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DESOXYCODEINE STUDIES. II. THE DIHYDRODESOXYCODEINES¹

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In the preceding paper² the preparation of three isomeric desoxycodeines, $C_{18}H_{21}O_2N$, was described. The present communication deals with the dihydrodesoxycodeines obtained by partial reduction of the desoxycodeines, as well as with certain dihydrodesoxycodeines whose relationship to the desoxycodeines is not certain. Any systematic nomenclature of the dihydrodesoxycodeines as derivatives of the desoxycodeines is complicated by the fact that two of the latter reduce to give the same dihydro derivative, whereas the third, non-phenolic desoxycodeine yields on reduction a phenolic product which must be regarded as a dihydro derivative of the phenolic desoxycodeines. Until evidence is available through which the structure of the individual dihydrodesoxycodeines can be demonstrated, we will designate them by Roman letters, which are arbitrary and imply no genetic relationship to the desoxycodeines already described by the same device.

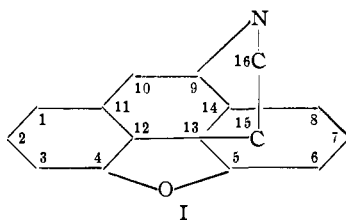
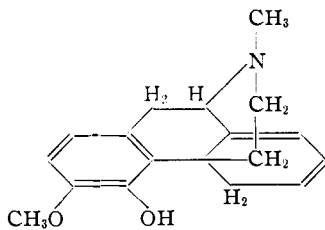
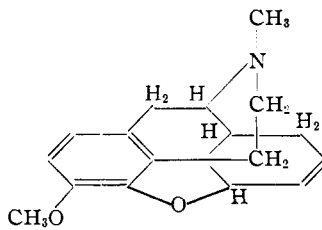
If the possibility of isomerism in this series due to differences in the spatial arrangement of the hydrogen atom on C-14, be disregarded, there are theoretically possible³ two phenolic desoxycodeines of the type shown in Formula II, both of which have been described (desoxycodeine-A and desoxycodeine-B), and four non-phenolic desoxycodeines of the type of Formula III, whose isomerism will be due to differences in position of the double linkage in Ring III. Only one of the non-phenolic desoxycodeines is known, desoxycodeine-C.

By addition of two hydrogen atoms to either of the phenolic desoxycodeines of type II, there are possible four isomeric phenolic dihydrodesoxycodeines (Formula IV), all of which still contain one double bond, which may be imagined as occupying any one of the four possible positions in the hydroaromatic ring, and all of which must reduce to the same tetrahydrodesoxycodeine, provided addition of hydrogen at C-14 takes place always in but

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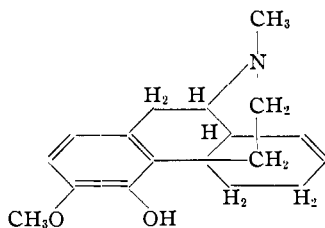
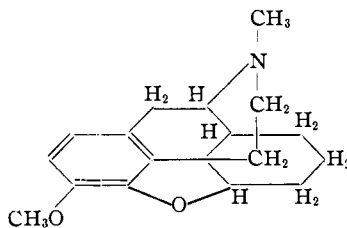
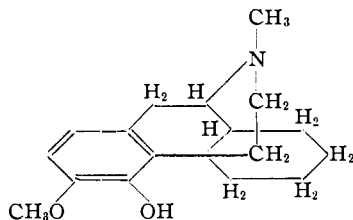
² Small and Cohen, *THIS JOURNAL*, **53**, 2214 (1931).

³ No evidence exists in morphine chemistry which would make necessary the hypothesis of stereoisomerism at any other point, as at the asymmetric carbon atoms 5 or 9. The recent work of Schöpf and Pfeifer [*Ann.*, **483**, 157 (1930)] on closure of the ether ring at C-5 includes theoretical speculations to the effect that but one configuration at C-5 is sterically possible (*loc. cit.*, page 164). An arrangement of double linkages other than in conjugation in Ring III scarcely comes into consideration.

I
Numbering systemII
Desoxycodine, phenolicIII
Desoxycodine, non-phenolic

one way sterically. The four phenolic dihydrodesoxycodines described below are, by addition of two hydrogen atoms, all converted to the same substance, β -tetrahydrodesoxycodine (VI).

By addition of two hydrogen atoms to the double linkage of any of the hypothetical desoxycodines of type III, only one non-phenolic dihydrodesoxycodine (V) will be formed, again postulating addition of hydrogen in but one way at C-14 in the case where the double linkage lies between C-8

IV
Dihydrodesoxycodine,
phenolicV
Dihydrodesoxycodine,
non-phenolicVI
 β -Tetrahydrodesoxy-
codeine

and C-14. By further addition of hydrogen, conducted under such conditions that the 4,5-ether linkage is opened, the same phenolic tetrahydrodesoxycodeine (VI) as resulted from complete reduction of the hydroaromatic ring in type II must be formed.

Desoxycodeine-A (m. p. 126° , Formula II, or the alternative formula with double bond at C-5 and C-7), which was first prepared by Knorr and Waentig in 1907,⁴ reduces with sodium and alcohol to give a product of m. p. $134-136^{\circ}$ (Knorr, melting point about 132°),^{4,5} which these investigators believed to be a dihydrodesoxycodeine, and which may be more conveniently prepared by direct reduction of α -chlorocodide with sodium and alcohol.⁴ Fourteen years later Freund, Melber and Schlesinger⁶ conducted an investigation on dihydro- and tetrahydrodesoxycodeines which must be briefly summarized here. The relevant experiments will be numbered and referred to in the discussion by these numbers.

§1. Chlorodihydrocodide, derived from dihydrocodeine by substitution of the alcoholic hydroxyl by chlorine, was reduced by the electrolytic method of Tafel, and yielded a pale brown crystalline solid, m. p. $117-119^{\circ}$, which analyzed approximately for a dihydrodesoxycodeine, $C_{18}H_{25}O_2N + \frac{1}{2} H_2O$.

§2. α -Chlorocodide, reduced electrolytically, gave a compound of m. p. $117-119^{\circ}$, which was claimed to be identical with the dihydrodesoxycodeine of §1.

§3. β -Chlorocodide, reduced electrolytically, gave a product of m. p. $126-130^{\circ}$, which showed the m. p. $117-119^{\circ}$ when mixed with the product from §2 and was therefore considered to be identical with it.

§4. Desoxycodeine (m. p. 126°), on electrolytic reduction, gave a product of m. p. $117-119^{\circ}$ which was said to be identical with the product from §1.

§5. Desoxycodeine (m. p. 126°), in the form of the hydrochloride, hydrogenated in the presence of palladium, took up two molecules of hydrogen to give a product $C_{18}H_{25}O_2N + \frac{1}{2} H_2O$, which was named β -tetrahydrodesoxycodeine.

§6. The supposed dihydrodesoxycodeine of m. p. $117-119^{\circ}$, source not given, on hydrogenation in the presence of palladium took up one molecule of hydrogen to give a substance which crystallized in leaflets or rods, sintered at 130° and melted at 132° , of which the authors write, "Die Base scheint danach identisch zu sein mit der von Knorr und Waentig aus Desoxykodem durch Reduktion mit Natrium und Alkohol hergestellten und von denselben als Desoxydihydrokodem bezeichneten Base." ("The base appears according to this to be identical with the base prepared by Knorr and Waentig from desoxycodeine by reduction with sodium and alcohol, and designated by them as desoxydihydrocodeine.") Nowhere in Freund's paper is a direct comparison of this substance, which he calls α -tetrahydrodesoxycodeine, with the desoxydihydrocodeine of Knorr mentioned, nor are analytical data on it given.

