[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, AND THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

REDUCTION STUDIES IN THE MORPHINE SERIES. IX. HYDROXYCODEINONE*

ROBERT E. LUTZ AND LYNDON SMALL

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When thebaine (I), in glacial acetic acid solution, is treated with hydrogen peroxide[1] the ketone, hydroxycodeinone, of the generally accepted[2,3] structure II is formed. The process apparently involves a 1,4-addition reaction, with the equivalent of hydrolysis at the enol ether group of thebaine, whereby a tertiary alcoholic hydroxyl appears at C-14, and a carbonyl group at C-6 in the end product. The position of the carbonyl group and the existence of the intact morphine skeleton in hydroxycodeinone seem well established by the facts that bromocodeinone (III) can be transformed to hydroxycodeinone oxime through the action of hydroxylamine, and can also, by reductive elimination of bromine, be converted to the well known morphine derivatives codeinone (IV)[2,4] and dihydrocodeinone.[5] The only structural features of hydroxycodeinone involving any uncertainty beyond that inherent in the morphine formula, are the locations of the alicyclic unsaturation and of the alcoholic hydroxyl group. (See p. 221.)

The hydroxycodeinone formula originally advanced by Freund and Speyer represented the hydroxyl as occupying C-7, and since the group has not the properties of an enolic hydroxyl, this necessitated locating the unsaturation between C-8 and C-14. As Robinson has pointed out, hydroxycodeinone does not behave like an α-hydroxy ketone, nor do the results of cyanogen bromide degradation[1,5] point to location of the double

* The work reported in this paper is part of a unification of effort by a numbr of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the Nationa 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. Public Health Service.

Number VIII of this series, see Small and Browning, J. ORG. CHEM., **3**, 618 (1939). This communication was erroneously numbered VII.

[1] FREUND AND SPEYER, *J. prakt. Chem.*, **94**, 135 (1916).

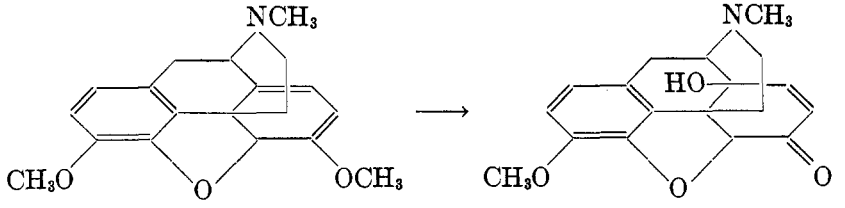
[2] GULLAND AND ROBINSON, *Mem. Proc. Manchester Lit. Phil. Soc.*, **69**, 79 (1925).

[3] SCHÖPF AND BORKOWSKY, *Ann.*, **452**, 211 (1927).

[4] FREUND, *Ber.*, **39**, 844 (1906).

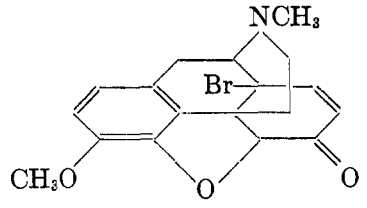
[5] SPEYER AND SARRE, *ibid.*, **57**, 1404 (1924).

bond in the β, γ position to nitrogen. The hydroxyl group can scarcely be at carbon 8, for such a β-hydroxy ketone should undergo dehydration easily, in contrast to hydroxycodeinone and its derivatives; this structure would, moreover, make it impossible to locate an unsaturated linkage in ring III. The remaining probability, C-14, permits a reasonable mechanism for the formation of hydroxycodeinone from thebaine, and explains the retention of the vinyl group on C-13 in the degradation reactions that lead to dihydrohydroxycodeinone.[1, 3]

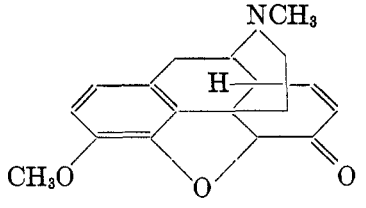


I. Thebaine

II. Hydroxycodeinone



III. Bromocodeinone



IV. Codeinone

The present studies on hydroxycodeinone were undertaken to increase our knowledge of the physiological action of derivatives of this series, as well as with the hope of obtaining more direct evidence concerning the nuclear position of the hydroxyl group. Although the last objective has not been attained, the results of the investigation must be brought to publication at this time because of the unavoidable termination of our collaborative work.

