was shaken quickly with two small portions of water, dried over anhydrous sodium sulfate and poured into a concentrated ethereal solution of slightly more than the amount of salicylic acid calculated on the basis of 100% yield. The salicylate separated immediately and quickly crystallized. It weighed 14 g. after being washed with ether to remove salicylic acid. The salicylate was purified by several recrystallizations from 95% alcohol and melted at 248–251° with decomp. In absolute methanol $[\alpha]_D^{26}$ +84.0°, +85.1°, c = 0.881, was found.

Anal. Calcd. for $C_{17}H_{19}O_2N \cdot C_7H_6O_3$: C, 70.73; H, 6.20. Found: C, 70.55; H, 6.33.

Desoxymorphine-A base was obtained by suspending the pure salicylate in water under a layer of ether and adding enough 3 *N* hydrochloric acid to give a clear solution. Saturated sodium carbonate solution was added slowly until the aqueous layer showed a permanent alkaline reaction after the liberated alkaloid had all been extracted into the ether layer. The ether was dried with sodium sulfate and distilled, the last traces of ether being removed in a vacuum. The white crystalline desoxymorphine-A so obtained is soluble with difficulty in most organic solvents, moderately soluble in ether. In organic solvents, excepting ether, it is unstable and becomes colored rapidly. It melts at 260–262°, and shows in 10% acetic acid $[\alpha]_D^{28}$ +105.9°, +106.1°, c = 2.333. With ferric chloride solution it gives an olive-green color soon changing to brown. The base was analyzed without recrystallizing.

Anal. Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11. Found: C, 75.86; H, 7.44.

Desoxymorphine-A benzoate was prepared and purified in the same way as the salicylate; this salt may be used advantageously instead of the salicylate in isolating desoxymorphine-A from the reduction. The salt sinters at 215–223° and melts at 240–245° with decomp. In 95% alcohol $[\alpha]_D^{31}$ +81.9°, +82.9°, c = 0.537, was found.

Anal. Calcd. for $C_{17}H_{19}O_2N \cdot C_7H_6O_2$: C, 73.62; H, 6.44. Found: C, 73.63; H, 6.70.

Desoxymorphine-A sulfate is only sparingly soluble in water, and was prepared by dissolving the base in a very slight excess of hot 5% sulfuric acid and evaporating nearly to dryness in a vacuum desiccator. The crystalline solid was dissolved again in hot water, and the solution concentrated to crystallization in the desiccator. The salt softens at 130° and melts at 145–151°. A saturated aqueous solution at 27° contains 0.698 g. in 100 cc. The specific rotation in water is $[\alpha]_D^{32}$ +61.6°, c = 0.698.

Anal. Calcd. for $(C_{17}H_{19}O_2N)_2H_2SO_4$: SO_4, 15.10. Found: SO_4, 14.98.

Methylation of Desoxymorphine-A.—The methylation could not be accomplished with methyl iodide and sodium methylate, nor with dimethyl sulfate and alkali, both methods yielding only amorphous products. The base is so sensitive that it was necessary to use a salt for the reaction with diazomethane.[18] Two grams of pulverized desoxymorphine-A benzoate was suspended in 50 cc. of absolute ether and treated with an ethereal solution (150 cc.) of the diazomethane from 5 cc. of nitrosomethylurethan. After addition of 10 cc. of methanol the solution was allowed to stand in the dark for fifty-eight hours. The methylated base was extracted from the ether with *N* hydrochloric acid, the acid covered with fresh ether, and treated with sodium carbonate. The residue from distillation of the ether was taken up in hot alcohol, and the alkaloid thrown out with water. It was purified by several sublimations at 135° (0.001 mm.), and melted at 152–155° and did not depress the m. p. of desoxycodeine-A.

Anal. Calcd. for $C_{18}H_{21}O_2N$: OCH_3, 10.95. Found (micro-Zeisel): OCH_3, 11.04.

The methylated base did not dissolve in 3 *N* sodium hydroxide, but dissolved when excess of alkali was added to a solution in acid. Ammonium chloride precipitated it from alkaline solution. The salicylate prepared from it melted at 219–220° and gave no depression with desoxycodeine-A salicylate.

