

2. Each of these two latter compounds formed an individual series of derivatives—namely, the diacetoxyquinone, the dibutyroxyquinone, the diacetoxyhydroquinone, the tetrahydroxy compound, the tetraacetoxy and tetrabutyroxy compounds.

3. The two series were designated as α and β . The α denotation was given to the series of higher melting and less soluble compounds, the β was given to the series of lower melting and more soluble compounds. On the assumption that the higher melting tetrahydroxy and tetraacylated derivatives are the *trans* modifications, it follows that throughout the two series, the *trans* or α forms are meso, the *cis* or β forms are racemic.

4. The α and β tetrahydroxy, tetraacetoxy and tetrabutyroxy derivatives represent pairs of *cis* and *trans* isomers. No individual in any pair is capable of resolution. On the other hand, the α and β hydroxyquinones, acetoxyquinones, butyroxyquinones and the acylated hydroquinones represent pairs of *cis* and *trans* forms, in each pair of which one is a meso and the other a racemic modification.

5. The β -dihydroxyquinone, the β -diacetoxyquinone and the β -dibutyroxyquinone can be converted to the corresponding α forms by heating in a high boiling solvent. The β -diacetoxyquinone on hydrolysis gives the α -dihydroxyquinone.

6. The α and β tetraacetoxy compounds, on bromination, give the same compound, 2,5-di-(3,5-dibromo-2,4,6-trimethylphenyl)-1,3,4,6-tetraacetoxybenzene.

URBANA, ILLINOIS

[CONTRIBUTION NO. 73 FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

DESOXYCODEINE STUDIES. I. THE DESOXYCODEINES¹

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RECEIVED FEBRUARY 9, 1931

PUBLISHED JUNE 8, 1931

The name desoxycodeine has been used to designate the compound $C_{18}H_{21}O_2N$, containing one less oxygen atom than codeine. It was first described and investigated by Knorr and Waentig,^{2,3} who prepared it by refluxing α -chlorocodide (II), bromocodide, β -chlorocodide⁴ or pseudo-

¹ This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc.

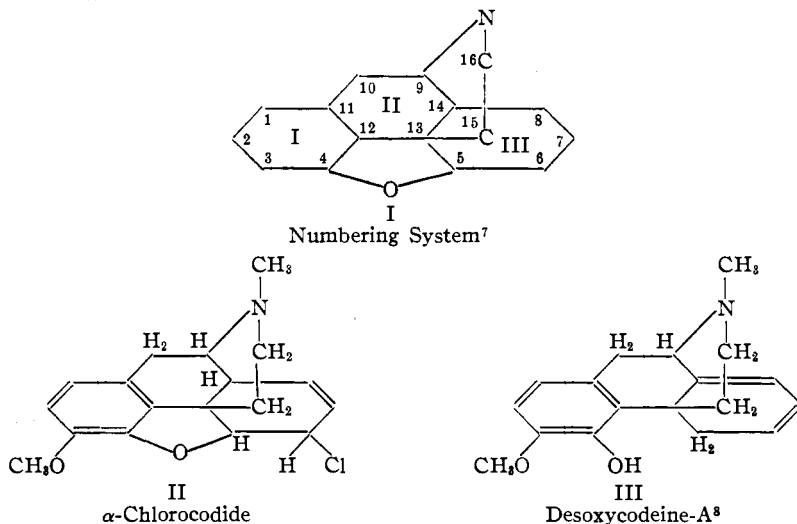
² Knorr and Waentig, *Ber.*, **40**, 3860 (1907).

³ A base having the same formula was mentioned by Wright [*Proc. Roy. Soc. (London)*, **19**, 371 (1870); *J. Chem. Soc.*, **24**, 404 (1871)] as being formed when codeine is heated with hydrobromic acid; Wright's desoxycodeine has never been further investigated.

⁴ Knorr and Hörlein, *Ber.*, **40**, 4883 (1907).

chlorocodide^{2,5} with zinc dust in absolute alcohol; the fact that the isomeric chlorocodides all yield the same desoxycodeine in this reduction has been taken as evidence that the fundamental carbon-nitrogen skeleton in all of them is the same.

Desoxycodeine is a phenolic base (Formula III) which must be formed from the halogenocodides by addition of one molecule of hydrogen and loss of hydrogen halide or the equivalent of this process.⁶



α -Chlorocodide is derived from codeine through replacement of the alcoholic hydroxyl by chlorine, and is distinguished by the activity of this halogen atom. It may be hydrolyzed out by boiling with water⁹ or with dilute acetic acid^{4,10} to yield the isomers of codeine, or replaced with iodine¹¹ or the dimethylamino group¹² by suitable treatment with potassium iodide or dimethylamine, respectively. An experiment seemed warranted, therefore, to determine whether α -chlorocodide would react with methylmagnesium halide to yield, at least in part, a homolog of desoxycodeine,

⁵ Knorr and Hörlein, *Ber.*, **40**, 3341 (1907).

⁶ Cf. Freund, *J. prakt. Chem.*, **101**, 8 (1921).

⁷ The linkage of C-15 to C-13, in accordance with the Gulland and Robinson [*Mem. Proc. Manchester Lit. Phil. Soc.*, **69**, 79 (1925)] conception of the morphine structural formula is here adopted for the sake of uniformity with contemporary publications in the field of morphine chemistry.

⁸ The position of the double bonds in ring III is arbitrary.

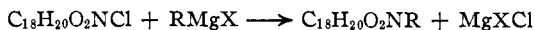
⁹ Matthiessen and Wright, *Ann. Suppl.*, **7**, 364 (1870); Göhlich, *Arch. Pharm.*, **231**, 235 (1893).

