

[CONTRIBUTION NO. 82 FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

## DESOXYCODEINE STUDIES. IV. TETRAHYDRODESOXYCODEINE<sup>1</sup>

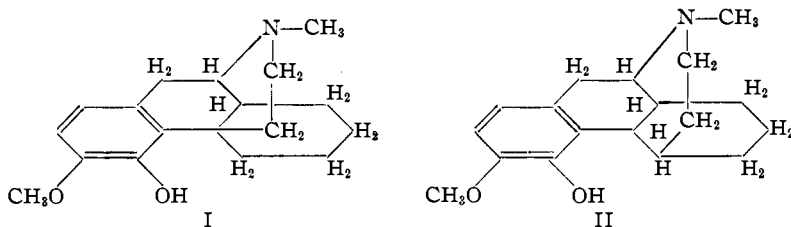
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It has been shown in the previous papers of this series<sup>2</sup> that the end-product of reduction of all the known desoxycodines (3) and dihydrodesoxycodines (5) is a hydrated base, having the empirical formula  $C_{18}H_{25}O_2N + \frac{1}{2} H_2O$ , tetrahydrodesoxycodine. The same compound may also be obtained directly from  $\alpha$ - or  $\beta$ -chlorocodide by catalytic reduction under special conditions.<sup>3</sup> The base formerly designated as  $\alpha$ -tetrahydrodesoxycodine and for many years believed to be an isomer of the tetrahydrodesoxycodine under consideration is actually a dihydrodesoxycodine, dihydrodesoxycodine-A.<sup>4</sup>

The generally accepted formulas for tetrahydrodesoxycodine (I or II) represent it as a phenolic compound. Its remarkable insolubility in alkali and its indifference toward acetylation or benzylation<sup>5</sup> and toward the usual methylating agents are difficult to bring into accord with such a structure.



Solid tetrahydrodesoxycodine dissolves in dilute or concentrated alkali to the extent of about one part in 100,000, which is of the same order as its solubility in water. The base is extracted from its ethereal solution by alkali only to about the same degree. This insolubility in alkali is more striking in view of the fact that tetrahydrodesoxycodine can be prepared from six different *alkali-soluble* desoxycodines and dihydrodesoxycodines by simple addition of hydrogen to a ring remotely removed from that which

<sup>1</sup> 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.

<sup>2</sup> Small and Cohen, *THIS JOURNAL*, **53**, 2214, 2227 (1931).

<sup>3</sup> Mosettig, Cohen and Small, *ibid.*, **54**, 793 (1932).

<sup>4</sup> In this connection we wish to mention the statement of Ochiai and Hakozaki, *J. Pharm. Soc. Japan*, **578**, 58, April (1930) (omitted from *Chem. Abstracts*, **24**, 3793 (1930)) to the same effect.

<sup>5</sup> (a) Freund, *J. prakt. Chem.*, **101**, 29 (1921); (b) Mannich and Löwenheim, *Arch. Pharm.*, **258**, 304 (1920).

carries the hydroxyl group. As other investigators have observed,<sup>6a,6</sup> it is possible to dissolve tetrahydrodesoxycodeine in alkali under special conditions. Whereas slow addition of alkali to a solution of the base in hydrochloric acid causes complete and permanent precipitation, if the alkali be added in 200% excess and all at once, only a momentary cloudiness appears at the isoelectric point, and a perfectly clear solution results. This is, however, unstable or supersaturated, and after several minutes tetrahydrodesoxycodeine base separates in sparkling hexagonal plates. The final alkaline solution has an alkaloidal content of but one part in 5000.

While tetrahydrodesoxycodeine does not behave normally toward alkali, we have nevertheless been able to demonstrate the presence of the phenolic hydroxyl by the preparation of a methyl ether. The base does not methylate with diazomethane nor with phenyltrimethylammonium hydroxide<sup>7</sup> but reacts with methyl iodide in the presence of alkali to give a methyl ether methiodide.<sup>8</sup> By conversion of the methyl ether methiodide to the methochloride and distillation in high vacuum, the methyl ether itself is obtained as a colorless oil, which may be crystallized as the hydriodide.

