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# Desoxycodeine Studies. V. The So-Called Dihydrodesoxycodeine-A[1]

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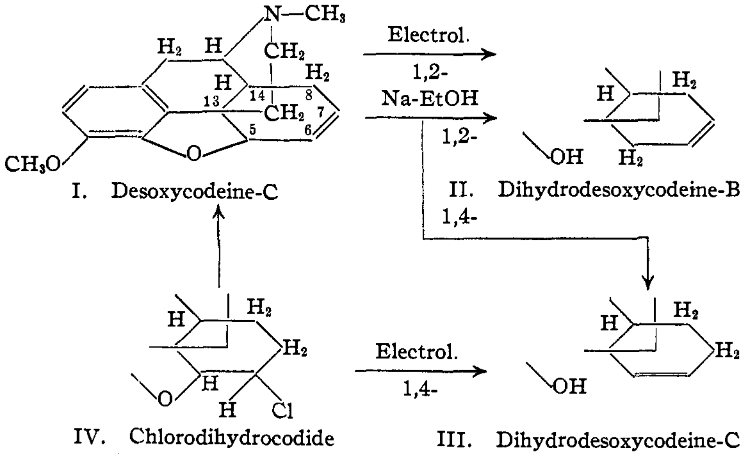
Reduction of α-chlorocodide (V) or desoxycodeine-A results in the formation of a crystalline base which was shown in the second paper of this series to be a dihydrodesoxycodeine having the formula $C_{18}H_{23}O_2N + 0.5H_2O$. The reappearance of this base, dihydrodesoxycodeine-A, in reductions in the pseudocodeine series, led to the structural speculations included in this and the following communications, from which it could be predicted that one of the isomeric dihydrodesoxycodeines-A, -B, and -C must be a mixture.

Investigation of the three substances from this viewpoint demonstrates that the so-called dihydrodesoxycodeine-A consists of a mixture of dihydrodesoxycodeines-B and -C in a nearly constant ratio of 1 to 3. The apparent attainment of a compound of constant properties as recorded by several investigators[2] depends upon the extraordinary tendency of isomers-B and -C, as well as their salts, to crystallize together. The separation of the components can be accomplished only through laborious fractional crystallization of the mixture or of the methine bases obtained from its degradation.



The establishment of the true nature of "dihydrodesoxycodeine-A" as well as that of the supposed desoxycodeine-B[3] permits the assignment of reasonable structural formulas to the members of the desoxy- and dihydrodesoxycodeine series. Desoxycodeine-C (I) is derived from chlorodihydrocodide by loss of hydrogen chloride, and its structure is evident from its pseudocodeine-like behavior toward catalytic hydrogen or Grignard's reagent. Reduction of the allyl ether system present in desoxycodeine-C by metal combinations to produce two phenolic dihydrogenated products can be explained only by 1,2- and 1,4-addition of hydrogen, which results in II and III, *i. e.*, "dihydrodesoxycodeine-A."

The assignment of structures II and III to dihydrodesoxycodeines-B and -C, respectively, rests on the following considerations. Dihydrodesoxycodeine-C is obtained in excellent yield by electrolytic reduction of chlorodihydrocodide IV, a process which can hardly be explained as other than a 1,4-addition of hydrogen at oxygen and chlorine, with the formation of the new double bond at C-5, C-6, formula III.[4] On the basis of this supposition, dihydrodesoxycodeine-B would receive the alternative formula II, and its formation by electrolytic reduction of desoxycodeine-C appears to result from a 1,2-addition of hydrogen at oxygen and C-5 in the latter base. In the reduction of desoxycodeine-C with sodium and alcohol the 1,2-process is subordinate, and the main product dihydrodesoxycodeine-C is formed through 1,4-addition at the ends of the allyl ether system.

The appearance of dihydrodesoxycodeines-B and -C in the same ratio in the reduction of α-chlorocodide and of desoxycodeine-A indicates that the mechanism of both reductions is the same. The first step in the sodium and alcohol reduction of α-chlorocodide is undoubtedly the formation of desoxycodeine-A, which is further

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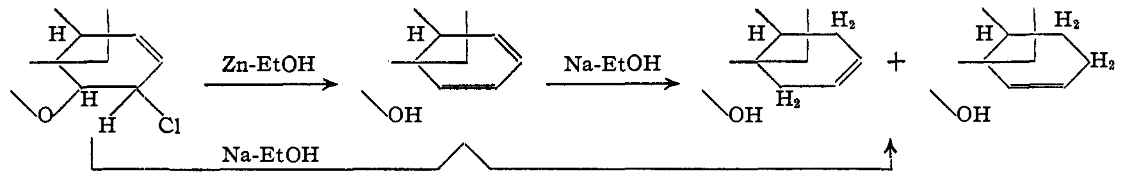
[2] Knorr and Waentig, *Ber.*, **40**, 3860 (1907); Cahn, *J. Chem. Soc.*, 2572 (1926); Small and Cohen, THIS JOURNAL, **53**, 2227 (1931).