¹⁰ Knorr and Hörlein, *Ber.*, **39**, 4409 (1906); Pschorr and Rollet, *Ann.*, **373**, 1 (1910); Schryver and Lees, *J. Chem. Soc.*, **79**, 563 (1901).

¹¹ Knorr and Hartmann, *Ber.*, **45**, 1350 (1912).

¹² Von Braun and Kindler, *ibid.*, **49**, 2655 (1916).

in which the alcoholic hydroxyl of codeine would be replaced by a methyl group in the sense of the equation



α -Chlorocodide in absolute ethereal solution does, in fact, react vigorously with methylmagnesium iodide, with copious evolution of gas and separation of a powdery white solid. Decomposition of this solid in the usual way yields instead of the expected homodesoxycodine, the known desoxycodine in approximately 60% of the theoretical amount. The remaining 40% of the material consists of a clear basic oil which does not crystallize nor give crystalline salts.

When ethylmagnesium iodide is used, the same product, desoxycodine, is obtained in somewhat better yields; it is evident from this that the organomagnesium halide functions in this reaction chiefly to remove the elements of hydrochloric acid, and to open reductively the 4,5-ether bridge of α -chlorocodide. Small amounts of iodocodide could frequently be isolated among the reaction products; further investigation has shown that iodocodide reacts with alkylmagnesium halide in the same way as α -chlorocodide to give desoxycodine. It therefore seems probable to us that iodocodide, in which the halogen is very loosely bound, forms an intermediate in this reaction. As would be expected, in a reaction where methylmagnesium halide acts in a reducing capacity, considerable amounts of ethylene are present in the gases evolved in the reaction. β -Chlorocodide, an isomer of α -chlorocodide which is believed to differ from it only in the spatial arrangement of H- and Cl- on the asymmetric carbon atom in Position 6, does not react with alkylmagnesium halide. It is well known that the halogen in β -chlorocodide is far less active than that in α -chlorocodide;¹³ it was further found in the present investigation that in contrast to the α -form, β -chlorocodide does not react with potassium iodide in boiling alcohol to give an iodocodide.

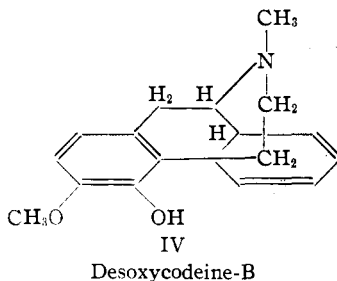
The iodocodide obtained as a by-product in the reaction of alkylmagnesium iodide with α -chlorocodide consisted of fine white needles, or clumps of thick white monoclinic prisms. The known iodocodide (from α -chlorocodide with potassium iodide)¹¹ is described as light orange needles, and it therefore seemed probable that our white iodocodide represented a stereoisomeric β -form, in analogy with α - and β -chlorocodide. This is, however, apparently not the case; careful comparison of physical and chemical properties of the bases and their salts indicates that they are identical. The orange color of the Knorr compound is due to traces of colored decomposition products formed through the use of higher boiling solvents.

¹³ Knorr and Hörlein, *Ber.*, **41**, 974 (1908) (hydrolysis); Knorr and Hörlein, *ibid.*, **40**, 4887 (1907) (reduction); Mannich and Löwenheim, *Arch. Pharm.*, **258**, 295 (1920) (reduction).

The desoxycodeine obtained from the Grignard reaction was identified by direct comparison with a sample prepared by refluxing α -chlorocodide with zinc dust in alcohol. With sodium and alcohol it reduced to the so-called α -tetrahydrodesoxycodeine,¹⁴ which was also identified by direct comparison. By hydrogen and platinum, it was converted to β -tetrahydrodesoxycodeine (VI). The reduction products from desoxycodeine as well as those derived from the two new desoxycodeines described in this paper will be discussed in the following communication.

The Knorr desoxycodeine, as depicted in Formula III, represents one of the two possible phenolic desoxycodeines, the second of which may be conceived as having the conjugated double linkages in the hydroaromatic ring arranged in the alternative Positions, 5,6 and 7,8 (Formula IV). We propose for the present to name the Knorr compound of m. p. 126° desoxycodeine-A, the phenolic isomer, desoxycodeine-B,¹⁵ and the non-phenolic desoxycodeine of the same empirical formula, to be described below, desoxycodeine-C.

Desoxycodeine-B, m. p. 119°, is formed when α -chlorocodide dissolved in 20% sulfuric acid is reduced electrolytically. Freund¹⁶ first carried out this experiment, which he believed led to the formation of a dihydrodesoxycodeine, $C_{18}H_{23}O_2N + \frac{1}{2}H_2O$ of m. p. 117–119°, which is obviously the same as the compound which we describe. He claimed that the same substance resulted from the electrolytic reduction of β -chlorocodide (a statement which we have verified), of chlorodihydrocodide, and of desoxycodeine-A. Freund's evidence for considering his base of m. p. 117–119° as a dihydrodesoxycodeine was as follows. (1) Analyses: only those made on the 117° base prepared from α - and β -chlorocodides need be considered. These are in fair agreement with the value calculated for a dihydrodesoxycodeine containing one-half molecule of water. The bases prepared by electrolytic reduction of desoxycodeine-A and of chlorodi-