According to formula II, the reduction product, dihydrohydroxycodeinone, is a saturated, tertiary alcohol, and should undergo dehydration with relative ease to yield the ketone corresponding to the secondary alcohol neopine or, by rearrangement, codeinone. All of our attempts to dehydrate dihydrohydroxycodeinone have failed. Dehydration with phosphorus pentoxide[6] resulted in extensive decomposition, and with phos-

[6] HILL AND FISCHER, *J. Am. Chem. Soc.*, **44**, 2582 (1922).

phorus oxychloride gave unchanged material. Dehydration in the presence of iodine[7] was not more successful. Dehydration with anhydrous oxalic acid[6, 8] at elevated temperatures, which has been carried out with other tertiary alcohols, yielded unchanged material, as did also Willstätter's method,[9] phthalic anhydride in benzene or in dekalin. Attempts to split acetic acid out of 14-acetyldihydrohydroxycodeinone likewise failed, although the higher esters[10] were not investigated. The only evidence of a dehydration of this tertiary alcohol appears in the work of Schöpf,[11] who believed he had split out water between C-14 and C-8 in dihydrohydroxythebainonemethine. Since, however, the hydrogenation product (not analyzed) obtained from this supposed dehydration compound was not identical with dihydrothebainonedihydromethine, nor with the C-14 diastereoisomeric β-dihydrothebainonedihydromethine which Small and Browning[12] claim to have isolated from degradation of β-dihydrothebainone, the Schöpf experiments cannot be advanced as valid evidence for a dehydration of a dihydrohydroxycodeinone derivative. It is nevertheless remarkable that a tertiary alcohol of this type should offer such resistance to dehydration.

Speyer[5] investigated the zinc-acetic acid reduction of hydroxycodeinone, from which isomeric phenolic and non-phenolic compounds were obtained. The non-phenolic isomer, which exhibited no ketonic properties, was designated hydroxycodeine and, according to the Robinson idea, would be represented by V. Speyer's conception of the secondary alcoholic group is probably correct, for we find that hydroxycodeine forms two acetyl derivatives (one of which may be a diacetyl compound) that readily undergo hydrolysis with alkali to regenerate hydroxycodeine. It is remarkable that Speyer mentions no difficulty in the analysis of the hydroxycodeine base. Analysis in this laboratory indicate that it holds a molecule of water with unusual tenacity, and only after boiling out with chlorobenzene, and crystallization from this solvent could it be obtained in anhydrous form for analysis.

Catalytic hydrogenation of hydroxycodeine proceeds slowly with absorption of one mole of hydrogen. The product, for which formula VI is logical, we have named dihydrohydroxycodeine-A, to distinguish it from the isomers to be described. It shows a striking similarity to hydroxycodeine in physical properties, but gives analytical values corresponding to the

[7] HIBBERT, *ibid.*, **37**, 1748 (1915).

[8] WALLACH, *Ann.*, **275**, 107 (1893). SAYTZEFF, JUN., *J. prakt. Chem.*, **57**, 38 (1898). ZELINSKY AND ZELIKOW, *Ber.*, **34**, 3249 (1901).

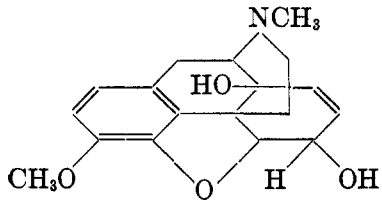
[9] WILLSTÄTTER, *Ann.*, **378**, 109 (1911).

[10] Method of KRAFFT, *Ber.*, **16**, 3020 (1883).

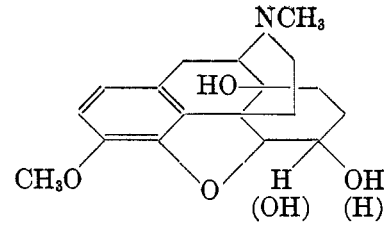
[11] SCHÖPF AND BORKOWSKY, *Ann.*, **452**, 255 (1927).

[12] SMALL AND BROWNING, J. ORG. CHEM., **4**, 00 (1939).

expected formula, $C_{18}H_{23}NO_4$, and shows a decisive depression in mixture melting point with hydroxycodeine.



V. Hydroxycodeine



VI. Dihydrohydroxycodeines-A (?), -B and -C

Hydroxycodeinone is reduced readily in the presence of palladium-barium sulfate to give the well-known dihydrohydroxycodeinone. This compound still contains the carbonyl and hydroxyl groups; it forms an oxime, or a monoacetyl derivative, and we find that under more vigorous acetylation conditions it yields acetyldihydrohydroxycodeinone enol acetate, the analog of the drug Acedicon (dihydrocodeinone enol acetate). Gentle acid hydrolysis converts the enol acetate back to acetyldihydrohydroxycodeinone, and by vigorous hydrolysis both acetyl groups are removed.

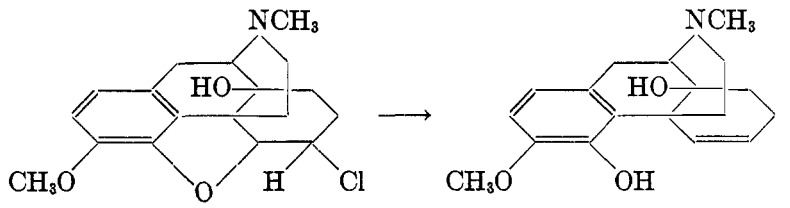
Dihydrohydroxycodeinone can be hydrogenated further (platinum catalyst), and takes up one mole of hydrogen to give unequal amounts of two compounds that can be separated through salts of their diacetyl derivatives. The major product is dihydrohydroxycodeine-B, the minor product is an isomer, dihydrohydroxycodeine-C. Both compounds have the same empirical formula as the above described dihydrohydroxycodeine-A, are non-phenolic, and contain two alcoholic hydroxyl groups, as is shown by the results of acetylation. The method of preparation predicts that the A isomer should be identical with one of the last described isomers. These were prepared under such mild conditions, catalytic reduction in two stages, that a rearrangement (at C-14?) hardly comes into consideration. It seems more probable that a structural change took place in the zinc and acid reduction to the supposed hydroxycodeine, the first stage in the formation of dihydrohydroxycodeine-A. This idea is supported by the pharmacological studies,[13] for the isomers B and C differ in their physiological action in about the same degree as the members of other diastereoisomeric pairs that have been compared, such as dihydrocodeine and dihydroisocodeine, whereas dihydrohydroxycodeine-A deviates widely in effect from the other two isomers.