Hydrogenation of Desoxymorphine-A.—Because of the instability of desoxymorphine-A in organic solvents, the hydrogenation was carried out on the salicylate. Shaken under hydrogen in 125 cc. of ethanol with 0.3 g. of platinum oxide, 3.09 g. of the salt absorbed 445 cc. of hydrogen in thirty minutes; calcd. for two moles, 445 cc. The salicylate of tetrahydrodesoxymorphine crystallized out when the solution was con-

(18) This method was used by Pschorr, *Ber.*, **35**, 4387 (1902), for the methylation of the very sensitive apomorphine.

centrated to 50 cc. After purification from alcohol it melted at 237–239° and did not depress the m. p. of samples from other sources. In methanol, $[\alpha]_D^{28}$ −30.2°, −30.6°, c = 1.126.

Other Reductions of α-Chloromorphide.—Reduction of α-chloromorphide with sodium and alcohol under the conditions used in the preparation of dihydrodesoxycodeine-A from α-chlorocodide gave only a dark resinous product which could not be crystallized and gave no crystalline salts. Refluxing chloromorphide with zinc and alcohol likewise gave only amorphous (halogen-free) products, with some unchanged chloromorphide. The reduction of α-chloromorphide with tin and concd. hydrochloric acid according to the procedure of Schryver and Lees[19] gave a pale yellow powdery hydrochloride which could not be crystallized. From it, a small amount of crystalline base was obtained, which still contained halogen and appeared to be β-chloromorphide.

Chlorodihydromorphide.—Forty grams of dihydromorphine hydrate (m. p. 132°, solidifying, and remelting at 204–206°) was treated cautiously with 60 cc. of thionyl chloride (purified by distillation from beeswax), and finally refluxed gently for one and one-half hours. The thionyl chloride was removed in vacuum, leaving a brittle mass, which was decomposed with 500 cc. of ice, and brought into solution in 2.5 liters of water. Most of the excess acid was neutralized with ammonia, and satd. sodium bicarbonate solution added until no further precipitate formed. The precipitate (weight 16 g., nature unknown) was filtered out and discarded. A little ether was added to the filtrate, and the chlorodihydromorphide was precipitated out with a large excess of ammonia. After two hours, crystallization was complete; yield, after recrystallization from alcohol, 28 g. The base sinters at 155° and melts at 228–229°. In absolute ethanol, $[\alpha]_D^{30}$ −144.3°, −145°, c = 1.421. Chlorodihydromorphide hydrochloride (cryst. from water) melts at 323–326° and has the rotation $[\alpha]_D^{28}$ −131.0° (water), c = 0.966.

Anal. Calcd. for $C_{17}H_{21}O_2NCl_2$: C, 59.63; H, 6.20; Cl, 20.73. Found: C, 59.57; H, 6.32; Cl, 20.68.

The chlorodihydromorphide so prepared gave on methylation with diazomethane chlorodihydrocodide of m. p. 173–175°.

Desoxymorphine-C.—Ten grams of sodium was dissolved in 400 cc. of absolute methanol[20] in a steel autoclave, and 10 g. of chlorodihydromorphide added. The autoclave was heated for thirty-six hours in a bath of boiling xylene. The dark red solution was diluted with an equal volume of water, acidified with hydrochloric acid, and boiled down to 300 cc. It was decolorized with E. K. Special charcoal and the pale yellow filtrate allowed to crystallize for twelve hours. Desoxymorphine-C hydrochloride separated in thick, nearly colorless needles and was purified by several crystallizations from water; yield of pure salt, 7 g. The freshly prepared salt decomposed to a black mass at 240–245°, but after long standing it showed the dec. p. 291–294° probably through loss of hydrate water. In aqueous solution the hydrate showed $[\alpha]_D^{30}$ −146.3°, −147°, c = 2.262.

Anal. Calcd. for $C_{17}H_{19}O_2N\cdot HCl + 1.5H_2O$: C, 61.33; H, 6.97; Cl, 10.66. Found: C, 61.03, 60.96; H, 6.97, 6.98; Cl, 10.45, 10.52.

A direct determination of hydrate water was not possible because of partial distillation.

Desoxymorphine-C base was prepared by dissolving the hydrochloride in water, adding ether and precipitating the base with ammonia, extracting into the ether. At least three extractions are necessary. Distillation of the ether gave a yellow oil, which quickly crystallized. The alkaloid was purified from ethyl acetate, and showed the

(19) Schryver and Lees, *J. Chem. Soc.*, **77**, 1024 (1900).