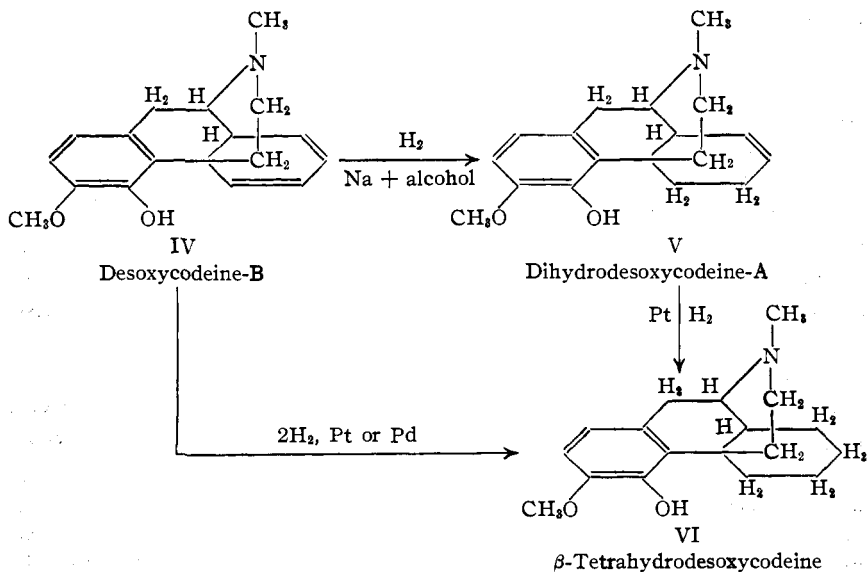
¹⁴ Knorr and Waentig² reduced desoxycodeine with sodium in boiling alcohol to what they believed to be a dihydrodesoxycodeine, $C_{18}H_{23}O_2N$, which could also be obtained directly from α -chlorocodide through reduction with the same agents. This was disputed by Freund, who claimed that the reduction product was formed by addition of four atoms of hydrogen to desoxycodeine, and named it α -tetrahydrodesoxycodeine, to distinguish it from the tetrahydrodesoxycodeine which he obtained by reduction of desoxycodeine with palladium and hydrogen, and which was named β -tetrahydrodesoxycodeine.

¹⁵ There is no evidence to show which of the Formulas III and IV should be assigned to desoxycodeine-A and which to desoxycodeine-B.

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

hydrocodide which were thought to be identical with the 117° base are actually two different dihydrodesoxycodeines, of m. p. 134 and 111°, respectively, as will be shown in the next paper. (2) Catalytic reduction: this was carried out on but 0.4 g. of material, the source of which is not given. We can explain the absorption of but one molecule of hydrogen as noted by Freund only by the assumption that the sample taken for reduction was prepared from desoxycodeine-A or chlorodihydrocodide.

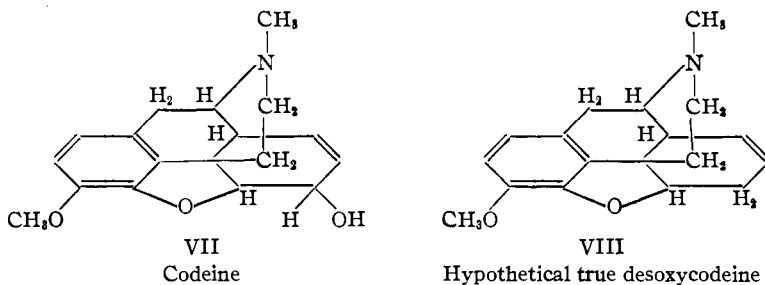
Since analytical proof of the presence of two hydrogen atoms more or less in a compound of molecular weight 292 is open to some question, we wish to stress the fact that our statement to the effect that the 119° base from electrolytic reduction of α - or β -chlorocodide is actually a desoxycodeine rests on reduction experiments. Desoxycodeine-B takes up two molecules of hydrogen on reduction by the catalytic method, using Adams' platinum oxide catalyst or palladium on barium sulfate, to give a quantitative yield of β -tetrahydrodesoxycodeine. When reduction of desoxycodeine-B is effected with sodium and alcohol, a dihydrodesoxycodeine is formed, which may be further reduced by the catalytic method, with absorption of but one molecule of hydrogen to β -tetrahydrodesoxycodeine (VI).



The results of reduction, therefore, show beyond question that the phenolic base of m. p. 119° which Freund thought to be a dihydrodesoxycodeine is unsaturated to a degree corresponding to the presence of two double linkages, and is isomeric with desoxycodeine-A. It seems quite certain that the isomerism of these two phenolic desoxycodeines is due only

to a difference in the arrangement of the unsaturated linkages in the hydroaromatic ring; on addition of two or four hydrogen atoms, the isomerism disappears.

The name desoxycodeine, which was introduced by Knorr, was somewhat unfortunately chosen. While the phenolic bases III and IV described above have the empirical formula $C_{18}H_{21}O_2N$ of codeine minus one oxygen, they correspond structurally to codeine less HOH, plus 2H. The name desoxycodeine should logically be applied to a compound derived from codeine (VII) through replacement of the alcoholic hydroxyl group by hydrogen (VIII) without scission of the 4,5-ether linkage.¹⁷



We have been successful in preparing a compound of this nature, in whose structure, if the Gulland-Robinson formula (VII) for codeine be accepted, the only uncertain point is the position which the double linkage occupies in the hydroaromatic ring III. On the grounds given below, we consider it probable that the double bond lies between C-6 and C-7 (IX).