[13] SMALL, EDDY, MOSETTIG, AND HIMMELSBACH, "Studies on Drug Addiction", p. 33 (Suppl. No. 138 to the Public Health Reports, Washington, 1938).

Dihydrohydroxycodeine-B methiodide undergoes ring scission in the normal way, and the product, dihydrohydroxycodeine-B-methine, takes up one mole of hydrogen to form the dihydromethine.

The action of thionyl chloride on dihydrohydroxycodeine-B resulted in substitution of a chlorine atom into the aromatic nucleus, presumably at the 1 position.[14] This was evident not only from the analytical values, but also from the course of the sodium and alcohol reduction of the chloro compound, which regenerated dihydrohydroxycodeine-B. The nuclear chlorination is not surprising, for we have observed a similar reaction of all four isomeric dihydrocodeines. It is apparent that the success of the thionyl chloride reaction in replacement of the alcoholic hydroxyl of morphine and codeine by chlorine[15] is due to the activation of the hydroxyl group by the 7,8 double bond, although it is remarkable that with these alkaloids the reaction does not proceed further, with involvement of the aromatic nucleus.

Phosphorus pentachloride replaces a hydroxyl group of dihydrohydroxycodeine-B with chlorine, yielding a dihydrohydroxychlorocodide (VII). Proof that the hydroxyl replaced is that at the 6 position rests on sodium and alcohol reduction, in which the chlorine is eliminated with simultaneous reductive rupture of the ether bridge, to give a new phenolic compound, dihydrodesoxyhydroxycodeine (VIII). The reaction is analogous to the sodium-alcohol reduction of dihydrochlorocodide to dihydrodesoxycodeine-C, and indicates that the halogen and the ether-linked oxygen in dihydrohydroxychlorocodide are reacting as though in a conjugated system,[16] *i. e.*, in such a way that reductive elimination of chlorine involves the ether bridge. Were the chlorine at C-14, its replacement by hydrogen should yield dihydrocodeine or dihydroisocodeine. Dihydrodesoxyhydroxycodeine takes up one mole of hydrogen, giving tetrahydrodesoxyhydroxycodeine. Repeated attempts to reduce dihydrohydroxychlorocodide to a non-phenolic product, or to eliminate hydrogen chloride to obtain a substance of the desoxycodeine-C type (of pharmacological interest) have failed.



VII. Dihydrohydroxychlorocodide VIII. Dihydrodesoxyhydroxycodeine

[14] Small and Turnbull, *J. Am. Chem. Soc.*, **59**, 1541 (1937).
[15] Wieland and Kappelmeier, *Ann.*, **382**, 306 (1911).
[16] *Cf.* Small and Lutz, *J. Am. Chem. Soc.*, **56**, 1378 (1934).

The different chlorinating reactions of thionyl chloride and phosphorus pentachloride can be carried out successively, regardless of the order, to produce chlorodihydrohydroxychlorocodide, in which a hydroxyl group and a hydrogen atom have been replaced by chlorine.

If formula VI is correct for dihydrohydroxycodeine-B, it is surprising that only one of the two hydroxyls should be replaced in the reaction with phosphorus pentachloride, and that this one should be the 6-hydroxyl rather than the tertiary hydroxyl at C-14. The unexpected resistance of this group toward replacement (or dehydration) reactions might be ascribed to its position at the junction of two fused rings, yet the bromine atom in bromocodeinone shows no reluctance to reaction with hydroxylamine (elimination as hydrogen bromide to the contrary, however), nor do similarly located (angular) hydroxyl groups in the cyclopentenophenanthrene series (heart poisons, toad poisons) display a like inertia.

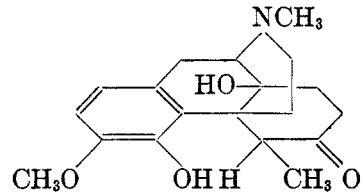
Dihydrohydroxycodeine-C reacts with phosphorus pentachloride to give products containing phosphorus. This difference in the behavior of the B and C isomers is reminiscent of that already observed in the epimeric pair, dihydrocodeine and dihydroisocodeine. This fact can scarcely be considered as valid evidence for the assignment of the comparative configurations, but is suggestive of a similar relationship in the two pairs of isomers. Lacking more direct evidence, we may mention that there is nothing in the pharmacological picture that is inconsistent with the conception that dihydrohydroxycodeine-B has the dihydrocodeine configuration at C-6, and that dihydrohydroxycodeine-C has the dihydroisocodeine configuration.