§7. α -Chlorocodide, hydrogenated in the presence of colloidal palladium, yielded an amorphous alkali-insoluble base which did not crystallize nor give crystalline salts. It analyzed very poorly for dihydrodesoxycodeine + $\frac{1}{2} H_2O$, and was named α -dihydrodesoxycodeine.

§8. The amorphous so-called α -dihydrodesoxycodeine of §7, on further reduction

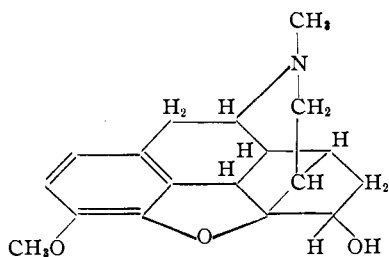
⁴ Knorr and Waentig, *Ber.*, **40**, 3860 (1907).

⁵ Cahn, *J. Chem. Soc.*, 2572 (1926), found it to sinter at 125° and melt at $134-135^{\circ}$.

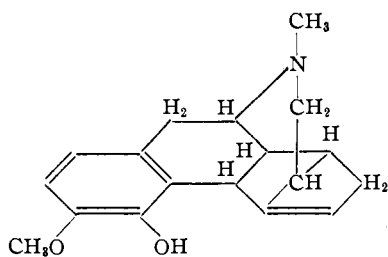
⁶ Freund, Melber and Schlesinger, *J. prakt. Chem.*, **101**, 1 (1921).

by the electrolytic method, gave a crystalline product of m. p. 131–132°, whose hydrochloride melted at 155°, and methyl ether methiodide melted at 247°. The substance of m. p. 131–132° was considered to be identical with that mentioned under §6, and with Knorr and Waentig's desoxydihydrocodeine.

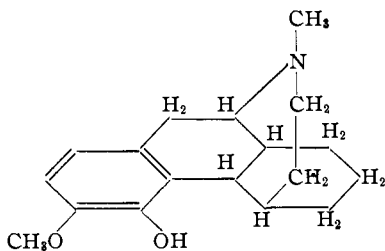
On the basis of the experimental evidence outlined above, Freund believed that the Knorr and Waentig desoxydihydrocodeine was actually formed by addition of four atoms of hydrogen to desoxycodine, *was therefore a tetrahydrodesoxycodine, and isomeric with the β -tetrahydrodesoxycodine* obtained in §5. The possibility of the appearance of stereoisomeric tetrahydrodesoxycodines which might owe their existence to differences in the spatial arrangement of hydrogen at C-14 was not recognized by Freund, nor by Gulland and Robinson⁷ in their first publication in this field. Freund⁶ used the supposed isomerism of α - and β -tetrahydrodesoxycodines as a support for the bridge bond formula (VII) for codeine which had already been developed in connection with phenyldihydrothebaine,⁸ and represented the formation of the isomers as below, where in Formula VIII reduction was thought to take place in the one case with saturation of Δ^5 , and opening of the linkage C-15, C-8 to give IX, in the other case Δ^5 was saturated, but linkage C-15, C-5 was opened and X resulted.



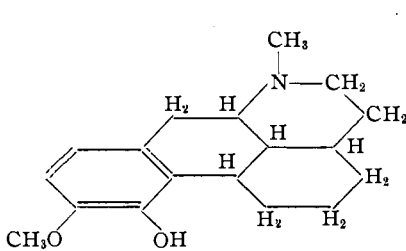
VII
Codeine (Freund 1916)



VIII
Desoxycodine (Freund 1921)⁹



IX
 α -Tetrahydrodesoxycodine



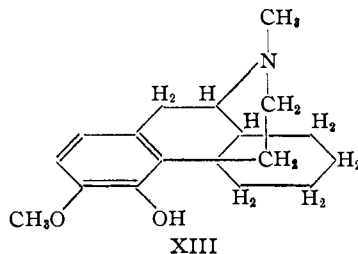
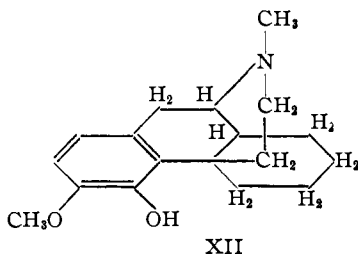
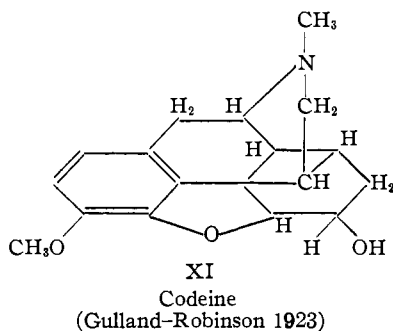
X
 β -Tetrahydrodesoxycodine

⁷ Gulland and Robinson, *J. Chem. Soc.*, 123, 980 (1923).

⁸ Freund and Speyer, *Ber.*, 49, 1287 (1916).

⁹ Through a typographical error the double linkage between C-5 and C-6 was omitted in Freund's representation of desoxycodine in Plate I (to page 9), *J. prakt. Chem.*, 101, 9 (1921).

Gulland and Robinson¹⁰ adopted a similar hypothesis to account for the two tetrahydrodesoxycodeines; in this case C-15 was linked to C-13 and C-8 in codeine (XI), and the change from desoxycodeine to the two tetrahydrodesoxycodeines was explained by rupture of the bond C-15, C-13 or C-15, C-8, respectively. In a later publication by the same authors¹¹ the possibility of accounting for the isomerism through a stereochemical relationship, analogous to the decahydronaphthalene type of isomerism was recognized, with the implication that α - and β -tetrahydrodesoxycodeines should be represented as in XII and XIII



a suggestion which was generally accepted by workers in the field of morphine chemistry.¹²

In 1926, Cahn⁵ conducted an investigation, the purpose of which was to show that the important isomerism of α - and β -tetrahydrodesoxycodeines actually existed. He prepared the supposed α -tetrahydrodesoxycodeine in a hitherto unattained state of purity, showed that it differed from β -tetrahydrodesoxycodeine, *but failed to demonstrate that it was isomeric with this substance.*

We find that the so-called α -tetrahydrodesoxycodeine of Freund is not a *tetrahydro* derivative of desoxycodeine, but is actually a *dihydrodesoxycodeine*, as originally claimed by Knorr and Waentig. Hereby is eliminated a troublesome isomerism which has been difficult to explain on the basis of any of the existing structural formulas for morphine.

With the disappearance of the supposed isomerism of the tetrahydrodesoxycodeines, certain other difficultly explicable cases of isomerism in the morphine series, which have been more or less generally considered to be of the tetrahydrodesoxycodeine type, lose an important support. This is

¹⁰ Gulland and Robinson, *J. Chem. Soc.*, 123, 983 (1923).

¹¹ Gulland and Robinson, *Mem. Proc. Manchester Lit. Phil. Soc.*, 69, 79 (1925).

¹² Cf. Schöpf, *Ann.*, 458, 164 (1927).

especially true in the case of the isomers of dihydrothebainone, and the suggestion that the relationships in this series may be of the type represented by the tetrahydrodesoxycodeines¹³ must be reconsidered.