Desoxycodeine-C (IX) is prepared by treatment of chlorodihydrocodide in absolute methyl alcoholic solution with sodium methylate for twenty-four hours at 140°. Knoll and Co.,¹⁸ heating chlorodihydrocodide with sodium methylate in methyl alcohol at 140° for forty-eight hours,¹⁹ obtained a product of m. p. 111° which was called dihydrodesoxycodeine, and which is apparently identical with our desoxycodeine-C (whose melting point we have not been able to bring above 106°). The method of preparation of the two compounds is the same; the shorter period of heating was adopted by us because it resulted in better yields. The hydrochloride of desoxycodeine-C melts at the point given by Knoll and Co. for their dihydrodesoxycodeine hydrochloride (114°); the methiodide, on the other hand, we find to melt at 236-240°, in comparison with Knoll's 135-136°; we are forced to believe that this discrepancy in melting point of the methiodide arises from a misprint in Knoll and Co.'s patent. It is difficult

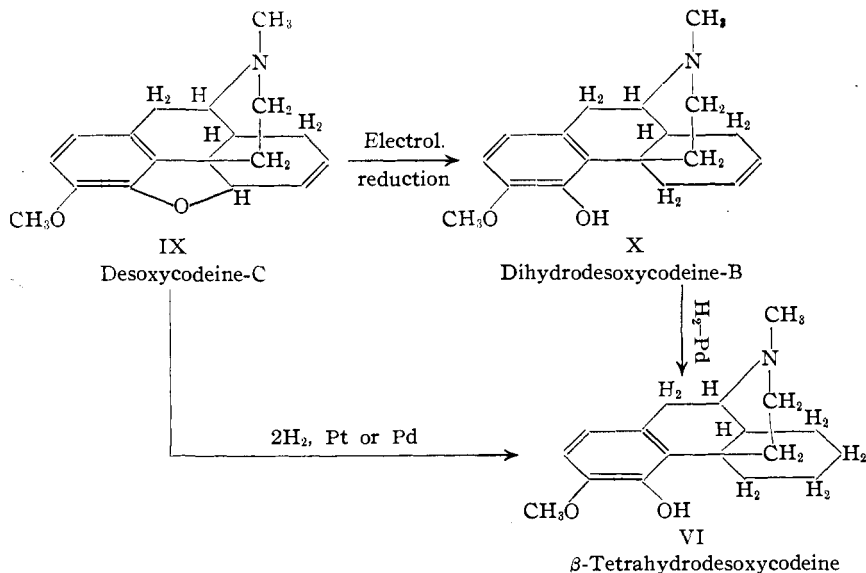
¹⁷ Cf. Freund, *J. prakt. Chem.*, **101**, 7 (1921).

¹⁸ Knoll and Co., German Patent 414,598 (1922); *Friedländer*, **15**, 1518; *Jahresb. Chem. Tech.*, **71**, 123 (1925).

¹⁹ Mannich and Löwenheim [*Arch. Pharm.*, **258**, 295 (1920)] state that chlorodihydrocodide with sodium methylate at 120° forms no sodium chloride.

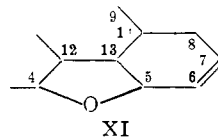
to explain, in any case, the formation of a dihydrodesoxycodeine, $C_{18}H_{23}-O_2N$, as claimed by Knoll from chlorodihydrocodide, $C_{18}H_{22}O_2NCl$, through the agency of sodium methylate, since such a transformation involves reduction, *i. e.*, loss of HCl and addition of $2H$, or direct replacement of Cl by H. The chemical behavior and analyses of desoxycodeine-C and its derivatives, on the other hand, show it to have been formed by loss of hydrochloric acid from chlorodihydrocodide.

Desoxycodeine-C (m. p. $105-106^\circ$) is not phenolic in nature. It is insoluble in alkali, and does not yield a methyl ether or acetyl derivative. In the presence of a palladium or platinum catalyst, it takes up two molecules of hydrogen, yielding β -tetrahydrodesoxycodeine (VI). By the electrolytic method, on the other hand, desoxycodeine-C is reduced to a new phenolic dihydrodesoxycodeine (X) of m. p. 128° , containing two more hydrogen atoms than desoxycodeine-C. This phenolic dihydrodesoxycodeine, on catalytic hydrogenation (palladium-barium sulfate catalyst), takes up one molecule of hydrogen to give β -tetrahydrodesoxycodeine. This may be represented by the following formulas, in which, however, we wish to make no claim concerning the exact location of the unsaturation in the hydroaromatic ring of desoxycodeine-C and its dihydro derivative.



The structure which we assign to desoxycodeine-C is based primarily upon its relationship to β -tetrahydrodesoxycodeine, and is put forward tentatively on the assumption that the latter substance actually possesses the generally accepted Formula VI. The fact that desoxycodeine-C cannot be reduced catalytically with saturation of the double bond only, to give a

non-phenolic dihydrodesoxycodeine, recalls the similar behavior of other compounds in the codeine series. While codeine and isocodeine, and the methylmorphimethines, α -, β -, γ - and δ -, can be reduced by simple saturation of the double linkages present, yielding non-phenolic hydrogenation products, pseudocodeine and allopseudocodeine, as well as ϵ - and ζ -methylmorphimethines take up two more hydrogen atoms than the corresponding isomeric substances mentioned above, to give phenolic hydrogenated derivatives. As Schöpf²⁰ has pointed out, the behavior of the grouping $-\text{O}-\text{CH}-\text{CH}=\text{CH}-$, generally accepted as being present in pseudo-, allopseudo-codeine, and ϵ - and ζ -methylmorphimethines, is to a certain degree comparable with that of a conjugated system of double linkages $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, and the fact that hydrogenation of the substances mentioned takes place always with opening of the ether ring may be explained through the assumption that a 1,4-addition of hydrogen (at $-\text{O}-$ and C-7) first takes place, followed by a saturation of the double linkage 5,6 in the intermediately formed compound. It is therefore not unreasonable to assume that in desoxycodeine-C the arrangement in the hydroaromatic ring corresponds to that shown in XI.