With compounds of the hydroxycodeinone series, phosphorus pentachloride and phosphorus tribromide gave for the most part intractable products. The reaction of hydroxycodeinone with phosphorus pentachloride has been most extensively studied. Under various conditions, yields of crystalline material amounting to about 20 per cent. of the starting material have been obtained. The crude product is a complex mixture, from which six compounds have so far been isolated. Four of these are so weakly basic that they do not dissolve in dilute acetic acid, but do dissolve in hydrochloric acid, a property that was utilized for partial separation. Of the six compounds, one is monochlorinated, two are dichlorinated, and three are trichlorinated derivatives. The dichloro compounds are believed to contain a ketochloride group, and are analogous to the ketochlorides obtained from the α,β-unsaturated ketones. The trichloro compounds are probably also ketochlorides, but have, in addition, the 14-hydroxyl replaced by chlorine. This replacement reaction contrasts with the indifference of the hydroxyl in the saturated derivatives, and may be ascribed to the activating influence of the 7,8-double bond. The work which is now under way to elucidate the nature and relationships of

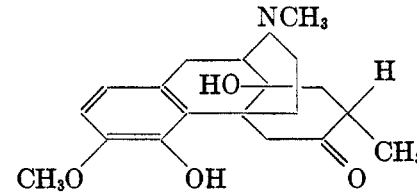
these compounds and to apply the reaction to other ketones of the morphine series will be reported in later papers. The catalytic reduction of one of the trichloro compounds, 14-chlorocodeinone ketochloride-A may be mentioned at this time. The products isolated were dihydrodesoxycodeine-D and tetrahydrodesoxycodeine. Thereby is demonstrated conclusively, that in the trichloro compound as well as in hydroxycodeinone, the original morphine skeleton has been maintained intact.

Reduction of hydroxycodeinone with stannous chloride results in rupture of the oxide ring and formation of hydroxythebainone, which is further reduced catalytically (or by metal combinations) to dihydrohydroxythebainone.[1] The last named compound is obtained also from dihydrohydroxycodeinone through the action of metal combinations. We have carried out many such reductions in this series, and in the sodium-alcohol and Clemmensen reductions of hydroxythebainone have found only dihydrohydroxythebainone, with no evidence of a non-phenolic compound such as the so-called "dihydrohydroxythebacodine" of Ochiai.[17]

It has been shown in previous papers from this laboratory that organomagnesium halides react with pseudocodeine types,[18] and that the products resulting from the reaction of the enol ethers and enol esters of the morphine dihydroketones are of special interest because they can be reconverted through 4,5-ether ring closure to nuclear substituted dihydromorphine derivatives.[19] The promising therapeutic action of methyldihydromorphinone has led us to undertake the preparation of a similar compound derived from the 14-hydroxy series, an attempt that has met with only partial success.



IX.



X.

Methyldihydrohydroxythebainones

As in several of the examples already reported, the reaction of methylmagnesium iodide with acetyldihydrohydroxycodeinone enol acetate produced two phenolic compounds in unequal amounts. Neither the bases

[17] OCHIAI, *J. Pharm. Soc. Japan*, No. **568**, 91 (1929). KONDO AND OCHIAI, *Ann.*, **460**, 224 (1929).

[18] SMALL AND YUEN, *J. Am. Chem. Soc.*, **58**, 192 (1936).

[19] SMALL, FITCH, AND SMITH, *ibid.*, **58**, 1547 (1936). SMALL, TURNBULL, AND FITCH, J. ORG. CHEM., **3**, 204 (1938).

nor their salts have been isolated in crystalline condition, but the two compounds were separated and characterized as the crystalline oxime hydrochlorides. In analogy with the still unsettled speculative constitutions already referred to, the phenolic compounds may be tentatively represented as in formulas IX and X.

The oxime of the major product, on hydrolysis, gives a *new, non-phenolic* crystalline base, which, in turn, gives a new oxime. The oximation or hydrolysis seems to have involved simultaneous ring closure, but the exact nature of the reaction must await further investigation. Bromination of the phenolic bases from the Grignard reaction, followed by ring closure in the usual way resulted in non-phenolic products that have not yet been obtained in well defined condition. These results, which constitute only a preliminary report on the reaction, demonstrate again the applicability of the Grignard reagent to those of the morphine derivatives having a double bond "conjugated" with the cyclic ether group.

We are indebted to Merck and Co., Inc., Rahway, N. J. for the gift of thebaine used in this research.

EXPERIMENTAL*

Hydroxycodeinone.—[1] The preparation of starting material was carried out by the general method of Freund and Speyer, adapted to a larger scale. In a series of runs, 50 g. of thebaine was added to 200 cc. of glacial acetic acid, the solution was heated quickly to boiling, and the flame removed. Twenty-five cubic centimeters of 30% hydrogen peroxide solution was added, and the ensuing vigorous ebullition was maintained by heating until ten minutes had elapsed from the start of the reaction. The solution was poured immediately onto a large quantity of ice, and succeeding oxidations were added to the same mixture. After neutralization of the acetic acid with concentrated ammonia (ice addition), the crude dark-brown solid was separated by filtration, and purified by trituration with successive portions of cold ethanol, which removed resinous impurities. The yield of brown crystalline powder was 36–40% of the thebaine employed. Further purification was effected by dissolving the product in boiling chloroform, cooling, and diluting with ethanol. The product retains color obstinately, and a colorless sample can be obtained through purification as the hydrochloride. The pure base melts at 275–276° (evac. tube) and has $(\alpha)_D^{25}$ −111° (10% acetic acid, c = 0.90).