[3] Small and Morris, *ibid.*, **55**, 2874 (1933).

[4] This type of mechanism for analogous reductions was first proposed by Finkelstein; see Henrich, "Theorien der organischen Chemie," 1921, p. 56. The alternative hypothesis that hydrogen chloride might be eliminated at C-6, C-7 or C-5, C-6 before (or after) the reductive opening of the oxide ring, to give either II or III, is most improbable; chlorodihydrocodide loses hydrogen chloride only on protracted treatment with sodium methylate at 140°. The product which would result from direct replacement of chlorine by hydrogen, namely, dihydrodesoxycodeine-D, is stable under the conditions involved.



V. α-Chlorocodide VI. Desoxycodeine-A Dihydrodesoxycodeines-B and -C

reduced as fast as formed to the mixture of dihydrodesoxycodeines.

Desoxycodeine-A, which all evidence shows to be an individual,[3] is best represented by the structure VI. Its formation from α-chlorocodide involves a 1,4-addition of hydrogen as postulated in the reduction of chlorodihydrocodide, and its transformation to the two dihydrodesoxycodeines is explained as the result of competing 1,2- and 1,4-addition of hydrogen. The 1,2-addition might take place in more than one way, but a third isomer has not yet been found. The fact that C-5 is attached to a quaternary carbon atom (C-13) may tend to inhibit 1,4- or 1,2-addition involving C-5. On the basis of the not yet abandoned Knorr formula[5] a steric influence at C-5 might be very great.

## Experimental

**The So-called Dihydrodesoxycodeine-A.**—Fifty grams of α-chlorocodide having $[\alpha]^{28}_{\text{D}}$ −386° was reduced in boiling alcohol with 250 g. of sodium. The crude product (28 g.) isolated from ether melted at 110–116° and had $[\alpha]^{30}_{\text{D}}$ −18.7° in absolute alcohol ($c$ = 2.29). In a parallel reduction, 56 g. of desoxycodeine-A (purified through the salicylate, which had the m. p. 226° and $[\alpha]^{25}_{\text{D}}$ +103.2°) in 2200 cc. of boiling absolute alcohol was reduced under hydrogen with 230 g. of sodium. The crude product, 56 g., melted at about 116° and had $[\alpha]^{25}_{\text{D}}$ −18°. Purification through the hydrochloride gives a salt of practically constant rotation (−39°) between the ninth and twelfth crystallizations. The mixture of dihydrodesoxycodeines-B and -C obtained from the above reductions sinters and melts unsharply at 120–125° after several recrystallizations. If the substance is recrystallized from boiling ethyl acetate, the melting point rises abruptly to a quite sharp value of 157°. This change can be brought about by merely rubbing with a trace of the higher-melting form, and also takes place spontaneously. The analytical sample of Small and Cohen which had the m. p. 134–136° in February, 1931, showed the m. p. 162.5–163°, but was unchanged in composition. Under certain conditions the high-melting form may be converted back to the low-melting by crystallization from alcohol.

*Anal.* (high-melting form). Calcd. for $C_{18}H_{23}O_2N$ + 0.5 $H_2O$: C, 73.43; H, 8.21. Found: C, 73.45; H, 8.32.

Reduction of desoxycodeine-C with sodium and alcohol under nitrogen gave 70% yield of a hydrochloride of m. p. 154–155° (foaming), solidifying and remelting at 248–249° (dec.), having $[\alpha]^{27}_{\text{D}}$ −3.1°. The corresponding base melted at 107–111°, and gave a hydriodide of $[\alpha]_{\text{D}}$ 0°. Its nature as dihydrodesoxycodeine-C was demonstrated by degradation to the characteristic methine base of m. p. 173–174° (no depression with known samples) and by hydrogenation to tetrahydrodesoxycodeine of m. p. 157° anhydrous. A trace of dihydrodesoxycodeine-B was also formed in the reduction.