(20) Freshly distilled from potassium hydroxide. It is essential for the success of this preparation, and that of desoxycodeine-C by the same method, that the methanol give no trace of color with sodium.

m. p. 189–190° (slight sintering at 130°). In 95% alcohol $[\alpha]_D^{31}$ −155.7°, c = 1.188. The ferric chloride reaction is blue-green.

Anal. Calcd. for $C_{17}H_{19}O_2N + 0.5H_2O$: C, 73.36; H, 7.23. Found: C, 73.37; H, 7.45.

Desoxymorphine-C hydriodide, prepared in the usual way and recrystallized from water melted at 292–294°. In aqueous solution it showed $[\alpha]_D^{32}$ −109.6°, −111.0°, c = 0.721.

Anal. Calcd. for $C_{17}H_{19}O_2N \cdot HI$: I, 31.96. Found: I, 31.76.

Desoxymorphine-C methiodide, purified from 85% alcohol, softens at 155–160° becomes solid, and melts at 260–264°, evolving gas at 265°. In absolute methanol, $[\alpha]_D^{32}$ −98.2°, −96.9°, c = 0.774.

Anal. Calcd. for $C_{17}H_{19}O_2N \cdot CH_3I + 0.5H_2O$: C, 51.42; H, 5.51; I, 30.21; H_2O, 2.14. Found: C, 51.53; H, 5.51; I, 30.21; H_2O, 2.17.

Methylation of Desoxymorphine-C.—Two grams of the alkaloid suspended in 75 cc. of ether was treated with an excess of diazomethane and allowed to stand for twenty hours. Ten cc. of methanol was added, and after forty-eight hours longer the solution was acidified, made alkaline with excess of dilute sodium hydroxide, and extracted into ether. The ethereal solution was washed twice with dilute sodium hydroxide, and gave on evaporation 2 g. of yellow oil, which was crystallized as the tartrate. Desoxycodeine-C was thrown out crystalline by addition of alkali to a solution of the tartrate; m. p. 98–100°. It did not depress the m. p. of known samples, and had the rotation $[\alpha]_D^{31}$ −192.7°, −197.4°, in alcohol. Its hydriodide melted at 272–275°, whereas desoxycodeine-C hydriodide melts at 155–160°, solidifies and remelts at 268–270°. The difference is probably due to the presence of hydrate water in one sample.

Desoxycodeine-C acid tartrate is sparingly soluble in cold water and melts unsharp at 161–165°, evolving gas at 170°.

Anal. Calcd. for $C_{22}H_{27}O_8N + 2H_2O$: C, 56.26; H, 6.65; H_2O, 7.67. Found: C, 56.20; H, 6.73; H_2O, 7.32.

Demethylation of Desoxycodeine-C.—Treatment of desoxycodeine-C with boiling hydriodic acid yields traces of an alkali-soluble crystalline base of m. p. 235–245°, which is not desoxymorphine-C; it is probably a rearrangement product. Demethylation with hydrochloric acid under various conditions failed, but by the use of sodium methylate the desired result was obtained. Three and six-tenths grams of desoxycodeine-C was dissolved in 60 cc. of absolute methanol containing 1.5 g. of sodium, and heated at 140° for seventy-two hours. From this reaction 1.7 g. of desoxycodeine-C was regained, and 0.5 g. of desoxymorphine-C isolated as the hydrochloride, m. p. 290–292°, $[\alpha]_D^{30}$ −142.8°, −143.9°. This same hydrochloride, $[\alpha]_D^{28}$ −140.4°, could be found in the mother liquors from the preparation of desoxycodeine-C by treatment of chlorodihydrocodide with sodium methylate.