The half molecule of water of crystallization which is normally present in tetrahydrodesoxycodeine (and notably in all the other phenolic bases of the desoxycodeine series) is readily removed when the base is distilled or sublimed in high vacuum. Anhydrous tetrahydrodesoxycodeine melts sharply at 123–124°, and slowly changes over into a second anhydrous form of m. p. 157–158°. Both forms show the same optical rotation in anhydrous benzene, and both are converted back to the hitherto known hydrated form by recrystallization from dilute alcohol or acetone. The anhydrous and hydrated bases give the same methiodide and the same salts.

Tetrahydrodesoxycodeine degrades readily by the method of A. W. Hofmann, and we have thus been able to establish a connection between the desoxycodeine series and the desoxymethylmorphimethines. Des-N-methyltetrahydrodesoxycodeine (III)<sup>9</sup> is formed in good yield when tetrahydrodesoxycodeine methiodide is boiled with strong alkali. The unsaturation established in the 9,10-position through the breaking of the nitrogen ring is readily saturated by catalytic hydrogen, yielding dihydro-des-N-methyltetrahydrodesoxycodeine (IV) which is identical in properties with dihydrodesoxytetrahydromethylmorphimethine. The latter substance was prepared by Cahn<sup>10</sup> through catalytic reduction of desoxytetrahydro-

<sup>6</sup> Kondo, *Ber.*, **63**, 646 (1930).

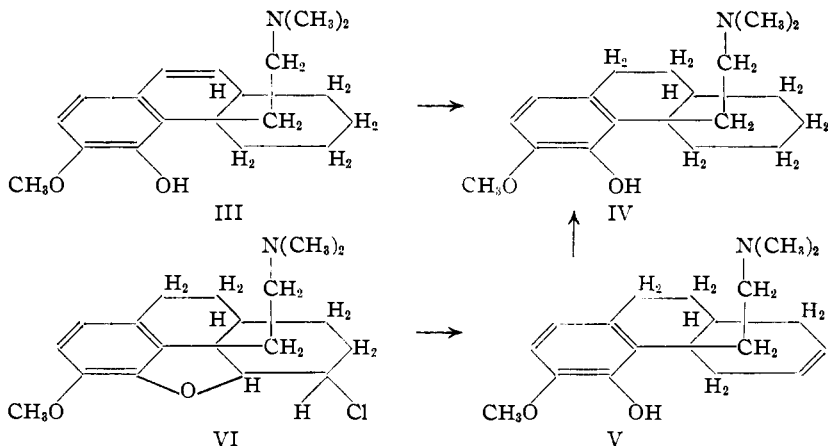
<sup>7</sup> Professor C. Schöpf, Darmstadt, states in a private communication that methylation of tetrahydrodesoxycodeine by the Rodionov method was successful.

<sup>8</sup> Freund, *J. prakt. Chem.*, **101**, 32 (1921).

<sup>9</sup> The optical antipode of this substance, des-N-methyl-desoxydemethoxydihydrosinomenine, derived from the sinomenine series, has already been described by Goto and Mitsui, *Bull. Chem. Soc. Japan*, **6**, 33 (1931).

<sup>10</sup> Cahn, *J. Chem. Soc.*, 2562 (1926).

methylmorphimethine (V), the product which results when tetrahydrochloromethylmorphimethine (VI) is reduced with sodium and alcohol.



An attempt to arrive at the same result by degradation of dihydrodesoxycodeine-A was only partly successful. Dihydrodesoxycodeine-A methiodide, on boiling with alkali, gave a crystalline methohydroxide which was unexpectedly resistant to degradation and was at first mistaken for the methine base.<sup>11</sup> When the methohydroxide was boiled for a long time with strong alkali, ring scission took place to some extent, although the des-N-methyl-dihydrodesoxycodeine-A could not be isolated from the tarry product. The total degradation mass, on catalytic hydrogenation, yielded small amounts of the above-described dihydro-des-N-methyltetrahydrodesoxycodeine.