**Separation of the So-called Dihydrodesoxycodeine-A.**—Twenty-eight grams of crude reduction product (from α-chlorocodide) having $[\alpha]^{28}_{\text{D}}$ −18.7° was crystallized twice as the hydrochloride, and then fractionated as the base from alcohol, combining fractions of the same rotatory power. After over 100 crystallizations, 0.8 g. of the less soluble isomer was obtained, whose properties did not change during six crystallizations as hydrochloride. The base had the properties of pure dihydrodesoxycodeine-B: $[\alpha]^{25}_{\text{D}}$ −102°; m. p. 127–128°; high-melting form, m. p. 170–173° (no depression in mixed m. p.). The hydrochloride showed $[\alpha]^{25}_{\text{D}}$ −76.5°.

Of the more soluble fraction, only 0.2 g. could be obtained pure, the remaining intermediate fractions being contaminated with dihydrodesoxycodeine-B. This end-fraction was identified as dihydrodesoxycodeine-C by melting point and mixed m. p., 106–110°, specific rotation $[\alpha]^{25}_{\text{D}}$ +5.0° (alcohol, $c$ = 1.38), rotation of hydrochloride $[\alpha]^{25}_{\text{D}}$ +10.8° (water, $c$ = 0.93) and of the hydriodide $[\alpha]^{25}_{\text{D}}$ +2.2° (water, $c$ = 0.89).

The two (or more) constituents of "dihydrodesoxycodeine-A" are so similar in basicity that fractional extraction results in a constant ratio mixture of $[\alpha]_{\text{D}}$ −28°. A mixture of 101 mg. of B-isomer with 290 mg. of C-isomer showed great similarity to "dihydrodesoxycodeine-A": $[\alpha]^{25}_{\text{D}}$ −26.1°, m. p. 125° unsharp; on seeding, the m. p. rose to 148–151°; hydrochloride, m. p. 151–152°, $[\alpha]^{27}_{\text{D}}$ −30.3°.

**Separation through the Methine Base.**—Ten grams of "dihydrodesoxycodeine-A" methiodide of $[\alpha]^{26}_{\text{D}}$ −16.4°, in 60 cc. of hot water, was treated with 97 cc. of 0.242 *N* thallous hydroxide. Thallous iodide was filtered out and the lavender (oxidation) filtrate evaporated to dryness at room temperature in a vacuum desiccator. The product, 7.0 g. of sheets of purple needles (hygroscopic), was sublimed in 2-g. lots at 140° and 0.001 mm. pressure. The yield of pale yellow crystals was 5.55 g. or 79% of the theoretical. The crystalline mass was washed with a little cold acetone, which removed about 0.5 g. of yellow oil (very sensitive, gave a crystalline hydrochloride, not further characterized) and was then fractionated from acetone. After 54 crystallizations, in which fractions of the same melting point were combined, 0.8 g. of difficultly soluble material of constant m. p. 175–176° and 0.25 g. of very soluble material of constant m. p. 144–145.5° were

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[5] See for example M. Gradsztain, "Dissertation," Frankfurt a. M., 1932.

obtained. The remainder of the material was in intermediate fractions melting at 130–136° or 150–155° depending upon the proportion of the constituents.

The high-melting fraction was identified as des-N-methyldihydrodesoxycodeine-C by mixed melting point (175–176°) and rotation $[\alpha]^{25}_{D}$ −13.8° (abs. $CHCl_3$, $c$ = 0.506).

*Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.20; H, 8.42. Found: C, 76.16; H, 8.53.

The des-base absorbed 2 moles of hydrogen catalytically, giving dihydro-des-N-methyltetrahydrodesoxycodeine of m. p. 156–157°.

The low-melting fraction was identified as des-N-methyldihydrodesoxycodeine-B by mixed melting point (143.5–144.5°) and by rotation $[\alpha]^{26}_{D}$ +9.5° (abs. $CHCl_3$, $c$ = 0.519).

*Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.20; H, 8.42. Found: C, 76.10; H, 8.56.