Hydrogenation of Desoxymorphine-C.—(1) To tetrahydrodesoxymorphine: one gram of desoxymorphine-C hydrochloride in 15 cc. of water with 0.08 g. of platinum oxide absorbed 192 cc. of hydrogen; calcd. for 2 moles, 185 cc. The filtered solution was layered over with ether, and the base thrown out with 3 *N* ammonia. Addition of salicylic acid to the ethereal solution caused precipitation of an oily salicylate which soon crystallized. Purified from alcohol, it melted at 236–238°, and showed $[\alpha]_D^{30}$ −30.0° in methanol, c = 0.999. (2) To dihydrodesoxymorphine-D and tetrahydrodesoxymorphine: one gram of desoxymorphine-C hydrochloride (equivalent to 0.88 g. of base) suspended in 10 cc. of glacial acetic acid with 0.05 g. of platinum oxide absorbed 129 cc. of hydrogen (1.54 moles) in two hours, when the absorption stopped completely. The solution was freed from catalyst, diluted and treated with excess of solid sodium bicarbonate. The resinous precipitate was extracted into ether, and obtained as a yellow

oil, 1.0 g., after removal of the solvent. The oil was rubbed up with acetone, and 0.33 g. of tetrahydrodesoxymorphine separated crystalline. It was characterized as the salicylate, m. p. 235–238° and $[\alpha]_D^{25}$ −31.6°. The acetone mother liquor was evaporated to dryness (the isolation of dihydrodesoxymorphine-D itself will be described in a later paper), the residue taken up in methanol, and poured into an excess of ethereal diazomethane. After forty hours the ether was distilled and the half-crystalline residue treated with saturated aqueous tartaric acid. The crystalline dihydrodesoxycodeine-D acid tartrate obtained weighed 0.5 g., and after three crystallizations melted at 124–125°. It yielded a base of m. p. 103–105°, identified by mixed m. p. with dihydrodesoxycodeine-D.

Normal Hydrogenation of Desoxycodeine-C.—A suspension of 1.5 g. of desoxycodeine-C hydrochloride, hydrogenated as described in the preceding paragraph, absorbed 149 cc. (1.27 moles) of hydrogen in thirty minutes. The reduction product was worked up as described above, and the residue from distillation of the ether converted to dihydrodesoxycodeine-D acid tartrate; weight 1.64 g., m. p. after two crystallizations, 124–125°. It was found that the acid tartrate, by intensive drying, can be obtained in an anhydrous form of m. p. 154–154.5° and having $[\alpha]_D^{18}$ −29.9° (water), c = 1.773.

Anal. Calcd. for $C_{22}H_{29}O_8N + 2H_2O$: H_2O, 7.64. Found: H_2O, 7.29.

The mother liquors from the acid tartrate preparation gave 0.27 g. of tetrahydrodesoxycodeine, m. p. 143–145°, gas evolution at 151°. It was sublimed at 160° (3 mm.), yielding the anhydrous form of m. p. 124–125°. A portion of this, seeded with the high melting anhydrous form described in a previous paper, changed over entirely in twelve hours to the m. p. 156–157.5° while the unseeded portion retained the lower melting point.

Demethylation of Tetrahydrodesoxycodeine: Tetrahydrodesoxymorphine.—A solution of 5 g. of tetrahydrodesoxycodeine in 25 cc. of hydriodic acid (sp. gr. 1.7) was boiled vigorously under reflux for twelve minutes. The hydriodide of tetrahydrodesoxycodeine which at first separated went into solution during the first five minutes, and methyl iodide could be observed in the condenser. The red solution was poured into 800 cc. of warm water (60°) containing 5 g. of sodium bisulfite. The light green solution was cooled, ether added, and the base thrown out with 3 *N* ammonia. The ether was freed of ammonia by washing with water, dried, and poured into concentrated ethereal salicylic acid. Tetrahydrodesoxymorphine salicylate separated as an oil which slowly crystallized. The yield was 70%. After purification from alcohol the salt melted at 238–240° and gave the value $[\alpha]_D^{31}$ −31.0° (absolute methanol), c = 1.032.

Anal. Calcd. for $C_{24}H_{29}O_5N$: C, 70.04; H, 7.10. Found: C, 69.87; H, 7.25.

Tetrahydrodesoxymorphine base was prepared from the pure salicylate by suspending the latter in water, adding 3 *N* ammonia and extracting with ether. After the ether was distilled nearly to dryness the base was obtained as a white crystalline powder which could be best purified from methyl acetate using the temperature range 35 to −20°. In most other organic solvents it turns red rapidly. Because of rapid darkening of the solution, an accurate value for the rotation could not be obtained; in methyl acetate $[\alpha]_D^{24}$ −77° ± 5°, c = 0.923. The base shows a green-brown ferric chloride reaction. The analytical sample was sublimed at 150° (0.3 mm.).