The hydrochloride dihydrate crystallizes from water and melts at 272–274° (evac. tube); $(\alpha)_D^{24}$ −89° (water, c = 0.86). Freund[1] described the salt as the monohydrate and observed $(\alpha)_D^{20}$ −149.7°.

Anal. Calc'd from $C_{18}H_{20}ClNO_4 + 2H_2O$: H_2O, 9.3. Found: H_2O, 9.4.
Calc'd for $C_{18}H_{20}ClNO_4$: Cl, 10.1. Found: Cl, 10.1.

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* Previously known compounds, for which supplementary data are given are designated with literature references.

All melting points are corrected.

The hydriodide crystallizes from water as flat needles, or thin, broad, striated scales, and melts at 255–260° (evac. tube) with decomp.; $(\alpha)_D^{22}$ −74° (water, c = 0.42).

Anal. Calc'd for $C_{18}H_{20}IO_4N + H_2O$: H_2O, 3.9. Found: H_2O, 3.6.
Calc'd for $C_{18}H_{20}IO_4N$: I, 28.8. Found: I, 28.4.

The perchlorate crystallizes from water as long, thin, rectangular plates of m. p. 241–242° (decomp.), having $(\alpha)_D^{25}$ −80° (water, c = 0.58).

Anal. Calc'd for $C_{18}H_{20}ClNO_8 + 2H_2O$: H_2O, 8.0; Cl, 7.9.
Found: H_2O, 7.8; Cl, 8.2.

Acetylhydroxycodeinone[1] was obtained in good yield by heating the base under reflux for 5 minutes in acetic anhydride. It crystallizes from 80% ethanol in thin rectangular or six-sided scales and melts at 185°; $(\alpha)_D^{25}$ +21° (10% acetic acid, c = 0.77). The compound gives hydroxycodeinone in good yield when boiled with alcoholic alkali.

Acetylhydroxycodeinone hydrochloride[1] crystallizes from water in thin scales of m. p. 260–261° (evac. tube); $(\alpha)_D^{25}$ +15.7° (water, c = 0.87).

Anal. Calc'd for $C_{20}H_{22}ClNO_5$: Cl, 9.1. Found: Cl, 9.0.

Dihydrohydroxycodeinone[1,20] was obtained readily by catalytic reduction of partly purified hydroxycodeinone in 10% acetic acid with palladium barium sulfate. The reduction product was purified easily from ethanol, m. p. 218°, $(\alpha)_D^{25}$ −97° (10% acetic acid, c = 0.76).

Anal. Calc'd for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.7.
Found: C, 68.6; H, 6.7.

It was not affected by the action of zinc and acetic acid at 80–90°. Clemmensen reduction of 3 g. of the base with amalgamated zinc and a total of 50 cc. of concentrated technical hydrochloric acid during 8 hours produced an oil from which treatment with ethyl acetate gave 1.2 g. of dihydrohydroxythebainone (m. p. 143°, no depression in mixture melting point). Continued Clemmensen reduction had no further effect on the product (*cf.* Ochiai, Kondo and Ochiai[17]). Attempts to demethylate dihydrohydroxycodeinone with 48% hydrobromic acid or hydriodic acid resulted in non-crystalline products.

Dihydrohydroxythebainone hydrochloride[1] was prepared in absolute ethanol and purified from 95% ethanol. It melts at 270–272° (decomp.); $(\alpha)_D^{25}$ −123° (water, c = 0.67). Freund described the salt as anhydrous, and found $(\alpha)_D^{20}$ −52.47°.

Anal. Calc'd for $C_{18}H_{24}ClNO_4 + 2.5H_2O$: H_2O, 11.3. Found: H_2O, 10.9.
Calc'd for $C_{18}H_{24}ClNO_4$: Cl, 10.0. Found: Cl, 9.9.

Acetyldihydrohydroxythebainone, prepared according to Freund and Speyer, was found to agree in physical properties with the description in the literature.

Acetyldihydrohydroxycodeinone enol acetate.—A mixture of 500 cc. of acetic anhydride, 60 g. of fused sodium acetate, and 67 g. of dihydrohydroxycodeinone was boiled under reflux for 6 hours, and decomposed with ice and water. The solution was kept cold during neutralization with ammonia, and the filtered precipitate was washed with water. The yield (crude) was 71 g., m. p. after crystallization from ethanol 207.5°; $(\alpha)_D^{29}$ −167° (ethanol, c = 0.6).

Anal. Calc'd for $C_{22}H_{25}NO_6$: C, 66.1; H, 6.3; $COCH_3$, 21.6.
Found: C, 65.8; H, 6.5; $COCH_3$, 21.8.

The enol acetate yielded acetyldihydrohydroxycodeinone when heated for 4 minutes with 6*N* hydrochloric acid, and with more concentrated acid was converted to dihydrohydroxycodeinone.