Dihydrodesoxycodeine-A.—The so-called α -tetrahydrodesoxycodeine, which we will hereafter designate as dihydrodesoxycodeine-A, is formed in good yields by reduction of α -chlorocodide or of desoxycodeine-A with sodium and alcohol, as described by Knorr and Waentig.⁴ Following the procedure of Cahn,⁵ we purified it exhaustively through the hydrochloride, obtaining constants for this salt nearly identical with those given by this investigator for his purest substance. The free base was precipitated by addition of dilute ammonia to a dilute solution of the hydrochloride, as beautiful snow white crystals, which appeared under the microscope as chains or clumps of diamond-shaped plates. It was recrystallized to constant rotation from dilute methyl alcohol; further purification from acetone did not change the melting point or rotatory power. This base, which sintered at 120–125° and melted at 134–136°, and analyzed for a dihydrodesoxycodeine, $C_{18}H_{25}O_2N + \frac{1}{2} H_2O$, on reduction with hydrogen in the presence of a platinum catalyst *was found to absorb one molecule of hydrogen, to give a quantitative yield of β -tetrahydrodesoxycodeine.* Dihydrodesoxycodeine-A in the form of its hydrochloride of m. p. 158–160° may likewise be hydrogenated, using palladium, to give quantitatively β -tetrahydrodesoxycodeine. This end-product was identified by analysis, rotation, melting point and the melting points of its derivatives, and by its conversion to the crystalline anhydrous β -tetrahydrodesoxycodeine of sharp melting point 123–124° which will be described in our next paper. Since there is but one tetrahydrodesoxycodeine the use of the Greek letter becomes unnecessary, and we will hereafter refer to the β -tetrahydrodesoxycodeine discovered by Freund as tetrahydrodesoxycodeine.

Dihydrodesoxycodeine-A is also obtained in practically quantitative yield when desoxycodeine-B (m. p. 119°),² hitherto believed to be a dihydrodesoxycodeine, is reduced with sodium and alcohol. The reduction product was identified not only by melting point and rotation, but by melting point and rotation of the hydrochloride, analysis of the latter, and its further reduction to tetrahydrodesoxycodeine.

It is sufficiently demonstrated in the foregoing paragraphs that the so-called α -tetrahydrodesoxycodeine is non-existent. There remains only an examination of the evidence upon which its supposed existence rested. The confusion of dihydrodesoxycodeine-A with a tetrahydrodesoxycodeine arose primarily from the mistaken conception that the electrolytic re-

¹³ See, for example, Gulland and Robinson, *J. Chem. Soc.*, 123, 984, 1000 (1923); Schöpf and co-workers, *Ann.*, 452, 239, 240 (1927); 458, 155, 159, 164 (1927); Wieland and Kotake, *ibid.*, 444, 80 (1925). The speculations of Schöpf, *Ann.*, 458, note 2, page 164 (1927), regarding the relationships between the tetrahydrodesoxycodeines and dihydrothebainone naturally become invalid.

duction products from α - and β -chlorocodides (§2 and 3), chlorodihydrocodide (§1) and desoxycodine-A (§4) were identical, and from an insufficient examination of the end-product of catalytic reduction obtained in §6. Freund (§6) hydrogenated a "dihydrodesoxycodine, m. p. 117-119°" to a base which was stated to melt at 130-132°. From the fact that one molecule of hydrogen was absorbed he concluded that the product was a tetrahydrodesoxycodine, which on the basis of its melting point and the shape of its crystals he believed identical with the Knorr and Waentig desoxydihydrocodine; he claimed that the latter was actually a tetrahydrodesoxycodine and therefore isomeric with the (β -) tetrahydrodesoxycodine obtained in §5.

It is certain that Freund obtained in this hydrogenation (β) tetrahydrodesoxycodine (cf. diagram, page 2238) which when pure melts at 144-145°, but as obtained crude from catalytic reduction of all desoxy- and dihydrodesoxycodines generally shows a melting point of about 130-133°. ¹⁴

From the electrolytic reduction of α - and β -chlorocodides (§2 and 3), chlorodihydrocodide (§1) and desoxycodine 126° (§4) Freund obtained bases which all showed the melting point 117-119°, gave no depression in melting point when mixed, and which he regarded as identical. In a repetition of these reductions we find: (a) that α - or β -chlorocodide, on electrolytic reduction, yield a base of m. p. 119°, which is however a desoxycodine² (desoxycodine-B, which reduces catalytically to tetrahydrodesoxycodine by addition of *two* H₂); (b) that chlorodihydrocodide reduces electrolytically to give a dihydrodesoxycodine, m. p. 111° (which in the crude state shows a melting point of 114-117°); (c) that desoxycodine-A (126°) reduces electrolytically with great difficulty to give dihydrodesoxycodine-A (m. p. 134-136°) in small amounts.

As a result of our experiments it seems very probable that the Freund "dihydrodesoxycodine 117-119°" which was supposed to have reduced to " α -tetrahydrodesoxycodine" actually was dihydrodesoxycodine-C (m. p. 111°) in an impure state, which takes up one molecule of hydrogen to give a quantitative yield of " β -"tetrahydrodesoxycodine.

Freund claimed further (§8) that an amorphous product which he called " α -dihydrodesoxycodine" (§7) on electrolytic reduction, gave our dihydrodesoxycodine-A. We have examined " α -dihydrodesoxycodine" and find it to consist of a mixture of at least two hydrogenated desoxy-

¹⁴ No mention is made in Freund's paper of a direct comparison of his 130-132° product with the Knorr-Waentig base. We have found that crude tetrahydrodesoxycodine, m. p. *ca.* 130-133°, does not depress the melting point (134-136°) of pure dihydrodesoxycodine-A, and that a mixture of pure tetrahydrodesoxycodine (m. p. 144-145°) with dihydrodesoxycodine-A melts at an intermediate temperature (138-140°). This lack of melting point depression in the desoxycodine series is further discussed under dihydrodesoxycodine-B.

codeines,¹⁵ one of which reduces electrolytically to give tetrahydrodesoxycodeine (m. p. 144–145°). We are at a loss to explain the hydrochloride of m. p. 155° and methyl ether methiodide of m. p. 247° (§8) which Freund mentions.

We have been able to find in the literature only one other investigation where " α -tetrahydrodesoxycodine" was claimed as the end-product of reduction. In 1923 Speyer and Krauss,¹⁶ by catalytic reduction of what was then thought to be allopleurochlorocodide but was later¹⁷ shown to be the well-known β -chlorocodide, noted an absorption of three molecules of hydrogen and the formation of the so-called α -tetrahydrodesoxycodine (which was identified only by the melting point of the methyl ether methiodide). The identical reduction was carried out three years earlier by Mannich and Löwenheim,¹⁸ who found as the products two alkali-insoluble substances, which were named dehydroxydihydrocodeine and dehydroxytetrahydrocodeine. Neither substance resembled " α -tetrahydrodesoxycodine." We have carried out the hydrogenation of β -chlorocodide with palladium¹⁹ and can confirm the experimental results of Mannich. The absorption of hydrogen amounts to about 2.5 moles, and the only isolable products are a dihydrodesoxycodine (Mannich's dehydroxydihydrocodeine) to be described below, and the tetrahydrodesoxycodine of m. p. 144–145° (Mannich's dehydroxytetrahydrocodeine).²⁰

The desoxytetrahydropleurocodeine hydrochloride obtained by Speyer and Krauss²¹ through reduction of tetrahydropleurochlorocodide and stated to be identical with " α -tetrahydrodesoxycodine" hydrochloride is too inadequately described to permit of critical discussion. It is obviously impossible that a reduction product of tetrahydropleurochlorocodide can be identical with dihydrodesoxycodine-A.

There is no convincing evidence in the literature to show that dihydrodesoxycodine-A has ever been obtained as the final product of catalytic reduction.

Dihydrodesoxycodine-B.—Dihydrodesoxycodine-B, m. p. 128°, results from the electrolytic reduction of desoxycodine-C (m. p. 106°, non-phenolic) which was described in the preceding paper. It is a phenolic base, formed by addition of two hydrogen atoms at the 4,5-ether bridge

¹⁵ The separation of the constituents of the so-called α -dihydrodesoxycodine will be described in our next paper.