There are at present three isomeric desoxycodeines known, two of which, desoxycodeine-A and desoxycodeine-B, are phenolic in nature. As will be shown in the next paper, the evidence which primarily led to the belief in an isomerism in the morphine series due to spatial differences in the hydrogen atom on C-14 is invalid. If this questionable configurational isomerism be disregarded, there are possible four non-phenolic desoxycodeines (isomerism due to differences in position of the double bond), only one of which is now known, and two phenolic desoxycodeines, as described above.

Experimental

α -Chlorocodide.—The α -chlorocodide used in these experiments was prepared by modifying the method of Freund,¹⁶ in that the codeine and phosphorus pentachloride were allowed to react for only two hours instead of twenty-four hours as given by Freund. This resulted in an increased yield and less formation of amorphous by-products. Starting with crude codeine, the yield averaged 84–86% of the theoretical, while from pure codeine a 94% yield was obtained. The use of thionyl chloride²¹ proved to be less advantageous. Since no crystalline salts of α -chlorocodide have been previously described, we include the preparation of two of these.

α -Chlorocodide Acid Sulfate.—This salt was prepared by dissolving α -chlorocodide in the calculated amount of 20% sulfuric acid, whereupon the sparingly soluble acid sulfate separated as a white crystalline mass. It was purified from water; it softens at 135–140°, and melts with decomposition at 192–193°.

²⁰ Schöpf, *Ann.*, **452**, 237 (1927); **483**, 157 (1930).

²¹ Wieland and Kappelmaier, *ibid.*, **382**, 337 (1911).

Anal. Calcd. for $C_{18}H_{20}O_2NCl \cdot H_2SO_4 + 2H_2O$: H_2SO_4 , 21.70. Found: H_2SO_4 , 21.83.

The substance was dried to constant weight at 135–140°.

Anal. Calcd. for $C_{18}H_{20}O_2NCl \cdot H_2SO_4 + 2H_2O$: H_2O , 7.97. Found: H_2O , 7.55.

Anal. Calcd. for $C_{18}H_{20}O_2NCl \cdot H_2SO_4$: H_2SO_4 , 23.02. Found: H_2SO_4 , 23.61.

The hydrated salt in aqueous solution shows $[\alpha]_D^{20} +101.1^\circ$: $c = 2.720$, $l = 1$, $\alpha = +2.75^\circ$.

α -Chlorocodide Acid Tartrate.—This salt was prepared by dissolving the base in a dilute aqueous solution of the calculated amount of *d*-tartaric acid, evaporating to dryness in vacuum, and recrystallizing from water. It is very soluble in hot water; at 18° 100 cc. of water dissolves 1.36 g. of the salt. In aqueous solution, $[\alpha]_D^{27.5} -219.3^\circ$: $c = 1.856$, $l = 1$, $\alpha = -4.07^\circ$.

Anal. Calcd. for $C_{18}H_{20}O_2NCl \cdot C_4H_4O_6$: Cl, 7.62. Found: Cl, 7.61.

β -Chlorocodide.—This substance was prepared by a method similar to that of Pschorr²² and Speyer,²³ by sealing α -chlorocodide (5 g.) in thin-walled test-tubes and heating for twenty-five minutes after complete melting in a bath of boiling bromoform or bromobenzene. The test-tube was cut while the contents were still soft, and 96% alcohol added, whereupon the brownish mass crystallized; yield after one recrystallization from alcohol, 75% of the theoretical. No salts of β -chlorocodide have been described previously.

β -Chlorocodide Hydrochloride.²⁴—On addition of the calculated amount of 3 *N* hydrochloric acid to the base the hydrochloride crystallized from the clear solution almost immediately, and was filtered off and washed with cold water. It was recrystallized from water or from a mixture of alcohol and acetone. The purified salt sinters slightly at 162°, and melts at 168–171° (decomp.); it is slightly levorotatory, $[\alpha]_D^{30} -3.85^\circ$: $c = 2.335$, $l = 1$, $\alpha = -0.09^\circ$.

Anal. Calcd. for $C_{18}H_{20}O_2NCl \cdot HCl$: Cl, 20.03. Found: Cl, 19.99, 20.02.

β -Chlorocodide Acid Tartrate.—Prepared by dissolving β -chlorocodide in a dilute aqueous solution of the calculated amount of *d*-tartaric acid, evaporating to dryness in vacuum, and recrystallizing the glass-like product from a small amount of water. It is very soluble in cold water; in aqueous solution, $[\alpha]_D^{20} +8.3^\circ$: $c = 1.683$, $l = 1$, $\alpha = +0.14^\circ$.

Anal. Calcd. for $C_{18}H_{20}O_2NCl \cdot C_4H_4O_6$: Cl, 7.62. Found: Cl, 7.67.

Iodocodide.—(1) Orange form: this was prepared according to the directions of Knorr and Hartmann²⁵ and varied in color from yellow to red. It sintered strongly at 153–155°, formed a black solid at 159–162°, and melted with decomp. at about 200°: red crystals, $[\alpha]_D^{25} +134.1^\circ$ in chloroform: $c = 3.72$, $l = 1$, $\alpha = +4.99^\circ$; yellow crystals, $[\alpha]_D^{26.5} +126.8^\circ$ in chloroform: $c = 2.30$, $l = 1$, $\alpha = +2.92^\circ$. (2) White form: this was obtained when the yellow or red crystals were dissolved in boiling ligroin (90–110°) or ethyl acetate, filtered, and cooled quickly. White crystals were also obtained when α -chlorocodide (15 g.) with finely powdered potassium iodide (9 g.) was refluxed for ten hours in 150 cc. of methyl alcohol, yield 12.7 g., m. p. 159–160° after one recrystallization from methyl alcohol. The same substance was obtained as a by-product from the reaction of α -chlorocodide with methyl- or ethylmagnesium iodide. It is soluble in chloroform or benzene, slightly soluble in ethyl acetate, methyl alcohol, ethyl alcohol or

²² Pschorr and Rollet, *Ann.*, **373**, 6 (1910).