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[20] FREUND AND SPEYER, German Patent 296,916 (1916); U. S. Patent 1,468,805 (1923); FREUND, U. S. Patent 1,485,673 (1924).

Hydroxycodeine[1].—The following is typical of several parallel reductions. To a solution of 60 g. of hydroxycodeinone in 300 cc. of glacial acetic acid, 50 g. of zinc dust was added slowly with mechanical stirring. The temperature rose to 50–55°, and was so maintained for 30 minutes. The mixture was then stirred for 1.5 hours without heating, and the product was isolated by filtering, washing the zinc residue with hot concentrated acetic acid, and neutralizing the filtrate with concentrated ammonia. The product was extracted into chloroform, and the bases were extracted fractionally from this solution with successive portions of 0.1*N* sulfuric acid, 100 cc., 100 cc., 200 cc., 300 cc., and 150 cc., the several extracts being separately neutralized with ammonia and extracted into chloroform, and the products crystallized from ethanol.

The three compounds present were separated by fractional crystallization from alcohol, and were easily recognizable by their different crystal form, hydroxycodeine, wedge-shaped (13–17%); hydroxycodeinone, prismatic rods; hydroxythebainol, long thin scales. Microscopic examination of the crystal fractions greatly facilitated the separation.

Hydroxycodeine was purified from alcohol-chloroform mixture and melted at 304–305° (evac. tube); $(\alpha)_D^{25}$ −143° (10% acetic acid, c = 0.48). (Freund observed the m. p. 293°, $(\alpha)_D^{20}$ −119°.)

Anal. Calc'd for $C_{18}H_{21}NO_4 + H_2O$: C, 64.9; H, 7.0.
Found: C, 65.7, 65.5; H, 6.7, 6.5.

Prolonged drying at 120° in a vacuum did not remove water. The sample was boiled in chlorobenzene until half the solvent had distilled, and was allowed to crystallize.

Anal. Calc'd for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.7.
Found: C, 68.4; H, 7.0.

The hydrochloride crystallized from dilute hydrochloric acid, but not from water; m. p. 269–275° (decomp.). It was difficult to purify the salt for analysis.

Anal. Calc'd for $C_{18}H_{22}ClNO_4$: C, 61.6; H, 6.3.
Found: C, 62.2; H, 6.5

Dihydrohydroxycodeine-A.—Five grams of hydroxycodeine in 55 cc. of 10% acetic acid with 0.1 g. of platinum oxide catalyst absorbed one mole of hydrogen in 12 hours. The product was isolated with ammonia and chloroform, and the oily product was crystallized from ethanol; yield, 4.4 g. The base did not form crystalline salts, and was purified from chloroform-ethanol mixture; rectangular scales of m. p. 301–302° (evac. tube); $(\alpha)_D^{20}$ −64° (10% acetic acid, c = 0.42). The mixture melting point with hydroxycodeine was 280–285°. The base showed no phenolic properties. Crystalline monoacetyl or diacetyl derivatives could not be obtained.

Anal. Calc'd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3.
Found: C, 68.1; H, 7.3.

Reduction of dihydrohydroxycodeinone.—Hydrogenation of 30 g. of dihydrohydroxycodeinone in 150 cc. of 10% acetic acid with platinum oxide catalyst proceeded very slowly, and necessitated addition of successive portions of catalyst to a total of one gram. In 24 hours, approximately one mole of hydrogen was absorbed. The product crystallized from ethyl acetate, yield 23.5 g. It was a mixture of dihydrohydroxycodeine-B with a small amount of dihydrohydroxycodeine-C, from which the former could be obtained by repeated crystallization from ethyl acetate. To obtain both isomers, 50 g. of crude product was dissolved in 175 cc. of acetic anhydride and 25 cc. of purified pyridine, the solution was heated in the water bath for one hour, and decomposed with ice. The base was precipitated with ammonia

(addition of ice) and the precipitate was rubbed with water and filtered several times. The pasty mass was treated with a solution of 30 g. of tartaric acid, and a coarse crystalline precipitate of the tartrate of the diacetylated C-isomer formed. From the cooled solution, on long standing with seed, the tartrate of the diacetylated B-isomer separated in fine needles. The diacetyl derivatives were regenerated from the salts with ammonia, purified, and hydrolyzed by heating under reflux with an excess of ethanolic sodium hydroxide for 8 minutes.

Dihydrohydroxycodeine-B.—The base is very soluble in alcohol, dilute alcohol, benzene, and butanone. It separated from ethyl acetate in thin rectangular plates of m. p. 145–145.5°, having $(\alpha)_D^{26}$ −136° (10% acetic acid, c = 0.81). It did not form an oxime.

Anal. Calc'd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3.
Found: C, 68.3; H, 7.3.

The methiodide was prepared by heating the base with excess methyl iodide in a sealed tube at 100° for 4 hours. It crystallized from absolute ethanol in nearly quantitative yield; m. p. 223–224° (decomp.), $(\alpha)_D^{21}$ −87° (water, c = 0.66).

Anal. Calc'd for $C_{19}H_{26}INO_4$: I, 27.6. Found: I, 27.8.