¹⁶ Speyer and Krauss, *Ann.*, **432**, 233 (1923).

¹⁷ Speyer and Rosenfeld, *Ber.*, **58**, 1113 (1925).

¹⁸ Mannich and Löwenheim, *Arch. Pharm.*, **258**, 295 (1920).

¹⁹ The reduction of β -chlorocodide with a platinum catalyst will be described in our next paper.

²⁰ Cf. Ochiai, *J. Pharm. Soc. Japan*, No. **568**, 91 (June, 1929); Kondo and Ochiai, *Ber.*, **63**, 646 (1930).

²¹ Speyer and Krauss, *Ann.*, **432**, 259 (1923).

which must be present in the non-phenolic desoxycodeine-C. Dihydrodesoxycodeine-B differs from dihydrodesoxycodeine-A in its melting point, in its rotation and that of its hydrochloride, and in the melting point of its methiodide. The isomers give no depression in melting point when mixed; we have encountered this phenomenon frequently in this series, as has also Cahn.²² Dihydrodesoxycodeine-B reduces catalytically, with the absorption of one molecule of hydrogen, to give a quantitative yield of tetrahydrodesoxycodeine.

Dihydrodesoxycodeine-C.—Dihydrodesoxycodeine-C (m. p. 111°) is a phenolic base which is formed when chlorodihydrocodide (XIV) is reduced by the electrolytic method. The crude product from the reduction melts at about 114–117°, a fact which we believe led Freund to confuse it with the base of m. p. 119° from the reduction of α -chlorocodide (see §1 and 6), desoxycodeine-B. Dihydrodesoxycodeine-C differs from desoxycodeine-B not only in melting point and in composition as determined by analysis, but in having a negative rotation, in forming a stable hydrochloride, in the rotation of its hydriodide and in forming a crystalline methiodide. In contrast to desoxycodeine-B, which absorbs two molecules of hydrogen, this base takes up but one molecule of hydrogen, giving tetrahydrodesoxycodeine.

Dihydrodesoxycodeine-D.—The only non-phenolic dihydrodesoxycodeine as yet prepared was first described by Mannich¹⁸ under the name dehydroxydihydrocodeine. He recognized it as a dihydrodesoxycodeine, isomeric with those which had just been reported by Freund in a preliminary communication,²³ but did not demonstrate that it could be further reduced. The base, which we will designate as dihydrodesoxycodeine-D,²⁴ may be prepared according to the directions of Mannich, by reduction of β -chlorocodide with a palladium catalyst²⁵ and is most advantageously separated from the other products of the reduction through its beautifully crystallized acid tartrate. The preparation of dihydrodesoxycodeine-D from α -chlorocodide or by methylation of dihydrodesoxymorphine will be described in further papers from this Laboratory.

Dihydrodesoxycodeine-D (XV) must be derived from our desoxycodeine-C (III) by addition of two hydrogens to the one remaining double linkage in the hydroaromatic ring, although for reasons which are probably connected with the position of the double linkage relative to the ether ring² this conversion has not yet been experimentally realized.

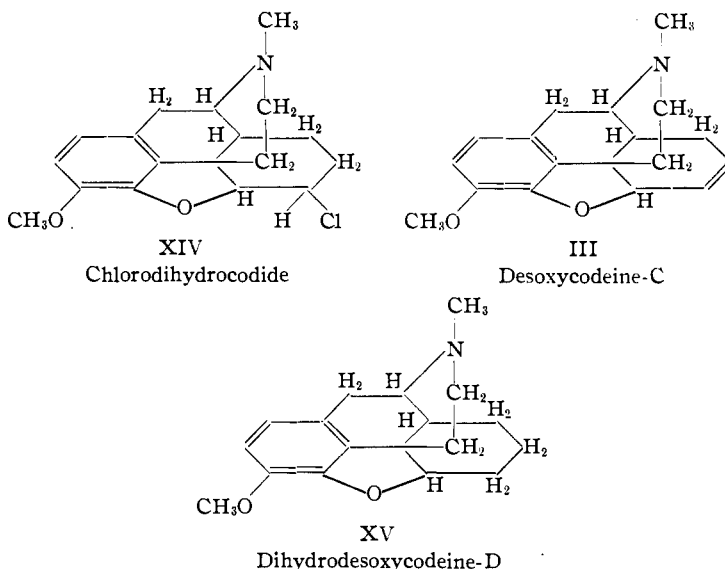
All attempts to prepare dihydrodesoxycodeine-D by addition of two hydrogen atoms to the double bond in III resulted in unchanged material

²² Cahn, *J. Chem. Soc.*, 2567, 2568, 2572 (1926).

²³ Freund, *Ber. deut. pharm. Ges.*, 29, 110 (1919).

²⁴ The name employed by Mannich does not correspond to the empirical or structural formula of the compound.

²⁵ When platinum is used the reduction takes a different course.



or in addition of four hydrogens, with reductive scission of the 4,5-ether bridge to give the end-product, tetrahydrodesoxycodeine.

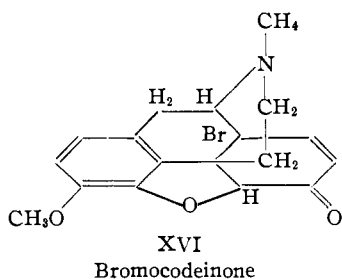
The nature of dihydrodesoxycodeine-D as a dihydrodesoxycodeine is shown by its analyses, and by its further reduction. On treatment with sodium in methyl alcohol, as well as by electrolytic reduction in sulfuric acid, it adds two hydrogen atoms, presumably opening the ether linkage, to give a nearly quantitative yield of tetrahydrodesoxycodeine (VI). This reduction could not be accomplished by the use of catalytic hydrogen.

A fifth dihydrodesoxycodeine, of m. p. 139–140°, which we will designate as dihydrodesoxycodeine-E, whose discovery is due to Speyer,²⁶ has been described.

We have verified its preparation by electrolytic reduction of bromocodeinone (XVI), and the fact that it hydrogenates with addition of one molecule of hydrogen to yield tetrahydrodesoxycodeine, as described by Speyer, but wish to leave the further investigation of this base to its discoverer. It must be formed from bromocodeinone (XVI) by reductive elimination of bromine, reduction of the carbonyl to a methylene group and reductive scission of the ether ring.

The relationships of the various known desoxycodeines and dihydrodesoxycodeines are expressed in the diagram below, which is accompanied by a table showing in condensed form the properties of these compounds. It

²⁶ Speyer and Sarre, *Ber.*, 57, 1404 (1924).



is a striking fact that all of the phenolic desoxycodeines and their hydrogenation products crystallize with one-half molecule of water; the two known non-phenolic members, desoxycodeine-C and dihydrodesoxycodeine-D, crystallize anhydrous.

As a result of the experiments described in this and the preceding paper, we believe that there is no evidence in the desoxycodeine series which warrants the assumption of an isomerism due to steric relationships on C-14 of the morphine structural skeleton, and we question seriously the validity of such an assumption in other series where the reality of otherwise unexplainable isomerism is less firmly established than it seemed to be in the case of the supposedly isomeric tetrahydrodesoxycodeines prior to the publication of the present account.