²³ Speyer and Rosenfeld, *Ber.*, **58**, 1115 (1925).

²⁴ We are indebted to Mr. L. Eilers for the preparation and analysis of this salt.

²⁵ Knorr and Hartmann, *Ber.*, **45**, 1352 (1912).

ligroin, almost insoluble in ether; $[\alpha]_D^{22.5} +136.5^\circ$ (chloroform): $c = 2.62$, $l = 2$, $\alpha = +7.15^\circ$.

Anal. Calcd. for $C_{18}H_{20}O_2NI$: C, 52.80; H, 4.93; I, 31.02. Found: C, 53.10; H, 5.04; I, 31.17.

When the white iodocodide was boiled in ethyl alcohol for a few minutes, the solution gradually turned yellow and the yellow or reddish crystals described by Knorr separated on cooling. After boiling in alcohol for three days, iodocodide could no longer be isolated.

Iodocodide Hydrochloride.—Five grams of pure iodocodide was treated with 10 cc. of cold 3 *N* hydrochloric acid. The gummy mass which first formed crystallized after a few minutes, and was recrystallized from methanol; yield 4.8 g.; after repeated crystallizations it melted at 190 – 191° . In water, $[\alpha]_D^{23} +126.9^\circ$, $+127.0^\circ$: $c = 1.43$, 0.693 , $l = 2$, 1 , $\alpha = +3.63^\circ$, $+0.88^\circ$. It is soluble in water at 26° to the extent of 2.6 g. in 100 cc.

Anal. Subs., 0.1623 g. Calcd. for $C_{18}H_{20}O_2NI \cdot HCl + 2H_2O$: silver halide, 0.1275 g. Found: silver halide, 0.1257 g.

The salt lost weight corresponding to 2.5 H_2O (water could be observed) on heating to the point where decomposition started.

Iodocodide Methiodide.—Iodocodide in benzene solution was heated with an excess of methyl iodide in a sealed tube at 100° for three hours. The product was washed with ether and recrystallized from hot water, in which it is only very slightly soluble; m. p. 187 – 188° , yellow needles.

Anal. Calcd. for $C_{18}H_{22}O_2NI_2$: I, 46.06. Found: I, 46.22.

Iodocodide and Methylmagnesium Iodide: Desoxycodeine-A.—To a suspension of one gram of powdered iodocodide (white) in 50 cc. of dry ether was added 25 cc. of molar ethereal methylmagnesium iodide solution. After the mixture had refluxed for twelve hours, the excess of Grignard reagent and the powdery white addition compound were decomposed with a slight excess of 10% acetic acid, and concd. ammonia added dropwise with shaking until the solution was strongly alkaline. The ether layer was dried with sodium sulfate and distilled, leaving a yellow oil which soon crystallized. The addition of a small amount of cold methanol served to dissolve the desoxycodeine (0.4 g.) away from unreacted iodocodide (0.3 g.).

Iodocodide (white or orange) reacted with zinc dust in boiling absolute alcohol as does α -chlorocodide, to give desoxycodeine. In view of the unstable nature of iodocodide, the low yield of desoxycodeine (about 30%) is not remarkable.

Hydrolysis of Iodocodide: Pseudocodeine.—Eight grams of the white iodocodide was suspended in 40 cc. of hot water and 4 cc. of glacial acetic acid added. The clear yellow solution was refluxed for four hours, cooled, and treated with an excess of 15% potassium hydroxide. The resinous precipitate was extracted out with ether and the ethereal solution dried with potassium carbonate and distilled, yielding an oily solid. This was dissolved in the minimum amount of absolute alcohol and treated with alcoholic hydrochloric acid to acid reaction. After standing for twelve hours at 0° , the solution yielded 4.5 g. of crystalline pseudocodeine hydrochloride. About 2 g. of oily solid was obtained by treating the mother liquors with alkali, but the separation of isocodeine and allopseudocodeine from this was unsuccessful.

Iodocodide and Silver Chloride: α -Chlorocodide.—A small amount of white (or yellow) iodocodide was dissolved in 75% alcohol and shaken with freshly precipitated silver chloride. After a few minutes a change in color of the silver salt could be noted, and in three hours it had become quite yellow. The liquid on evaporation yielded α -chlorocodide, of m. p. 145 – 147° , which showed no depression with α -chlorocodide, but depressed the melting point of β -chlorocodide to about 120° .

Desoxycodine-A (Desoxycodine).—The base prepared according to the directions of Knorr and Waentig, and Freund, by refluxing α -chlorocodide with zinc dust in absolute alcohol, showed the m. p. 121–122° even after the most careful purification by recrystallization from 50% methyl alcohol to constant rotation as well as over the hydrochloride or hydriodide; $[\alpha]_D^{22} +118.1^\circ$: $c = 3.32$ (96% alcohol), $l = 1$, $\alpha = +3.92^\circ$ (Knorr, m. p. about 126° with previous sintering; $[\alpha]_D^{15} +119^\circ$, $+121^\circ$).