**Des - N - methyldihydrodesoxycodeine - B.**—Dihydrodesoxycodeine-B was prepared in nearly quantitative yield by electrolytic reduction of desoxycodeine-C. The substance purified through the hydriodide had the m. p. 131–133° and the specific rotation $[\alpha]^{25}_{D}$ −104.4°, −106.0° (alcohol, $c$ = 1.0). When the base is sublimed at 120° (0.001 mm.) a form (anhydrous?) of m. p. 173–173.5° is obtained; samples of the low-melting form which had been kept in closed containers for several months showed the same melting point. The high-melting form can be recrystallized from dilute alcohol without change in melting point. It is probably the formation of this high-melting modification which causes the melting point of "dihydrodesoxycodeine-A" to rise 20–30° on seeding in the solid state. A sample of dihydrodesoxycodeine-B melting at 128° showed the m. p. 162–166° (evac. tube) four hours after seeding with the 173° form.

A solution of 2.8 g. of dihydrodesoxycodeine-B methiodide in 30 cc. of warm water was treated with 44 cc. of 0.15 *N* thallous hydroxide and filtered rapidly. The purple filtrate was evaporated to dryness in a vacuum desiccator and the residue sublimed at 160° and 0.001 mm. pressure. The faintly yellow crystals showed after three crystallizations from acetone the constant m. p. 144.5–145.5°, and the rotation $[\alpha]^{26}_{D}$ +7.4° (abs. $CHCl_3$, $c$ = 0.538).

*Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.20; H, 8.42. Found: C, 76.22; H, 8.43.

The des-base forms a crystalline hydrochloride. The base absorbs 2 moles of hydrogen to give a quantitative yield of dihydro-des-N-methyltetrahydrodesoxycodeine, m. p. 156–157°.

**Des - N - methyldihydrodesoxycodeine - C.**—Dihydrodesoxycodeine-C was prepared by electrolytic reduction of chlorodihydrocodide (10 g.); yield of crystals of m. p. 105–108°, 7.6 g. For purest samples of the base, m. p. 108–111°, the rotation $[\alpha]^{24}_{D}$ +5.6° (alcohol, $c$ = 1.16) was found, a value differing widely from that previously published. The value −61.6° found by Small and Cohen for the specific rotation of dihydrodesoxycodeine-C appears as an inexplicable experimental error; the original analytical sample of this base dating from 1931, twice recrystallized from alcohol, showed the m. p. 109–111° and the specific rotation 0°. For the salts we find: hydriodide, $[\alpha]^{24}_{D}$ +8.2° (water, $c$ = 0.848); hydrochloride, $[\alpha]^{27}_{D}$ +11.2° (water, $c$ = 1.16); methiodide, $[\alpha]^{29}_{D}$ +15.3° (water, $c$ = 1.30). The base distils at 140° and 0.001 mm. as colorless amorphous droplets.

*Anal.* Calcd. for $C_{18}H_{23}O_2N$: C, 75.74; H, 8.12. Found: C, 75.86; H, 8.49.

This material absorbed 2 moles of hydrogen in the presence of platinum, giving a quantitative yield of tetrahydrodesoxycodeine, m. p. 137–138°, m. p. 158° (anhydrous, sublimed).

The methiodide (1.8 g.) was degraded with thallous hydroxide as described above, giving 0.9 g. of crystalline sublimate. After four crystallizations the melting point of des-N-methyldihydrodesoxycodeine-C was constant, 175–176°; $[\alpha]^{26}_{D}$ −13.8° (abs. $CHCl_3$, $c$ = 0.507).

*Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.20; H, 8.42. Found: C, 76.23; H, 8.52.

The des-base absorbed 2 moles of hydrogen to give dihydro-des-N-methyltetrahydrodesoxycodeine, m. p. 157°; no mixed melting point depression with known samples, but with tetrahydrodesoxycodeine (anhydrous) of the same melting point, the mixed melting point was 120–130°.

**Reduction of Dihydrodesoxycodeine-D.**—Contrary to the experiments of Small and Cohen, we find that very vigorous reduction of dihydrodesoxycodeine-D with sodium and alcohol results only in traces of tetrahydrodesoxycodeine (5%); cleavage of the oxide ring by a 1,2-process is exceedingly difficult in saturated morphine derivatives, a point of great importance for the mechanism of reduction in the pseudocodeine series.

## Summary

1. The base heretofore known as α-tetrahydrodesoxycodeine and dihydrodesoxycodeine-A is a mixture of dihydrodesoxycodeines-B and -C in nearly constant proportion.

2. The methine bases derived from dihydrodesoxycodeines-B and -C have been prepared.

3. Tentative structures for the dihydrodesoxycodeines are proposed, and the mechanism by which they may be formed is discussed.

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