TABULAR SUMMARY

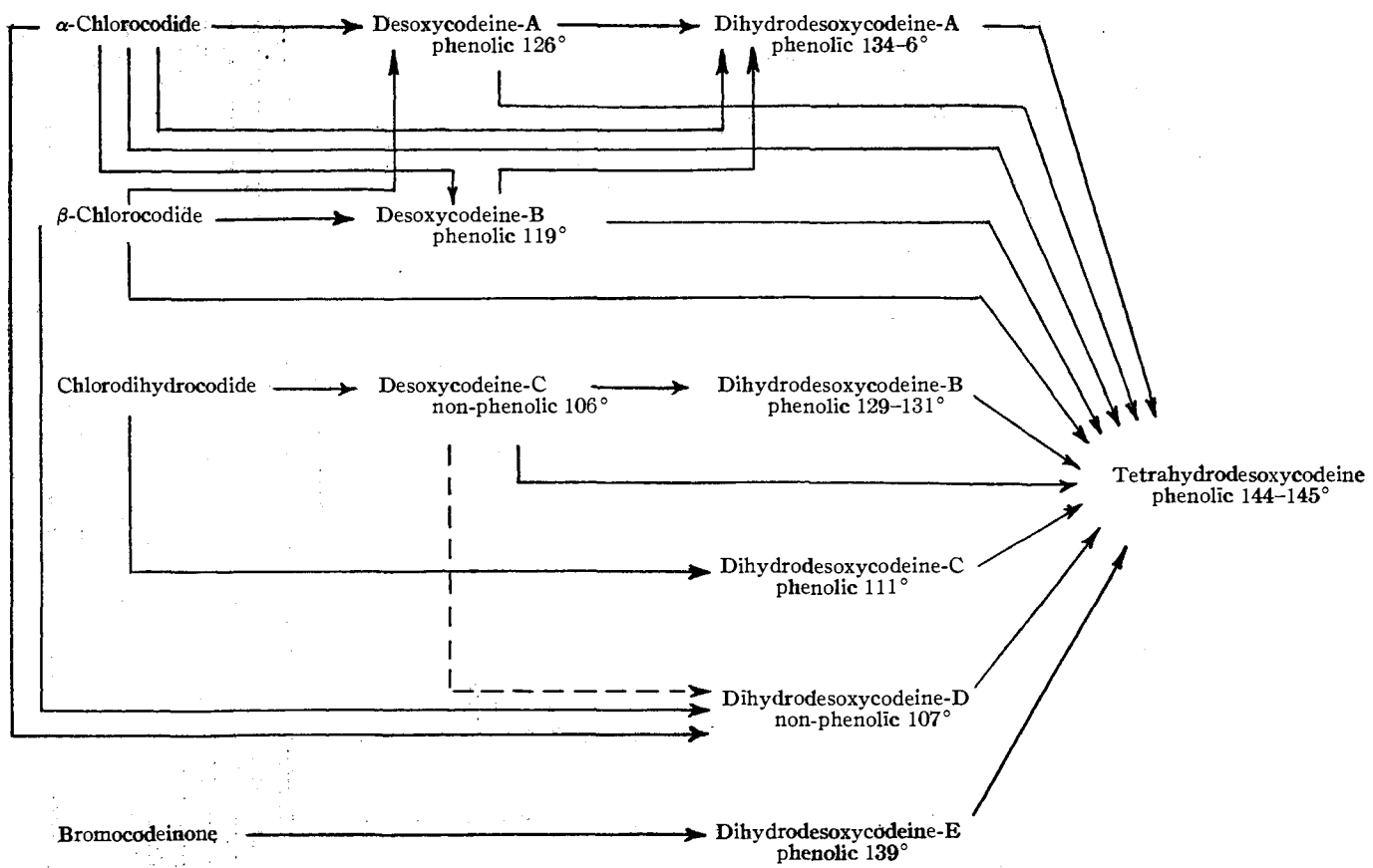
No.	Base	M. p., °C.	(α) _D	Hydrochloride M. p., °C.	(α) _D
1	Desoxycodeine-A	ca. 122	+118.1°	ca. 270	+ 87°
2	Desoxycodeine-B	119	+ 71.3°	Unstable
3	Desoxycodeine-C	106	-197.4°	114	-132.7°
4	Dihydrodesoxycodeine-A	134-136	- 27.1°	158-160	- 41.4°
5	Dihydrodesoxycodeine-B	128-131	-106.9°	154-156	- 76.4°
6	Dihydrodesoxycodeine-C	109-111	- 61.6°	241-242	- 3.6°
7	Dihydrodesoxycodeine-D	107	- 82.5°	123-125 ^a	- 39.6° ^{aa}
8	Dihydrodesoxycodeine-E	139	+ 58.1°
9	Tetrahydrodesoxycodeine	145	- 32.1°	262

No.	M. p., °C.	Hydriodide (α) _D	M. p., °C.	Methiodide (α) _D	
1	265	Phenolic
2	245	+ 38.3°	Oil	Phenolic
3	160-165	-131.6°	236-240	Non-phenolic
4	242	250-251	- 7.5°	Phenolic
5	255-256	- 79.3°	ca. 175	Phenolic
6	242-243	+ 52°	245-246	+ 15.4°	Phenolic
7	250-251	256	Non-phenolic
8	199	Phenolic
9	241	263	Phenolic

^a Acid tartrate.

Experimental

Dihydrodesoxycodeine-A.—No detailed description of the preparation of the so-called α -tetrahydrodesoxycodeine is given in the literature. We prepared the base as follows: (1) from α -chlorocodide. Ten grams of pure α -chlorocodide was dissolved in 300 cc. of 95% alcohol, and to the boiling solution was added 50 to 60 g. of sodium in pieces of about 0.5 g. During the reduction the addition of three 100-cc. portions of alcohol was necessary. When all sodium was in solution, the mixture was diluted with 400 cc. of water, and concd. hydrochloric acid (about 220 cc.) added until the solution was just acid to Congo red. Most of the alcohol was removed by distillation in vacuum at 30-40°; a large amount of sodium chloride separated in this process, and the hydrochloride of dihydrodesoxycodeine-A, which is only sparingly soluble in saturated sodium chloride solution, precipitated as a yellow oil. The solution was poured off, layered over



with ether, excess of ammonia added and the precipitate extracted. The oily hydrochloride was dissolved in water, treated in the same way, and the ether extracts combined. The ether was shaken out with two 15-cc. portions of normal hydrochloric acid, and then with successive small portions of 0.1 *N* hydrochloric acid until the acid layer gave no precipitate with Mayer's reagent. The hydrochloric acid extract was evaporated to dryness in a vacuum desiccator, leaving a brittle glassy mass, which crystallized immediately on rubbing with absolute alcohol: 8 g. of crude hydrochloride was obtained, of m. p. 148–150°. After five recrystallizations from absolute alcohol this showed the m. p. 158–160° (gas evolution), and gave the value $[\alpha]_D^{22} -41.4^\circ$: $c = 5.289$ (water), $l = 1$, $\alpha = -2.19^\circ$. (Cahn found m. p. 158–159°, $[\alpha]_D^{17} -40^\circ$.)

Eight and one-half grams of the purified hydrochloride was dissolved in 45 cc. of water, and treated dropwise with normal ammonia. The free base separated in the form of sparkling white flakes, which appeared under the microscope as chains and clumps of diamond-shaped plates. The base was recrystallized four times from dilute methyl alcohol and twice more from acetone. The last three fractions were identical in melting point and rotation. Due to the ease with which the base loses its hydrate water, the melting point is unsharp, as was observed by Cahn. Our purest product sintered and took on a wet appearance at 120–125°, and melted with slight gas evolution at 134–136°; $[\alpha]_D^{22} -27.1^\circ$, -26.7° : $c = 2.472$, 2.472 (abs. alcohol), $l = 2, 1$; $\alpha = -1.34^\circ$, -0.66° (Cahn, m. p. 134–135°; Knorr, $[\alpha]_D^{15} -24^\circ$).

Anal. Calcd. for $C_{18}H_{23}O_2N + \frac{1}{2} H_2O$: C, 73.43; H, 8.21. Found: C, 73.73, 73.79, 73.67; H, 8.24, 8.31, 8.16.