Anal. Calcd. for $C_{17}H_{23}O_2N$: C, 74.68; H, 8.52. Found: C, 74.98; H, 8.57.

Tetrahydrodesoxymorphine hydrochloride was prepared by adding ethereal hydrogen chloride to an ether solution of the base (prepared directly from the pure salicylate). After crystallization was complete the ether was decanted, and the salt washed onto a filter with acetone. It was recrystallized from absolute alcohol by addition of absolute ether. It is very soluble in water or alcohol. It softens at 255–260° and melts at 260–262°. In 95% alcohol $[\alpha]_D^{24}$ −45.5°, −47.1°, c = 1.254.

Anal. Calcd. for $C_{17}H_{23}O_2N \cdot HCl$: Cl, 11.45. Found: Cl, 11.58.

Tetrahydrodesoxymorphine hydriodide was prepared in the usual way and purified by recrystallization from water. It melts at 268–271°, and shows in aqueous solution $[\alpha]_D^{24}$ −32.7°, c = 0.963.

Anal. Calcd. for $C_{17}H_{23}O_2N \cdot HI$: I, 31.64. Found: I, 31.66.

Tetrahydrodesoxymorphine methiodide was prepared by warming the pure base with excess of methyl iodide, and purified from 95% alcohol. It is soluble with difficulty in cold water or alcohol, insoluble in acetone, soluble in methyl alcohol. It crystallizes in fine yellow prisms melting with decomp. at 269–271°; in absolute methanol $[\alpha]_D^{31}$ −31.4°, −29.9°, c = 0.797.

Anal. Calcd. for $C_{17}H_{23}O_2N \cdot CH_3I$: I, 30.58. Found: I, 31.24, 30.38.

Methylation of Tetrahydrodesoxymorphine.—Attempts to methylate the base or its methiodide with diazomethane, or the methiodide with sodium methylate and methyl iodide, led only to resinous products. The methylation was finally accomplished by the method used in the case of desoxymorphine-A. A solution of 0.2 g. of tetrahydrodesoxymorphine hydrochloride in 20 cc. of methanol was poured into an excess of ethereal diazomethane and allowed to react in the dark for twenty-four hours. The solution was evaporated to dryness at room temperature, and the methylated base isolated in the usual way. Purification was effected by sublimation at 0.3 mm.; the sublimate, of m. p. 157–158°, was identified as the anhydrous form of tetrahydrodesoxycodeine.

The So-called Desoxycodeine-B.—This alkaloid, originally described by Freund[21] as a dihydrodesoxycodeine of m. p. 117–119° and $[\alpha]_D$ +86.4° was shown by Small and Cohen[22] to be a desoxycodeine. Proof of its degree of saturation rested on hydrogenation experiments as well as analytical results. It was believed to differ from desoxycodeine-A chiefly on the basis of its rotation. The low rotation observed in both the investigations cited is due, however, to the presence of a most persistent crystalline impurity which is derived apparently from some foreign substance in the α-chlorocodide employed.[23] When the α-chlorocodide used is purified to $[\alpha]_D$ −380°, the crude product from electrolytic reduction shows a relatively high rotation and can be purified until its physical constants are practically identical with those of desoxycodeine-A.

Twenty-one grams of α-chlorocodide, $[\alpha]_D^{25}$ −379.9°, m. p. 151–152°, was reduced under the conditions described by Small and Cohen. The desoxycodeine obtained after one crystallization from alcohol had $[\alpha]_D^{24}$ +112.8°, and after eight more crystallizations this rotation reached $[\alpha]_D^{23}$ +119.8°, and remained unchanged by further crystallization. The material was now converted to the salicylate, which melted 2.5° below pure desoxycodeine-A salicylate. Three crystallizations of the salicylate brought its melting point and rotation up to those of desoxycodeine-A salicylate. The base and salts of the base derived from the salicylate are compared below with the corresponding desoxycodeine-A derivatives.