The unexpected alkali-insolubility noted for tetrahydrodesoxycodeine persists in its degradation products. Des-N-methyltetrahydrodesoxycodeine is precipitated from a 1% solution in N hydrochloric acid by excess of N alkali, and does not redissolve. It is present in the filtrate to the extent of about one part in 10,000. In 0.1% solution the same phenomenon is observed as in the case of tetrahydrodesoxycodeine: a clear solution is obtained temporarily, from which fine needles separate in the course of five minutes. Dihydro-des-N-methyltetrahydrodesoxycodeine, when precipitated from dilute acid by excess of alkali, is soluble in alkali to about 1:5000, but a temporarily clear alkaline solution could not be obtained under any conditions.

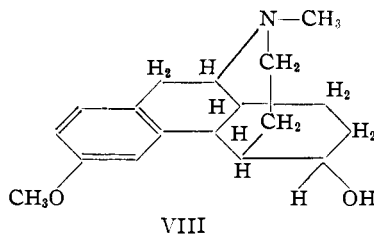
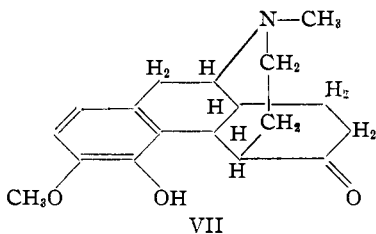
In 1920 Mannich<sup>12</sup> obtained by reduction of  $\beta$ -chlorocodide two alkali-insoluble bases, which he named dehydroxydihydrocodeine and dehydroxy-tetrahydrocodeine, respectively. The first of these we have already

<sup>11</sup> Small and Cohen, *THIS JOURNAL*, **53**, 2243 (1931).

<sup>12</sup> Mannich and Löwenheim, *Arch. Pharm*, **258**, 295 (1920).

described (dihydrodesoxycodeine-D), and have shown its relationship to other compounds in the desoxycodeine series.<sup>13</sup> The second, dehydroxy-tetrahydrocodeine, is identical with tetrahydrodesoxycodeine, a conclusion which was reached by Ochiai<sup>14</sup> while the present work was in progress. It is formed from  $\beta$ -chlorocodide by a mechanism different from that which results in dihydrodesoxycodeine-D, *i. e.*, it is not the product of further reduction of the latter, which is unaffected by catalytic reduction processes. The course which the reduction of  $\beta$ -chlorocodide takes is dependent in high degree upon the nature of the catalyst, as was demonstrated in the preceding paper of this series.

When the phenolic base dihydrothebainone (VII) is reduced electrolytically, a product is obtained which was named by its discoverers<sup>15</sup> dihydrothebacodine and was assigned formula VIII.



The base was insoluble in alkali and could not be methylated, and showed a great similarity to the Mannich dehydroxytetrahydrocodeine. The presence of an alcoholic hydroxyl group could be shown by reaction with phosphorus pentachloride, which resulted in the well-crystallized chlorodihydrothebacodide. In a repetition of the Speyer experiment, we have been able to obtain by electrolytic reduction of dihydrothebainone only tetrahydrodesoxycodeine, in quantitative yield. The properties of this and of its salts correspond in every way with the description given of dihydrothebacodine and its derivatives,<sup>16</sup> and the des-N-methyl base from it likewise has the same properties as Speyer's des-N-methyldihydrothebacodine.<sup>17</sup>

<sup>13</sup> Small and Cohen, *THIS JOURNAL*, **53**, 2235 (1931).

<sup>14</sup> Ochiai, *J. Pharm. Soc. Japan*, **568**, 91, June (1929); Kondo and Ochiai, *Ber.*, **63**, 646 (1930); experimental proof not given.

<sup>15</sup> Speyer and Siebert, *Ber.*, **54**, 1519 (1921); C-15 is linked to C-5 in the Speyer formulas in accord with the formula of Knorr and Hörlein for morphine.

<sup>16</sup> The discrepancy of 100° in the melting point of the hydriodides, probably due to a misprint, has already been noted by Kondo, *Ann.*, **470**, 224 (1929). Kondo and Ochiai [*Ber.*, **63**, 646 (1930); Ochiai, *J. Pharm. Soc. Japan*, **568**, 91, June (1929)] published the statement that the two bases are probably identical before the experiments here described were completed. In view of the convincing evidence advanced by Speyer for the presence of an alcoholic hydroxyl group in dihydrothebacodine, this identity seemed improbable, and our experiments were therefore continued to a conclusion.