Attempts to determine the hydrate water failed because of the ease with which the base distills. At 70° in vacuum it slowly sinters together and melts to a colorless liquid, losing its hydrate water but also distilling to a slight extent. The anhydrous glassy solid crystallizes from dry petroleum ether in white granular crystals of unsharp m. p. 76–82°; on exposure to the air, the crystals change in form, and the melting point rises rapidly (after twenty minutes, m. p. 117–118°) until after several hours only the leaflets showing the normal melting point of the hydrated base are present. The base distills readily at 160–170° (1 mm.) as a colorless liquid, solidifying to a glass.

Anal. Calcd. for $C_{18}H_{23}O_2N$: C, 75.74; H, 8.12. Found: C, 75.84; H, 8.22.

(2) Dihydrodesoxycodine-A from reduction of desoxycodine-A: 5.5 g. of desoxycodine-A of m. p. 122–124° was dissolved in 200 cc. of boiling alcohol and reduced with 30 g. of sodium, with addition of 200 cc. more of alcohol as necessary; the product was isolated and purified as in the case of the α -chlorocodide reduction above; 6.1 g. (86% of the calculated yield) of crude dihydrodesoxycodine-A hydrochloride (m. p. 148–150°) was obtained, which melted with decomposition at 158° after three crystallizations from absolute alcohol.

Anal. Calcd. for $C_{18}H_{23}O_2N \cdot HCl + C_2H_5OH$: C, 65.28; H, 8.22. Found: C 65.10; H, 8.05.

The base precipitated from this hydrochloride and purified from dilute methyl alcohol and acetone sintered at 123–127° and melted at 133–135°; it did not depress the melting point of the product obtained by reduction of α -chlorocodide above. It gave $[\alpha]_D^{22} -24.4^\circ$: $c = 4.068$ (alcohol), $l = 2$, $\alpha = -1.99^\circ$.

(3) Dihydrodesoxycodine-A from reduction of desoxycodine-B (m. p. 119–120°): 5 g. of carefully purified desoxycodine-B²⁷ was reduced in alcoholic solution with five

²⁷ The first time this experiment was carried out using slightly impure desoxycodine-B, a reduction product of m. p. 126–128° having $[\alpha]_D 0^\circ$ was obtained which was regarded as a new dihydrodesoxycodine. In the light of our theoretical conclusions, the existence of a fifth phenolic dihydrodesoxycodine seemed very improbable, and

times its weight of sodium; 4.3 g. of a base of m. p. 120–126° was obtained, which was purified through the hydrochloride until the melting point of the latter was constant at 158–159°. This hydrochloride showed $[\alpha]_D^{21} - 39.9^\circ$; $c = 2.003$ (water), $l = 1$, $\alpha = -0.80^\circ$. The base precipitated from an aqueous solution of the salt by ammonia melted at 128–129°, $[\alpha]_D^{21} - 22.6^\circ$; $c = 2.834$ (alcohol), $l = 2$, $\alpha = -1.28^\circ$. These values approach closely our constants for the purest samples of dihydrodesoxycodine-A and its hydrochloride. Mixed melting points showed no depression.

Anal. Calcd. for $C_{18}H_{25}O_2N \cdot HCl + C_2H_5OH$: C, 65.28; H, 8.22; Cl, 9.64. Found: C, 65.34; H, 8.09; Cl, 9.57.

(4) Dihydrodesoxycodine-A from electrolytic reduction of desoxycodine-A (compare § 4, page 2229): 5.5 g. of desoxycodine-A (m. p. 121–122°, $[\alpha]_D^{22} + 115.9^\circ$) in 200 cc. of 20% sulfuric acid was reduced electrolytically for nine hours, using a prepared electrode of 60 sq. cm. and a current of 8 amp. The product, worked up as described in our other electrolytic reductions, was obviously a mixture; conversion to the hydrochloride and three crystallizations from absolute alcohol gave a salt of m. p. 155–157°, $[\alpha]_D^{19} + 34.6^\circ$, which yielded a base of m. p. 124–128°, $[\alpha]_D^{19} + 41.3^\circ$. By laborious fractional crystallization of the hydrochloride it could be shown that the dextrorotation was due to the presence of a large amount of unchanged desoxycodine-A (3.3 g., m. p. 121–122°, $[\alpha]_D^{21} + 110^\circ$). The levorotatory fractions finally yielded a base of m. p. 126–129°, $[\alpha]_D^{22} - 18^\circ$; $c = 1.984$ (alcohol), $l = 2$, $\alpha = -0.71^\circ$, whose hydrochloride melted at 155–157°, $[\alpha]_D^{20} - 38.5^\circ$; $c = 1.011$ (water), $l = 2$, $\alpha = -0.78^\circ$.

Anal. Calcd. for $C_{18}H_{25}O_2N \cdot HCl + C_2H_5OH$: C, 65.28; H, 8.22. Found: C, 65.36; H, 8.03.

On the basis of the rotations given above (mixed melting points have no significance) we are convinced that this product is identical with dihydrodesoxycodine-A, but do not consider the point conclusively proved.

Catalytic Reduction of Dihydrodesoxycodine-A.—Three grams of pure dihydrodesoxycodine-A (the so-called α -tetrahydrodesoxycodine), prepared by sodium and alcohol reduction of α -chlorocodine, was dissolved in 30 cc. of methanol and shaken under hydrogen in the presence of 0.10 g. of platinum oxide. The absorption proceeded rapidly, and in eighteen minutes 265 cc. of hydrogen was taken up (calculated for one mole of hydrogen, 257 cc.). The reduction proceeded very slowly for one hour longer, with an absorption of 35 cc. more, and then stopped completely. The reduction mixture was filtered, brought to the boiling point, and water added slowly; 2.85 g. of crystalline material separated; after one crystallization from acetone it softened at 135°, melted at 143–146°, and evolved gas at 151°. It did not depress the melting point of (β -)tetrahydrodesoxycodine. The product was further identified by its rotation, $[\alpha]_D^{19} - 32.9^\circ$ ($c = 1.564$ (alcohol), $l = 2$, $\alpha = -1.03^\circ$), the melting point of its hydriodide, 243–245°, of its methiodide, 263°, and mixed melting points of these derivatives.

Anal. Calcd. for $C_{18}H_{25}O_2N + \frac{1}{2}H_2O$: C, 72.92; H, 8.84. Found: C, 72.85; H, 8.81.

The reduction product sublimed with loss of its hydrate water to give the anhydrous tetrahydrodesoxycodine of sharp m. p. 125–126° which will be further described in our next paper.

Catalytic Reduction of Dihydrodesoxycodine-A Hydrochloride.—2.7 g. of pure hydrochloride (from sodium-alcohol reduction of desoxycodine-A) in 35 cc. of water with 0.4 g. of palladium on barium sulfate took up 190 cc. of hydrogen in thirty-five

investigation showed that the base of $[\alpha]_D 0^\circ$ showed a levorotation on laborious purification. The dextrorotatory persistent impurities do not appear when the desoxycodine-B employed is purified to constant rotation.

minutes and stopped (calculated for one mole of hydrogen, 188 cc.); 2.5 g. of tetrahydrodesoxycodeine was obtained, which was purified as above described, melted at 143–145°, and had $[\alpha]_D^{21} -31.8^\circ$ ($c = 1.510$ (alcohol), $l = 1$, $\alpha = -0.48^\circ$). In a similar reduction, 1.0 g. of dihydrodesoxycodeine-A hydrochloride prepared by sodium and alcohol reduction of desoxycodeine-B took up 85 cc. of hydrogen in thirty minutes (calculated for one mole, 80 cc.). The product was tetrahydrodesoxycodeine, m. p. 144–145°.