	Desoxycodeine-A		"Desoxycodeine-B"	
	M. p., °C.	$[\alpha]_D$°	M. p., °C.	$[\alpha]_D$°
Base	158–160[a]	+124.3	157–159[a]	+123.4
Hydrochloride	255–257[b]	+ 93.6	255–257[b]	+ 94.2
Hydriodide	268–269	+ 71.4	268–270	+ 72.2
Methiodide	219–221	+ 95.7	218–220	+ 93.7
Salicylate	220.5–221[b]	+104.4	220–220.5[b]	+103.0

[a] Anhydrous. [b] M. p. in evacuated tube.

(21) Freund, Melber and Schlesinger, *J. prakt. Chem.*, **101**, 1 (1921).

(22) Small and Cohen, THIS JOURNAL, **53**, 2214 (1931).

(23) It cannot be due to the presence of β-chlorocodide, which is often found up to 10% in α-chlorocodide, for β-chlorocodide is reduced readily to desoxycodeine-A.

Desoxycodeine-A occurs in a hemihydrated form, m. p. 122–126° unsharp, as described in previous publications, also in a second hemihydrate form (the more stable form) of m. p. 151–152°, gas evolution 153°.

Anal. (High-melting hemihydrate) Calcd. for $C_{18}H_{21}O_2N + 0.5H_2O$: C, 73.93; H, 7.58; H_2O, 3.08. Found: C, 73.96; H, 7.57; H_2O, 3.27, 3.28.

Both hemihydrates have a tendency to lose water spontaneously, giving the anhydrous form, m. p. 159–161°, $[\alpha]_D$ −118.8° (alcohol), $c = 2.268$. The anhydrous form can be converted back to the high-melting hemihydrate by dissolving in a large excess of warm 95% alcohol, cooling and adding water while scratching the beaker walls with a glass rod.

Desoxycodeine-A salicylate has not been previously described. Its physical constants are given in the table above.

Anal. Calcd. for $C_{25}H_{27}O_5N$: C, 71.22; H, 6.46. Found: C, 71.23; H, 6.66; for "Desoxycodeine-B" salicylate, C, 71.08; H, 6.51.

Desoxycodeine-A methiodide has been hitherto found amorphous. It can be obtained crystalline by treating the very pure base in the usual way with methyl iodide and crystallizing from alcohol by addition of ether. Its constants are given in the table above.

Anal. Calcd. for $C_{18}H_{21}O_2N \cdot CH_3I + 0.5H_2O$: I, 29.24; H_2O, 2.08. Found: I, 28.86; H_2O, 1.91.

The low rotating impurity in "Desoxycodeine-B" was isolated from the salicylate filtrates after all crystalline material possible had been recovered. The base was liberated from the mother liquors and obtained from ether as a partly crystalline oily mass. After numerous sublimations in high vacuum, 63 mg. of white crystalline base melting at about 115° and having $[\alpha]_D^{26}$ +6.6° (10% AcOH), $c = 0.610$, was obtained. It is not certain whether the purification was complete. The solution used for rotation absorbed hydrogen with palladium, giving tetrahydrodesoxycodeine. The hydrogen absorption did not permit of a decision between one and two moles.

Summary

1. Electrolytic reduction of α-chloromorphide results in a halogen-free unsaturated base, desoxymorphine-A, which is the morphine analog of desoxycodeine-A.

2. Elimination of hydrogen chloride from chlorodihydromorphide leads to desoxymorphine-C. This base is a γ-isomorphine type, with a hydrogen atom in place of the alcoholic hydroxyl group of γ-isomorphine. Desoxymorphine-C is likewise formed when desoxycodeine-C is demethylated.

3. Hydrogenation of desoxymorphine-A, or of desoxymorphine-C in organic solvents, proceeds with addition of two moles of hydrogen and results in tetrahydrodesoxymorphine. This alkaloid can also be prepared by demethylation of tetrahydrodesoxycodeine.

4. Desoxymorphine-C and its methyl ether, desoxycodeine-C, can be hydrogenated under certain conditions to give dihydro derivatives in which the 4,5 ether bridge is still intact.

5. The so-called desoxycodeine-B is shown to consist mainly of desoxycodeine-A, accompanied by a base of low specific rotation which may be the true desoxycodeine-B.

UNIVERSITY, VIRGINIA

RECEIVED JANUARY 31, 1933
PUBLISHED JULY 6, 1933