<sup>17</sup> Goto and Mitsui, *Bull. Chem. Soc. Japan*, **6**, 33 (1931), attacking the problem of

The product which we obtain from the electrolytic reduction of dihydrothebainone, like known samples of tetrahydrodesoxycodeine, is practically indifferent toward phosphorus pentachloride. About 90% of the material was regained unchanged; the remaining 10% consisted of a halogen-free amorphous product, which was insoluble in practically all organic solvents and gave no crystalline salts. It did not resemble chlorodihydrothebaccodide in any way. In spite of the striking similarity in properties of dihydrothebacodine and tetrahydrodesoxycodeine and their derivatives, and of our failure to duplicate the Speyer and Siebert results, there can be no doubt that these investigators had in their hands a product which chlorinated smoothly and hence must have been different from tetrahydrodesoxycodeine. Until a direct comparison of the original Speyer dihydrothebacodine preparation with tetrahydrodesoxycodeine can be made, any decision concerning the identity of the two must be reserved.

The pharmacological action of tetrahydrodesoxycodeine and of the other bases of the desoxycodeine series has been investigated at the Pharmacological Laboratory of the University of Michigan and will be described in publications from that Institute.

We wish to acknowledge our indebtedness to Merck and Co., Rahway, N. J., who generously supplied us with the thebaine used in this research.

### Experimental

**Tetrahydrodesoxycodeine.**—The appearance of tetrahydrodesoxycodeine as the end-product of reduction of ten different bases was demonstrated in the second paper of this series.<sup>18</sup> Its formation through Clemmensen reduction of dihydrocodeinone<sup>19</sup> or of dihydrothebainone<sup>20</sup> should also be noted. The hydrated form which is always obtained when the base is crystallized from the ordinary organic solvents does not have a sharp melting point, but sinters down and becomes liquid between 141 and 147°, depending upon the rate of heating. Exhaustive fractional crystallization does not change the melting point or rotation. The anhydrous base which is first obtained by vacuum sublimation of the hydrate melts at 123–124°, and after several months changes to the second anhydrous form melting at 157–158°. After the second form appeared, the lower melting form could no longer be obtained.

**Tetrahydrodesoxycodeine Hemihydrate.**—*Anal.* Calcd. for  $C_{19}H_{24}O_2N + \frac{1}{2}H_2O$ : C, 72.92; H, 8.84;  $H_2O$ , 3.02. Found: C, 72.85; H, 8.81;  $H_2O$ , 3.47, 3.08. In 95% alcohol,  $[\alpha]_D^{20} -32.4^\circ$ :  $c = 1.883$ ,  $l = 1$ ,  $\alpha = -0.61^\circ$ . In dry benzene,  $[\alpha]_D^{19} -66.0^\circ$ ,  $-67.8^\circ$ :  $c = 1.666$ ,  $1.834$ ,  $l = 1, 2$ ,  $\alpha = -1.10^\circ$ ,  $-2.49^\circ$ .

Freund describes tetrahydrodesoxycodeine as crystallizing from alcohol with one-half molecule of alcohol. We have analyzed numerous samples crystallized in this way, but have never found anything excepting the hemihydrate.

the identity of the two bases in question by way of the sinomenine series, found that the des-N-methyl base from desoxydemethoxydihydrosinomenine (*d*-tetrahydrodesoxycodeine) melts at the same point as that given for des-N-methyldihydrothebacodine.

<sup>18</sup> Small and Cohen, *THIS JOURNAL*, **53**, 2238 (1931), diagram.

<sup>19</sup> Mannich and Löwenheim, *Arch. Pharm.*, **258**, 299 (1920).

<sup>20</sup> Ochiai, *J. Pharm. Soc. Japan*, **568**, 91, June (1929); also private communication from Dr. R. S. Cahn.

**Tetrahydrodesoxycodeine**, anhydrous, m. p. 123–124°.—*Anal.* Calcd. for  $C_{18}H_{25}O_2N$ : C, 75.22; H, 8.76. Found: C, 75.16, 75.31; H, 8.89, 8.76. In dry benzene,  $[\alpha]_D^{18} -72.0^\circ$ ,  $-72.3^\circ$ :  $c = 1.826$ ,  $l = 2$ ,  $1$ ,  $\alpha = -2.63^\circ$ ,  $-1.32^\circ$ .