Dihydrodesoxycodeine-B (m. p. 128–131°).—Three grams of desoxycodeine-C (non-phenolic, m. p. 105–106°) in 100 cc. of 20% sulfuric acid was reduced electrolytically, using an electrode of 60 sq. cm. area and a current of 8.2 amp. The reduction was carried out at 5 to 10°, and continued until a test portion was completely soluble in an excess of alkali, usually requiring three to four hours. The acid solution was filtered and treated with a slight excess of ammonia; a red oil separated, which soon solidified and could be collected on a filter. It was dissolved in 20 cc. of boiling alcohol, and water added dropwise until crystallization began. The yield was 2.4 g. of dihydrodesoxycodeine-B, melting at 117–120°. It was converted to the hydriodide, this salt recrystallized from water to constant melting point, and the free base liberated from the hydriodide, then crystallized several times from dilute alcohol. It separated in white flakes of m. p. 128–131°, and showed the rotation $[\alpha]_D^{20} -106.9^\circ$ ($c = 1.038$ (96% alcohol), $l = 1$, $\alpha = -1.11^\circ$), $[\alpha]_D^{20} -69.1^\circ$ ($c = 0.680$ (10% acetic acid), $l = 1$, $\alpha = -0.47^\circ$). Dihydrodesoxycodeine-B is very soluble in most organic media and soluble in alkali.

Anal. Calcd. for $C_{18}H_{23}O_2N + \frac{1}{2}H_2O$: C, 73.43; H, 8.21. Found: C, 73.58; H, 8.19.

Reduction of Dihydrodesoxycodeine-B.—1.1 g. of the base was dissolved in 6 cc. of normal hydrochloric acid, the solution made up to 30 cc. with water, and shaken under hydrogen, using 0.3 g. of palladium-barium sulfate catalyst. In thirty-five minutes 103 cc. of hydrogen was absorbed (calcd. for 1 mole, 95 cc.). It yielded 1.0 g. of product melting at 140–145°, which after purification proved to be identical with tetrahydrodesoxycodeine in every respect, and gave a hydriodide of m. p. 245° and a methiodide of m. p. 265°.

Dihydrodesoxycodeine-C (m. p. 111°).—The starting material for the preparation of this base was chlorodihydrocodide. For the reduction of codeine, platinum oxide was found to be an excellent catalyst; 60 g. of codeine with 0.7 g. of platinum oxide took up 4750 cc. of hydrogen in sixty-five minutes, yielding 60 g. of dihydrocodeine, which was converted to chlorodihydrocodide (yields varying from 85 to 50%) by the method of Freund.⁶

A solution of 10 g. of chlorodihydrocodide in 300 cc. of 20% sulfuric acid was reduced electrolytically, using a current of 8 amp. and an electrode of 60 sq. cm. area, temperature maintained between 10 and 20°. For complete reduction, which was indicated by the alkali solubility of a small test portion, about eight hours was required. The acid reduction solution was filtered, brought to neutrality (litmus) with ammonia, and extracted with ether. The aqueous layer was acidified, and ammonia in excess added dropwise while shaking with ether. The combined ether extract was dried and distilled, yielding a reddish oil which was dissolved in hot alcohol and thrown out crystalline by slow addition of water; m. p. crude, 114–117°. The base was crystallized from dilute alcohol to constant m. p., 109–111°, yield 6 g.; 2.5 g. of tar-like residues was obtained: $[\alpha]_D^{24} -61.6^\circ$ ($c = 1.591$ (96% alcohol), $l = 1$, $\alpha = -0.98^\circ$).

Anal. Calcd. for $C_{18}H_{23}O_2N + \frac{1}{2}H_2O$: C, 73.43; H, 8.21. Found: C, 73.30; H, 8.17.

Reduction of Dihydrodesoxycodeine-C.—A solution of 1 g. of the base in 30 cc. of methyl alcohol was hydrogenated in the presence of 0.05 g. of platinum oxide. In

seventeen minutes 80 cc. of hydrogen was absorbed (calcd. for one mole, 85 cc.). The product of the reduction was identified as " β "-tetrahydrodesoxycodeine by its melting point, 142–144°, its hydriodide of m. p. 245°, and its methiodide, m. p. 260°, none of which showed any depression of melting point with the corresponding " β "-tetrahydrodesoxycodeine derivatives. The reduction product showed the rotation $[\alpha]_D^{18} -33.1^\circ$ ($c = 1.544$ (alcohol), $l = 1$, $\alpha = -0.51^\circ$).

Dihydrodesoxycodeine-D (m. p. 107°).—Five grams of β -chlorococide in 100 cc. of 0.3 *N* hydrochloric acid was hydrogenated in the presence of 1.25 g. of palladium-barium sulfate catalyst.²⁸ The reduction was complete in two hours, with the absorption of 870 to 920 cc. of hydrogen (calcd. for two moles, 800 cc.). The excess absorption of 10 to 15% above the expected amount is accounted for by the formation of small amounts of tetrahydrodesoxycodeine. The reaction mixture was filtered, the mixed bases precipitated by a slight excess of ammonia, and extracted into ether. The residue from distillation of the ether was dissolved in 30 cc. of water containing approximately the amount of tartaric acid necessary for the formation of the acid tartrate, and cooled to 0°. After several hours the acid tartrate of dihydrodesoxycodeine-D separated nearly quantitatively as beautiful white needles, while the very soluble oily tartrate of tetrahydrodesoxycodeine remained in solution. The crystalline acid tartrate was further purified from hot water, and the base liberated from it with ammonia; yield, 3.5 to 4.0 g. It melts at 106–107°, and shows $[\alpha]_D^{20} -82.5^\circ$ ($c = 0.866$ (96% alcohol), $l = 2$, $\alpha = -1.43^\circ$), (Mannich, $[\alpha]_D^{18} -81.47^\circ$).

Anal. Calcd. for $C_{18}H_{23}O_2N$: C, 75.74; H, 8.12. Found: C, 75.53; H, 8.22.

The method of preparation, melting point, rotatory power and analysis of dihydrodesoxycodeine-D show its identity with the dehydroxydihydrocodeine of Mannich.¹⁸ The method of separation from tetrahydrodesoxycodeine given above is more effective than that described by Mannich. The tetrahydrodesoxycodeine was isolated from the mother liquors of the tartaric acid treatment by addition of excess ammonia, and purification of the crystalline precipitate from acetone; m. p. 143–145°, $[\alpha]_D^{25} -32.1^\circ$ ($c = 1.712$ (alcohol), $l = 1$, $\alpha = -0.55^\circ$).

Reduction of Dihydrodesoxycodeine-D.—Two grams of the base in 100 cc. of methyl alcohol was reduced with 12.5 g. of sodium, 100 cc. more of methyl alcohol being added during the reduction. The dark mixture was diluted with 150 cc. of water, acidified with hydrochloric acid, and a small amount of tarry material filtered out. The reduction product was isolated by precipitation with ammonia and extraction with ether, and after purification from acetone showed the m. p. 142–145° and did not depress the melting point of tetrahydrodesoxycodeine. The hydriodide melted at 243°, the methiodide at 260–263° and gave no depression with the same derivatives of known tetrahydrodesoxycodeine.

Reduction of 2.0 g. of dihydrodesoxycodeine-D in 250 cc. of 20% sulfuric acid with a current of 6 amp. on a 60 sq. cm. electrode for four hours gave a quantitative yield of tetrahydrodesoxycodeine, m. p. 144–145° (mixed m. p. 144–145°).

Dihydrodesoxycodeine-D was regained unchanged from attempted hydrogenation with platinum oxide in methyl alcohol or methyl alcohol-acetic acid, or palladium barium sulfate in dilute hydrochloric acid.