Preparation Using Methylmagnesium Iodide.—Eight grams of α -chlorocodide in 400 cc. of dry ether was treated with 75 cc. of molar methylmagnesium iodide solution. A precipitate formed immediately, the ether boiled, and considerable amounts of a gas which was largely unsaturated toward bromine were given off. The mixture was refluxed for six hours, the ether decanted from the heavy white precipitate and the latter brought into complete solution with 10% acetic acid. To the acid solution was added 100 cc. of ether, and an excess of ammonia sufficient to dissolve the magnesium hydroxide precipitate. The ammoniacal layer was extracted with a second 100 cc. of ether, and the combined dried ether distilled. The red oily residue crystallized on the addition of a little ether and was recrystallized from ether and then from 50% methanol. The product (5.5 g.) melted at 122°, $[\alpha]_D^{24} +115.1^\circ$: $c = 1.96$ (96% alcohol), $l = 2$, $\alpha = +4.51^\circ$. The same product was obtained when ethylmagnesium iodide was used: 3 g. of α -chlorocodide yielded 2 g. of crude desoxycodine and about 0.1 g. of white iodocodide. The iodocodide was separated from the desoxycodine through its comparative insolubility in ether.

Desoxycodine-A, prepared through the reaction of alkylmagnesium halide on α -chlorocodide, gave a hydrochloride of m. p. 265–270° and a hydriodide of m. p. 255–260°, identical with those obtained from Knorr's desoxycodine. Our product was further identified through its reduction products: with sodium and alcohol it reduced to the so-called α -tetrahydrodesoxycodine; with hydrogen and platinum it took up two molecules of hydrogen to give a quantitative yield of β -tetrahydrodesoxycodine of m. p. 143–145°.

The reduction of desoxycodine-A with sodium and alcohol as well as by the electrolytic method will be further described in the following paper.

Desoxycodine-B.—Ten grams of pure α -chlorocodide was dissolved in 200 cc. of 20% sulfuric acid (separation of the sparingly soluble crystalline acid sulfate often caused difficulty at this point) and electrolyzed, using a current of 8 amperes and a prepared lead cathode of 60 sq. cm. area, in a cell which was kept at about 10 to 20°. Usually five to six hours was required for the reduction, which was complete when a small test portion dissolved to a clear solution in excess alkali. The acid solution from the reduction was filtered and treated with ammonia until barely alkaline to litmus. The base which precipitated was redissolved in the minimum amount of dilute hydrochloric acid, and the solution cooled to 0°; 200 cc. of ether was added, and then 3 *N* ammonia dropwise with vigorous shaking. The clear yellow ether solution was dried with sodium sulfate and distilled, yielding 9.0 g. of crude desoxycodine-B of m. p. 110–115°. Two crystallizations from dilute alcohol gave a product melting at 118–119°, $[\alpha]_D^{24} +42.4^\circ$. By exhaustive crystallization from dilute alcohol the melting point changed only slightly (119–120°), but the rotatory power rose to $[\alpha]_D^{22} +71.3^\circ$: $c = 3.617$, $l = 1$, $\alpha = +2.58^\circ$.

Anal. Calcd. for $C_{18}H_{21}O_2N + \frac{1}{2}H_2O$: C, 73.93; H, 7.58. Found: C, 73.85; H, 7.84.

A dihydrodesoxycodine $C_{18}H_{23}O_2N + \frac{1}{2}H_2O$ which Freund claimed this base to be would require C, 73.43; H, 8.21.

Desoxycodine-B hydrochloride is formed when a saturated solution of the base in absolute alcohol is treated with alcoholic hydrochloric acid. The white crystals obtained darken rapidly on standing, and even after recrystallization from absolute alcohol are still unstable.

Desoxycodine-B hydriodide results from treatment of a dilute acetic acid solution of the base with excess of aqueous potassium iodide. The oil which first separates crystallizes on standing, and may be purified by recrystallization from water, from which it separates as light yellowish-brown needles of m. p. 245°; $[\alpha]_D^{22} + 38.3^\circ$; $c = 1.698$, $l = 1$, $\alpha = +0.65^\circ$.

Anal. Calcd. for $C_{18}H_{21}O_2N \cdot HI$: I, 30.87. Found: I, 30.92.

Desoxycodine-B Methyl Ether Methiodide.—The methiodide of the desoxycodine-B does not crystallize. The methyl ether methiodide, prepared in the usual way and recrystallized from dilute alcohol, melted at 242–243°. Freund gives the m. p. 245°.

Reduction of Desoxycodine-B.—Nine and one-half grams of the base was dissolved in dilute hydrochloric acid to neutral solution, made up to 100 cc. with water, and hydrogenated in the presence of 2.5 g. of palladium-barium sulfate; 1570 cc. (2 moles) of hydrogen was absorbed in three hours (when platinum oxide was used the reduction ran to completion in twenty to thirty minutes). The filtered solution was made alkaline with ammonia and extracted with ether. The product, recrystallized from acetone, consisted of 9.5 g. of white crystals of m. p. 139–143°, which melted at 144–145° after further purification from acetone and were identical in every respect with β -tetrahydrodesoxycodine; $[\alpha]_D^{20} - 33.3^\circ$; $c = 1.499$ (alcohol), $l = 1$, $\alpha - 0.50^\circ$. The reduction of desoxycodine-B with sodium and alcohol to a dihydrodesoxycodine (the so-called α -tetrahydrodesoxycodine) will be described in the following paper.