The base can be recrystallized from dry petroleum ether without change in m. p. or rotatory power.

**Tetrahydrodesoxycodeine**, anhydrous, m. p. 157–158°.—*Anal.* Calcd. for  $C_{18}H_{25}O_2N$ : C, 75.22; H, 8.76. Found: C, 75.14; H, 8.91. In dry benzene,  $[\alpha]_D^{20} -70.2^\circ$ :  $c = 1.930$ ,  $l = 2$ ,  $\alpha = -2.71^\circ$ . In 95% alcohol,  $[\alpha]_D^{24} -33.6^\circ$ :  $c = 1.874$ ,  $l = 1$ ,  $\alpha = -0.63^\circ$ .

The solubility of tetrahydrodesoxycodeine in water and in alkali was determined by a comparison of the precipitate formed by Mayer's reagent (potassium mercuric iodide) in acid solutions of known strength, with that produced in the test solution after filtering out excess base and acidifying. The base can be estimated easily down to dilutions of 1:100,000 by this method. The same procedure was used in determining the solubility of the degradation products of tetrahydrodesoxycodeine.

**Tetrahydrodesoxycodeine Derivatives.**—The derivatives listed below were analyzed by Freund. We have completed his description by determinations of the rotatory power: hydrochloride, large white prisms, m. p. 260–262°; in water,  $[\alpha]_D^{20} -23.5^\circ$ :  $c = 2.509$ ,  $l = 1$ ,  $\alpha = -0.59^\circ$ . Hydriodide, long yellow needles, m. p. 245–246° (decomp.); in 95% alcohol,  $[\alpha]_D^{19} -24.3^\circ$ :  $c = 2.360$ ,  $l = 2$ ,  $\alpha = -1.15^\circ$ . Methiodide, m. p. 260–263°; in water,  $[\alpha]_D^{26} -33.3^\circ$ :  $c = 1.800$ ,  $l = 1$ ,  $\alpha = -0.60^\circ$ .

**Tetrahydrodesoxycodeine Methyl Ether.**—Fifteen grams of tetrahydrodesoxycodeine in 70 cc. of methyl alcohol was treated with 1.85 g. of sodium in 30 cc. of methyl alcohol, and to the resulting deep purple solution 17.0 g. of methyl iodide was added with strong cooling. The mixture was warmed slowly, refluxed for an hour, and evaporated on the water-bath to 30 cc. On slow addition of ether to the cold solution, tetrahydrodesoxycodeine methyl ether methiodide separated crystalline. It was recrystallized four times from methyl alcohol–ether mixture, yield 14 g.; m. p. 256–257°;  $[\alpha]_D^{21} -3.54^\circ$ :  $c = 1.691$  (alcohol),  $l = 1$ ,  $\alpha = -0.06^\circ$ . The same compound was obtained by treatment of tetrahydrodesoxycodeine methyl ether (see below) with methyl iodide.

*Anal.* Calcd. for  $C_{20}H_{30}O_2NI$ : C, 54.15; H, 6.82; I, 28.64. Found: C, 54.23; H, 6.69; I, 28.39.

Twelve grams of tetrahydrodesoxycodeine methyl ether methiodide was dissolved in 400 cc. of water, and 6.8 g. of freshly precipitated silver chloride added at 70–80° with mechanical stirring. At the end of one hour at this temperature the reaction was finished, and the pale yellow solution obtained after filtering was evaporated to dryness in vacuum at 60°. The reddish gum so obtained was dissolved in 30 cc. of boiling acetone, filtered and concentrated to about 10 cc. After long standing in an ice-bath, the methochloride separated as a mass of fine white crystals, which were filtered off and washed with cold acetone. The yield was 7.1 g. of tetrahydrodesoxycodeine methyl ether methochloride, m. p. 255–256° (decomp.);  $[\alpha]_D^{22} -9.5^\circ$ :  $c = 2.63$  (water),  $l = 1$ ,  $\alpha = -0.25^\circ$ .

*Anal.* Calcd. for  $C_{20}H_{30}O_2NCl$ : C, 68.22; H, 8.59; Cl, 10.08. Found: C, 68.29; H, 8.55; Cl, 10.01.