Dihydrodesoxycodeine-E (m. p. 139°).—This was prepared by electrolytic reduction of bromococineone as described by Speyer²⁶ and was found to have the properties given by this author; 1.1 g. of the base in 30 cc. of 0.2 *N* hydrochloric acid with 0.3 g. of palladium barium sulfate took up 100 cc. of hydrogen (1 mol = 95 cc.) in thirty

²⁸ Houben, "Methoden der organ. Chem.," 1925, Vol. II, p. 500; Schmidt, *Ber.*, 52, 409 (1919).

minutes. The product, isolated in the usual way showed the m. p. 143-145°, $[\alpha]_D^{19}$ -32.6° ($c = 2.178$ (alcohol), $l = 1$, $\alpha = -0.71^\circ$), and was undoubtedly tetrahydrodesoxycodeine.

The salts and alkyl halides of the dihydrodesoxycodeines described above are listed in the following table.

DERIVATIVES OF THE DIHYDRODESOXYCODEINES							
Substance	M. p., °C.	$[\alpha]_D$	c	l , °C.	Formula	Calcd.	Found
A Methiodide ^a	Brown 245, m. 250-251	-7.5°, water,	2.27,	20	C ₁₉ H ₂₃ O ₂ Ni	C, 53.37 H, 6.13	C, 53.70 H, 6.27
B Hydrochloride ^b	154-156 (dec.)	-76.4°, water,	1.256,		C ₁₉ H ₂₃ O ₂ N·HCl	Cl, 11.03	Cl, 11.19 ^e
B Hydriodide ^d	Sint. 244-246, m. 255-256	-79.3°, 96% alc., 1.147, 19			C ₁₉ H ₂₃ O ₂ N·HI	I, 30.72	I, 30.87
B Methiodide ^e	About 175				C ₁₉ H ₂₃ O ₂ Ni	I, 29.71	I, 29.79
C Hydrochloride ^f	Sint. 157-163, m. 241-242	-3.6°, water,	2.345,	20	C ₁₉ H ₂₃ O ₂ N·HCl	Cl, 11.03	Cl, 10.97
C Hydriodide ^g	242-243	+52°, +51.6°, water, 0.980, 1.666, 22			C ₁₉ H ₂₃ O ₂ N·HI	I, 30.72	I, 30.66
C Methiodide ^h	245-246	+15.4°, 96% alc., 1.298, 21.5			C ₁₉ H ₂₃ O ₂ Ni	I, 29.71	I, 30.19
D Acid tartrate ⁱ	123-125	-39.6°, water,	1.793,	30	C ₁₉ H ₂₃ O ₂ N·C ₄ H ₄ O ₆	C, 60.65 H, 6.71	C, 60.50 H, 6.87
D Hydriodide ^j	250-251 (dec.)				C ₁₉ H ₂₃ O ₂ N·HI	I, 30.72	I, 30.88
D Methiodide	256						

^a Precipitated from methanol solution with absolute ether, purified from water, white crystals. The methiodide degrades to a crystalline methine base which will be described in a later paper. ^b Precipitated as white crystals by addition of alcoholic hydrogen chloride to a hot absolute alcohol solution of the base. ^c Subst. dried in vacuum at 100°. ^d Purified from water, long white needles. ^e Cryst. from water, white needles. ^f Base in hot absolute alcohol with alcoholic hydrogen chloride; white crystals from absolute alcohol. ^g Purified from water, white prisms. ^h Excess methyl iodide boiled out of methanol solution, this diluted with an equal volume of water, and methanol distilled off; white needles separated on cooling. ⁱ 7.0 g. of base in 50 cc. of hot water with 4.0 g. of *d*-tartaric acid; recrystallized from water; soluble 4.5 g. in 100 cc. of water at 28°. ^j Crystallized from water in long yellow needles. The corresponding hydrochloride could not be obtained crystalline.

Summary

1. An exhaustive investigation of the dihydrodesoxycodeines has resulted in the preparation of certain new dihydrodesoxycodeines, and in a clarification of the confused and incorrect statements in the literature. The compound resulting from reduction of α -chlorocodide or of desoxycodeine-A with sodium and alcohol is shown to be a dihydrodesoxycodeine, and not a tetrahydrodesoxycodeine as heretofore believed. The important supposed isomerism of α -tetrahydrodesoxycodeine and β -tetrahydrodesoxycodeine which has exerted a strong influence on theories of morphine structure does not exist. The significance of this fact for other cases of isomerism believed to be of the same type, is pointed out.

2. The derivation of dihydrodesoxycodeine-A from desoxycodeine-B (formerly thought to be a dihydrodesoxycodeine) is demonstrated.

3. Dihydrodesoxycodeine-B, the electrolytic reduction product from

desoxycodeine-C, is described, and its relationship to tetrahydrodesoxycodeine shown.

4. Dihydrodesoxycodeine-C, from electrolytic reduction of chlorodihydrocodide, is correctly described, and its relationship to tetrahydrodesoxycodeine shown.

5. The preparation of dihydrodesoxycodeine-D by catalytic reduction of β -chlorocodide is described, its relationship to the non-phenolic desoxycodeine-C pointed out, and its further reduction to tetrahydrodesoxycodeine accomplished.

6. The existence of dihydrodesoxycodeine-E is verified.

7. There is no evidence in the desoxycodeine series justifying the assumption of stereoisomerism due to spatial relationships on C-14. Until the existence of such an isomerism in the desoxycodeine or other series of morphine derivatives is demonstrated, it is improbable that more than six desoxycodeines can exist (three of which are known), and five dihydrodesoxycodeines, all of which have been described.

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CONDENSATIONS BY SODIUM INSTEAD OF BY THE GRIGNARD REACTION. I. TERTIARY CARBINOLS

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Sodium and magnesium show many similar properties in organic reactions, for example, in the Wurtz-Fittig synthesis, in the formation of pinacones, and in the condensation of acetylene derivatives. Many investigators¹ have observed the behavior of metal alkyls and aryls which may be likened to that of the Grignard reagent. The literature² also indicates that sodium may be used in mixtures of the halide and carbonyl compounds³

¹ Among others see Frankland, *J. Chem. Soc.*, **13**, 191 (1830); Acree, *Am. Chem. J.*, **29**, 588 (1903); Schorigin, *Ber.*, **41**, 2711 (1908); *ibid.*, **43**, 1938 (1910); Schlenk and Ochs, *ibid.*, **49**, 608 (1916); Schlenk and Holtz, *ibid.*, **50**, 262 (1917); Schlubach, *ibid.*, **52**, 1910 (1919); Ziegler and Schnell, *Ann.*, **437**, 227 (1924); Ziegler and Colonius, *ibid.*, **479**, 135 (1930).

² For reactions run without isolation of an intermediate aryl and alkyl see (a) Kekulé, *Ann.*, **137**, 181 (1866); (b) Frey, *Ber.*, **28**, 2515 (1895); (c) Acree, *Am. Chem. J.*, **29**, 588 (1903); (d) Schorigin, *Ber.*, **40**, 3114 (1907); (e) Schorigin, *ibid.*, **41**, 2711 (1908); (f) Nagai, Ogata and Takata, *J. Pharm. Soc. Japan*, No. 407, 3; *Chem. Abstracts*, **10**, 1186 (1916); (g) Blicke, *THIS JOURNAL*, **46**, 2560 (1924); **47**, 229 (1925); (h) Rodd and Linch, *J. Chem. Soc.*, 2174 (1927).

³ Schorigin, *Ber.*, **40**, 3111 (1907), has definitely stated that the halogen alkyls react with esters or acid chlorides in the presence of sodium in a manner similar to the behavior of the Grignard compounds. His conclusion is based on a limited number of experiments which included bromides only, and the aromatic esters and acid chlorides.