Diacetyldihydrohydroxycodeine-B.—Separated from the C-isomer as described above, or prepared from the purified B-isomer, the diacetyl compound was purified from dilute alcohol and had the m. p. 181–182°; $(\alpha)_D^{22}$ −127° (10% acetic acid, c = 1.31). The action of boiling acetic anhydride-pyridine caused no change in the compound.

Anal. Calc'd for $C_{22}H_{27}NO_6$: C, 65.8; H, 6.8; $(COCH_3)_2$, 21.4.
Found: C, 65.9; H, 6.8; $COCH_3$, 21.8.

The acid tartrate hydrate crystallized slowly from water in very fine needles, m. p. 181–182° (decomp.); $(\alpha)_D^{29}$ −78°, −82° (water, c = 0.72, 0.57).

Anal. Calc'd for $C_{26}H_{33}NO_{12} + H_2O$: C, 54.8; H, 6.2.
Found: C, 54.8; H, 6.0.

Dihydrohydroxycodeine-B-methine.—The methiodide prepared from 15 g. of crude dihydrohydroxycodeine-B was boiled for 15 minutes with 100 cc. of water containing 17 g. of sodium hydroxide. From ether, 14 g. of acicular crystals was obtained. The compound melted at 103° after purification from ether. $(\alpha)_D^{21}$ −70° (10% acetic acid, c = 0.14).

Anal. Calc'd for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.6.
Found: C, 68.5; H, 7.8.

The acid tartrate crystallized from water, m. p. 190–191° (gas evol.) $(\alpha)_D^{21}$ −25° (water, c = 0.38).

Anal. Calc'd for $C_{23}H_{31}NO_{10} + 4H_2O$: C, 50.0; H, 7.1; H_2O, 13.0.
Found: C, 50.0; H, 6.5; H_2O, 12.7.
Calc'd for $C_{23}H_{31}NO_{10}$: C, 57.4; H, 6.5.
Found: C, 57.4; H, 6.6.

Dihydrohydroxycodeine-B-dihydromethine.—Catalytic hydrogenation of 12 g. of the methine in 37 cc. of 75% acetic acid with platinum (oxide) proceeded with absorption of one mole of hydrogen. The product was precipitated crystalline by ammonia in nearly quantitative yield. After purification from ethyl acetate it melted at 168°; it was sublimed in a high vacuum for analysis. $(\alpha)_D^{22}$ −44° (10% acetic acid, c = 0.88).

Anal. Calc'd for $C_{19}H_{27}NO_4$: C, 68.5; H, 8.2.
Found: C, 68.7; H, 8.4.

The acetate of the dihydromethine occasionally separated crystalline from the

reduction, or could be prepared from the constituents. It could not be dehydrated without loss of acetic acid.

Anal. Calc'd for $C_{21}H_{31}NO_6 + 1.5\ H_2O$: C, 60.0; H, 8.1.
Found: C, 60.3; H, 8.0.

Dihydrohydroxychlorocodide.—To 5 g. of dihydrohydroxycodeine-B in 50 cc. of dry chloroform was added slowly 7 g. of phosphorus pentachloride, the mixture being kept at about room temperature. After one hour, the clear yellow solution was poured into water, and the aqueous layer was treated with an excess of sodium carbonate. When the milky emulsion was boiled, the product precipitated quickly in crystalline form, yield 4.1 g. It was sparingly soluble in ethanol, and was purified from ethyl acetate, m. p. 213.5–214°, $(\alpha)_D^{22}$ −151° (10% acetic acid, c = 1.26).

Anal. Calc'd for $C_{18}H_{22}ClNO_3$: C, 64.3; H, 6.6; Cl, 10.6.
Found: C, 64.2; H, 6.4; Cl, 10.6.

The chloro compound was not reduced by platinum and hydrogen in 5% acetic acid, nor by 5 hours Clemmensen reduction. After 32 hours at 140° in sodium ethoxide solution it gave a liquid phenolic product, halogen-free; gentler treatment yielded the starting material.

Chlorodihydrohydroxycodeine-B.—One part of dihydrohydroxycodeine-B was dissolved cautiously in eight parts of thionyl chloride, with cooling, and after a few minutes the solution was poured into water. The granular amorphous product was washed well with water, and distilled in a high vacuum, yielding an oil that was redistilled for analysis. It gave a negative test for sulfur, and could not be obtained crystalline.

Anal. Calc'd for $C_{18}H_{22}ClNO_4$: C, 61.4; H, 6.3.
Found: C, 61.2; H, 6.1.

The hydrochloride crystallized from acetone with alcoholic hydrogen chloride in hair-like needles, and was recrystallized from absolute ethanol (slow cooling, balls of radiating crystals). It melted at 238–239°, $(\alpha)_D^{21}$ −106° (water, c = 0.81).

Anal. Calc'd for $C_{18}H_{23}Cl_2NO_4$: Cl, 18.3. Found: Cl, 17.9.

Attempted hydrolysis (17 hours boiling in 10% acetic acid), or Clemmensen reduction, did not affect the base. Reduction with sodium and absolute ethanol under nitrogen gave a good yield of dihydrohydroxycodeine-B.