Six grams of the methochloride was distilled at 0.4 mm. pressure in a Pyrex tube having two 3-cm. bulbs. The decomposition of the methochloride began at about 250° (air-bath temperature) and was quite vigorous. Tetrahydrodesoxycodeine methyl ether distilled as a red oil, considerable tarry material remaining in the distilling bulb. After distilling twice more in vacuum, the compound was obtained as a colorless oil of disagreeable odor, which could not be induced to crystallize. The hydriodide crystallized

well from water, but the free base liberated from the pure hydriodide as a colorless, odorless oil did not crystallize.

*Anal.* Calcd. for  $C_{19}H_{27}O_2N$ : C, 75.69; H, 9.04. Found: C, 75.58; H, 9.15.

Tetrahydrodesoxycodeine methyl ether united with methyl iodide to give the methiodide of m. p. 256–257° described above.

Tetrahydrodesoxycodeine methyl ether hydriodide crystallizes from water in light brownish yellow needles sintering at 97–100°, melting at 217–218°;  $[\alpha]_D^{21} -21.8^\circ$ ;  $c = 2.011$  (alcohol),  $l = 1$ ,  $\alpha = -0.44^\circ$ .

*Anal.* Calcd. for  $C_{19}H_{28}O_2NI + H_2O$ : C, 50.98; H, 6.76; I, 28.37;  $H_2O$ , 4.02. Found: C, 50.65, 50.65; H, 6.63, 6.74; I, 28.24;  $H_2O$ , 3.79.

**Des-N-methyltetrahydrodesoxycodeine.**—Tetrahydrodesoxycodeine methiodide (4.8 g.) was boiled with 50 cc. of 50% potassium hydroxide solution for fifteen minutes. The oily reaction product solidified to a black cake when the solution was cooled. The solid was dissolved in hot alcohol and filtered; slow addition of water to the hot filtrate precipitated the base as sparkling flaky crystals. It was recrystallized from dilute alcohol and showed m. p. 152–154°; yield, 3.36 g., 87% of the calcd. amount. In methyl alcohol,  $[\alpha]_D^{24} +66.2^\circ$ ;  $c = 2.478$ ,  $l = 1$ ,  $\alpha = +1.64^\circ$ . The value was not permanent, and the solution turned red on standing. In hydrochloric acid (neutral solution)  $[\alpha]_D^{20} +58.8^\circ$ ,  $+61.3^\circ$ ;  $c = 4.124$ ,  $l = 2$ ,  $1$ ,  $\alpha = +4.85^\circ$ ,  $+2.53^\circ$ .

*Anal.* Calcd. for  $C_{19}H_{27}O_2N$ : C, 75.69; H, 9.02. Found: C, 75.83; H, 9.02.

**Dihydro-des-N-methyltetrahydrodesoxycodeine.**—Two grams of des-N-methyltetrahydrodesoxycodeine dissolved in 6 cc. of *N* hydrochloric acid and 20 cc. of water was hydrogenated in the presence of 0.2 g. of palladium-barium sulfate. One mol of hydrogen (170 cc.) was absorbed in one hour. The reaction mixture, in which the hydrochloride of the new base had begun to crystallize, was heated to boiling and filtered. The hydrochloride crystallized as short white needles from the cold solution; a second crop of crystals was obtained by concentrating the filtrate; the yield was quantitative. The salt melts at 251–252°, and is only sparingly soluble in cold water. In 95% alcohol,  $[\alpha]_D^{26} -82.1^\circ$ ;  $c = 1.425$ ,  $l = 2$ ,  $1$ ,  $\alpha = -2.34^\circ$ .

*Anal.* (Subs. dried in vacuum at 135°) Calcd. for  $C_{19}H_{30}O_2NCl$ : Cl, 10.44. Found: Cl, 10.17.

The free base precipitated crystalline on addition of dilute ammonia to an aqueous solution of the hydrochloride. It was purified from dilute alcohol or acetone, and consisted of long white needles of m. p. 148–150°. In 95% alcohol,  $[\alpha]_D^{26} -14.5^\circ$ ;  $c = 1.720$ ,  $l = 1$ ,  $\alpha = -0.25^\circ$ .