Desoxycodine-C.—A solution of 9 g. of sodium in 400 cc. of methanol was prepared in a steel autoclave, 5.0 g. of crystalline chlorodihydrocodide (m. p. 171–173°) added, and the mixture heated at 140° for twenty-four hours. After cooling, the clear deep red methanol solution was diluted with an equal volume of water, and the methyl alcohol removed with a bubble tube in vacuum at 40°. The alkali-insoluble desoxycodine-C separated crystalline as the alcohol was removed, and was filtered out and purified by repeated crystallization from ethyl acetate. The yield of crude crystalline product was 4.2 g., of purified substance melting at 105–106°, 3.0 g.; in 95% alcohol, $[\alpha]_D^{20} - 199.4^\circ$, -197.4° ; $c = 1.745$, 1.008; $l = 1$, 1; $\alpha = -3.48^\circ$, -1.99° .

Anal. Calcd. for $C_{18}H_{21}O_2N$: C, 76.28; H, 7.47. Found: C, 76.24; H, 7.65.

The formula of a dihydrodesoxycodine, $C_{18}H_{23}O_2N$, as claimed by Knoll and Co., requires C, 75.74; H, 8.12.

It is extremely soluble in methyl or ethyl alcohol, ether, chloroform or benzene, moderately soluble in ethyl acetate, insoluble in alkali.

Desoxycodine-C Hydrochloride.—A solution of the base in the minimum amount of 3 *N* hydrochloric acid was evaporated to dryness in vacuum and the white crystalline solid thus obtained was purified by recrystallizing from alcohol. It crystallizes with one molecule of water and melts at 114°; in aqueous solution $[\alpha]_D^{20.5} - 132.7^\circ$; $c = 1.771$, $l = 1$, $\alpha = -2.35^\circ$.

Anal. 0.1609 g. at 130° in vacuum lost 0.0088 g. Calcd. for $C_{18}H_{21}O_2N \cdot HCl + H_2O$: H_2O , 5.38. Found: H_2O , 5.50.

Anal. (dried substance) Calcd. for $C_{18}H_{22}O_2NCl$: Cl, 11.10. Found: Cl, 11.23.

Desoxycodine-C Hydriodide.—The base was dissolved in dilute acetic acid and treated with an excess of potassium iodide solution. An oil separated, which crystallized on standing, and was purified by recrystallization from hot water. It consisted of fine light yellow prisms, sintering at 135–140°, melting at 160–165°, and containing one molecule of hydrate water; in 95% alcohol, $[\alpha]_D^{19} - 131.6^\circ$; $c = 1.401$, $l = 1$, $\alpha = -1.84^\circ$.

Anal. Calcd. for $C_{18}H_{21}O_2N \cdot HI + H_2O$: H_2O , 4.19. Found: H_2O , 4.18. Calcd. for $C_{81}H_{22}O_2NI$: I, 30.88. Found: I, 30.96.

Desoxycodeine-C Methiodide.—A solution of the base in methyl alcohol was boiled for ten minutes with an excess of methyl iodide. After removal of methyl iodide by distillation, water was added; the oily methiodide which separated was obtained crystalline by dissolving in hot water and cooling very slowly. The crude product melted at 210–211°; after crystallization to constant melting point from methyl alcohol it melted at 236–240°.

Anal. Calcd. for $C_{19}H_{24}O_2NI$: I, 29.86. Found: I, 30.22.

Reduction of Desoxycodeine-C.—One gram of desoxycodeine-C in 30 cc. of methyl alcohol with 0.1 g. of Adams' platinum oxide catalyst took up 180 cc. of hydrogen in twenty minutes. The calculated absorption for 2 moles of hydrogen is 176 cc. The mixture was filtered from the platinum and evaporated to dryness in vacuum, giving a quantitative yield of crystalline β -tetrahydrodesoxycodeine, which after one crystallization from acetone melted at 143–144°, showed no depression in m. p. with β -tetrahydrodesoxycodeine, and yielded a hydriodide of m. p. 251°, a methiodide of m. p. 263–265° identical with those from β -tetrahydrodesoxycodeine. The reduction product likewise showed the rotation of β -tetrahydrodesoxycodeine: $[\alpha]_D^{20} -30.8^\circ$, $c = 1.980$ (alcohol), $l = 2$, $\alpha = -1.22^\circ$. The reduction of desoxycodeine-C with the Willstätter platinum black catalyst, or in hydrochloric acid solution with a palladium-barium sulfate catalyst gave identical results. Desoxycodeine-C is recovered unchanged from treatment with sodium and alcohol, or zinc and acetic acid. The electrolytic reduction of desoxycodeine-C yields a dihydrodesoxycodeine of m. p. 128–131° which will be described in the following paper.

Summary

1. A study of the desoxycodeines and of their conversion to the dihydrodesoxycodeines and to β -tetrahydrodesoxycodeine has been made.

2. Desoxycodeine-A is shown to be the chief product of the reaction between α -chlorocodide and methyl- or ethylmagnesium iodide. Iodocodide, which is obtained as a by-product of the reaction, may play a part in the reaction mechanism.

3. The compound resulting from electrolytic reduction of α - or β -chlorocodide, which was formerly thought to be a dihydrodesoxycodeine, is shown to be a second, phenolic desoxycodeine. It can be reduced directly to β -tetrahydrodesoxycodeine, or indirectly, through an intermediate dihydrodesoxycodeine, to the same tetrahydrodesoxycodeine.

4. The action of sodium methylate on chlorodihydrocodide does not give a dihydrodesoxycodeine as claimed in the literature, but the non-phenolic desoxycodeine-C, which reduces to a phenolic dihydrodesoxycodeine or to β -tetrahydrodesoxycodeine.

5. New crystalline salts of α -chlorocodide and of β -chlorocodide are described.

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