Chlorodihydrohydroxychlorocodide.—One-half gram of dihydrohydroxychlorocodide was added to 2 cc. of thionyl chloride, and after the vigorous reaction ceased, the mixture was decomposed with ice. The precipitate formed with sodium carbonate was crystallized from alcohol, yield 0.3 g.; from ethanol or ethyl acetate, rectangular prisms, m. p. 163.5°, $(\alpha)_D^{22}$ −141° (10% acetic acid, c = 0.47). The same compound was obtained when chlorodihydrohydroxycodeine-B was treated with phosphorus pentachloride.

Anal. Calc'd for $C_{18}H_{21}Cl_2NO_3$: C, 58.4; H, 5.7.
Found: C, 58.3, 58.1; H, 5.8, 5.6.

Dihydrodesoxyhydroxycodeine.—Dihydrohydroxychlorocodide was reduced under nitrogen with a large excess of sodium in boiling absolute ethanol with vigorous stirring, to the point where the sodium became molten, and could be churned through the solution in finely divided form. The base, recovered in the usual way, was an oil, which distilled in a high vacuum to form crystals on a cold finger, m. p. 134–137°, from ether or petroleum ether m. p. 137–138°, showing typical phenolic properties. $(\alpha)_D^{22}$ −19° (10% acetic acid, c = 0.62).

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.7.
Found: C, 71.6; H, 7.7.

Tetrahydrodesoxyhydroxycodeine.—A solution of dihydrodesoxyhydroxycodeine in 3% acetic acid, with platinum oxide catalyst, absorbed one mole of hydrogen, yielding a product that could be characterized only as the perchlorate, which crystallized from water or alcohol, m. p. 242–244°; $(\alpha)_D^{21}$ −28° (water, c = 0.43).

Anal. Calc'd for $C_{18}H_{26}ClNO_7$: C, 53.5; H, 6.5.
Found: C, 53.9; H, 6.6.

Dihydrohydroxycodeine-C.—A solution of 3.4 g. of the diacetyl derivative obtained from the above described separation of the B and C isomers was heated under reflux for 8 minutes with 3.5 g. of sodium hydroxide in 35 cc. of ethanol. The solution was diluted with water (no precipitate) and extracted several times with ether, from which was obtained 3 g. of oil that rapidly crystallized. From 40% ethanol it separated as long thin rectangular scales of m. p. 166–167°, $(\alpha)_D^{23}$ −152° (10% acetic acid, c = 0.56). It showed no phenolic properties.

Anal. Calc'd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3.
Found: C, 67.9; H, 7.3.

By treatment of the base with phosphorus pentachloride in chloroform, a phosphorus-containing product of m. p. 136–139° was obtained; it could not be sublimed. Thionyl chloride gave a liquid product that could be distilled in a high vacuum, but that yielded no crystalline derivatives.

Diacetyldihydrohydroxycodeine-C.—This product, separated from the acylation of the crude reduction product from dihydrohydroxycodeinone, crystallized from 80% ethanol as sheaves of needles melting at 203°; $(\alpha)_D^{22}$ −107° (10% acetic acid, c = 0.62).

Anal. Calc'd for $C_{22}H_{27}NO_6$: C, 65.8; H, 6.8; $(COCH_3)_2$, 21.4.
Found: C, 66.2; H, 7.35; $COCH_3$, 20.1.

No evidence of rearrangement to the B-isomer could be observed after prolonged treatment with boiling acetic anhydride-pyridine mixture.

The acid tartrate crystallized from water as long thin six-sided scales melting at 209–210°; $(\alpha)_D^{20}$ −67°, −72° (water, c = 0.80, 0.66).

Anal. Calc'd for $C_{26}H_{33}NO_{12} + H_2O$: C, 54.8; H, 6.2.
Found: C, 54.2; H, 6.1.

SUMMARY

1. Dihydrohydroxycodeine-A is formed when the unsaturated linkage in hydroxycodeine is hydrogenated.

2. Catalytic reduction of the ketonic group in dihydrohydroxycodeinone yields the isomeric pair, dihydrohydroxycodeines-B and -C. These probably differ in the configuration of the new asymmetric group at carbon 6, but the nature of their isomerism with dihydrohydroxycodeine-A is still uncertain.

3. Thionyl chloride acts on dihydrohydroxycodeine-B to chlorinate the aromatic nucleus, whereas phosphorus pentachloride replaces the 6-hydroxyl with chlorine to give dihydrohydroxychlorocodide. The latter compound undergoes stepwise reduction through dihydrodesoxyhydroxycodeine to tetrahydrodesoxyhydroxycodeine.

4. Hydroxycodeinone reacts with phosphorus pentachloride with formation of six halogenated derivatives, five of which appear to be ketochloride types. By reduction of 14-chlorohydroxycodeinone ketochloride-A,

dihydrodesoxycodeine-D and tetrahydrodesoxycodeine are obtained, which proves that the 14-hydroxyl group of hydroxycodeinone was replaced by halogen in this ketochloride.

5. Acetyldihydrohydroxycodeinone enol acetate reacts with methylmagnesium iodide to give two phenolic products that are probably analogous to the methyldihydrothebainones.

6. In none of the reactions of hydroxycodeinone and its derivatives can any direct evidence be found in support of, or against the 14-position for the hydroxyl group.