*Anal.* Calcd. for  $C_{19}H_{29}O_2N$ : C, 75.20; H, 9.63. Found: C, 75.09; H, 9.75.

**Degradation of Dihydrodesoxycodeine-A.**—The methiodide of this base was boiled with 20 or 50% potassium hydroxide solution. According to the length of treatment the unchanged methiodide, the methohydroxide (crystalline, insoluble in ether or acetone but very soluble in water) or the des-N-methyl base was obtained. The extreme resistance of the methohydroxide to degradation is surprising. One hour's boiling with 50% potassium hydroxide was necessary to accomplish this, whereby much of the degradation product was destroyed. By hydrogenation of the tarry mass it was possible to isolate dihydro-des-N-methyltetrahydrodesoxycodeine because of its extraordinary tendency to crystallize. Des-N-methyldihydrodesoxycodeine-A itself could not be freed from the resinous by-products of the degradation.

**The So-called Dehydroxytetrahydrocodeine.**—The reduction of  $\beta$ -chlorocodide in the presence of palladium and the advantageous use of tartaric acid to separate the products was described in our second paper.<sup>21</sup> The tetrahydro product obtained did

<sup>21</sup> Small and Cohen, *THIS JOURNAL*, 53, 2242 (1931).

not depress the melting point of known samples of tetrahydrodesoxycodeine and yielded salts identical with those from this base. For the base we found  $[\alpha]_D^{23} -32.9^\circ$  (for tetrahydrodesoxycodeine,  $[\alpha]_D^{21} -32.1^\circ$ ); the hydriodide melted at 241–243°, the methiodide at 260–265° and did not depress the melting points of the corresponding tetrahydrodesoxycodeine derivatives.

**Electrolytic Reduction of Dihydrothebainone.**—Two and one-half grams of dihydrothebainone in 150 cc. of 20% sulfuric acid was reduced for four hours with 8.8 amp. on a 60 sq. cm. prepared lead electrode; the temperature was kept below 20°. At the end of the reaction the mixture was filtered, treated with an excess of ammonia, and the reddish solid crystallized to constant m. p. from acetone; the yield was practically quantitative. It melted at 144–145° (dihydrothebacodine, 149°) and showed the characteristic behavior of tetrahydrodesoxycodeine toward alkali. It did not depress the melting point of tetrahydrodesoxycodeine, and sublimed to give the anhydrous form of this base, m. p. 123–124°, which changed to the second form, m. p. 157–158°, in several months. These anhydrous forms likewise showed no m. p. depression with known samples. The hydrated form had the rotation  $[\alpha]_D^{23} -32.1^\circ$  in alcohol, and gave a hydriodide and methiodide which were compared directly with known samples.

One gram of the dihydrothebainone reduction product in 6 cc. of chloroform with 1.0 g. of phosphorus pentachloride was allowed to stand at room temperature for two hours and then heated to reflux for a further two hours. Traces of hydrogen chloride were evolved during the heating. The cooled mixture was poured into 200 cc. of ether and the viscous mass which formed was separated from the liquid and treated with sodium carbonate solution. A tarry product was obtained which could be separated into two fractions with alcohol. The alcohol solution yielded most of the starting material unchanged. The alcohol-insoluble part (0.1 g.), m. p. about 200°, was halogen-free and was practically insoluble in all available solvents excepting pyridine. It dissolved in acids with difficulty and was reprecipitated by alkali; it formed an amorphous hydriodide, m. p. about 280°, and an insoluble tarry methiodide. Nothing corresponding to chlorodihydrothebacodide could be obtained from the reaction. A known sample of tetrahydrodesoxycodeine behaved in the same way in a parallel experiment.

### Summary

1. Tetrahydrodesoxycodeine has been prepared in two crystalline anhydrous modifications. The alkali-insolubility of the base has been studied, and the presence of a phenolic hydroxyl group demonstrated by the preparation of a methyl ether.
2. Through degradation of tetrahydrodesoxycodeine and hydrogenation of the product, a connection between the desoxycodeine and the tetrahydromethylmorphimethine series has been established.
3. The identity of tetrahydrodesoxycodeine with dehydroxytetrahydrocodeine and with dihydrothebacodine is discussed.