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# Reduction Studies in the Morphine Series. II. The Isomeric Phenolic Dihydropseudocodeines[1]

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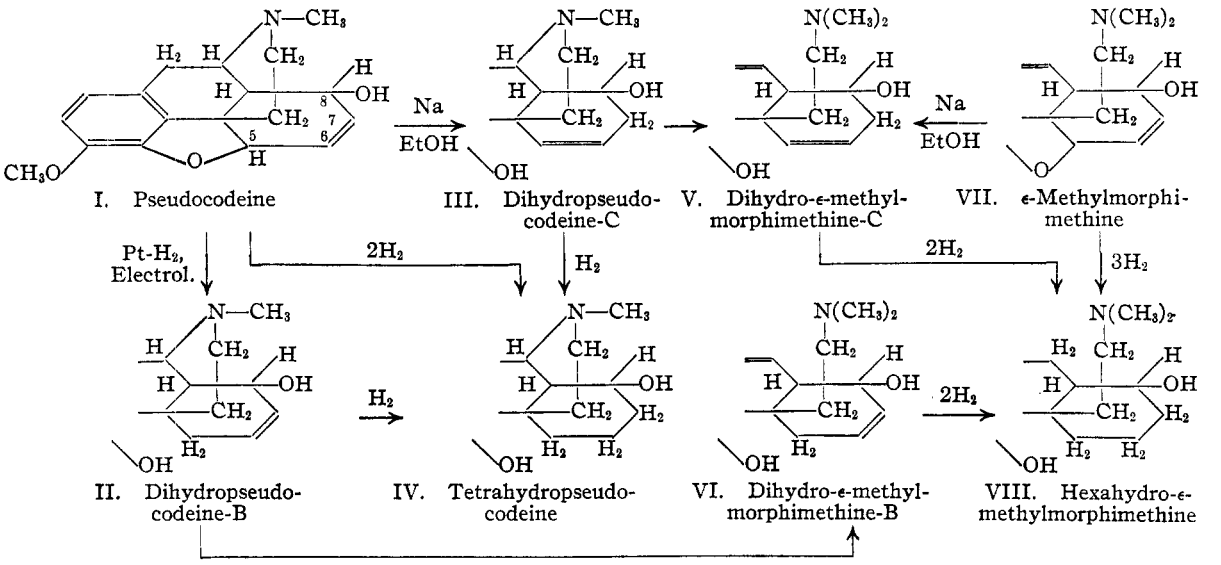
Catalytic hydrogenation of pseudocodeine (I) yields mainly either the non-phenolic dihydro- or the phenolic tetrahydro-pseudocodeine (IV) as end-products of two competing and independent reactions.[2] That the latter substance is, however, formed by a stepwise process in which the first stage involves reductive scission of the 4,5-ether linkage can be demonstrated by carrying out the hydrogenation in aqueous alcohol, from which the phenolic intermediate II, dihydropseudocodeine-B crystallizes during the reduction. The new base is isomeric with the phenolic dihydropseudocodeine III (which we will designate as -C) resulting from the reduction of pseudocodeine with sodium and alcohol;[3] both isomers absorb one mole of hydrogen to yield tetrahydropseudocodeine.




In a repetition of the sodium and alcohol reduction of pseudocodeine, we have obtained in addition to dihydropseudocodeine-C a considerable amount of the mixture of dihydrodesoxycodeines-B and -C described in the preceding communication. Electrolytic reduction, from which Speyer claimed to have obtained dihydropseudocodeine-C, gives almost exclusively the B-isomer.

The methiodides of II and III can be degraded to the corresponding dihydro-ϵ-methylmorphimethines-B (VI) and -C (V); the latter (V) is obtained also in small but significant yield from the reduction of ϵ-methylmorphimethine VII with sodium and alcohol. The isomeric methines V and VI both yield hexahydro-ϵ-methylmorphimethine by catalytic reduction. The reductions in the methine series are thus seen to parallel those of the parent pseudocodeine derivatives.

## Discussion of Results

The isomeric *phenolic* dihydropseudocodeines-B and -C can owe their isomerism only to a difference in the position of the alicyclic double bond in ring III, since on hydrogenation both give tetrahydropseudocodeine. It is evident, therefore, that catalytic hydrogenation (and also electrolytic reduction) involves a different mechanism than reduction with sodium and alcohol (both being distinct from a third mechanism, the "normal" saturation of the C-6,7 double bond[2]). Two mechanisms which may be suggested to account for the rupture of the ether bridge linkage involve as the primary steps (a) the 1,4-addition of hydro-

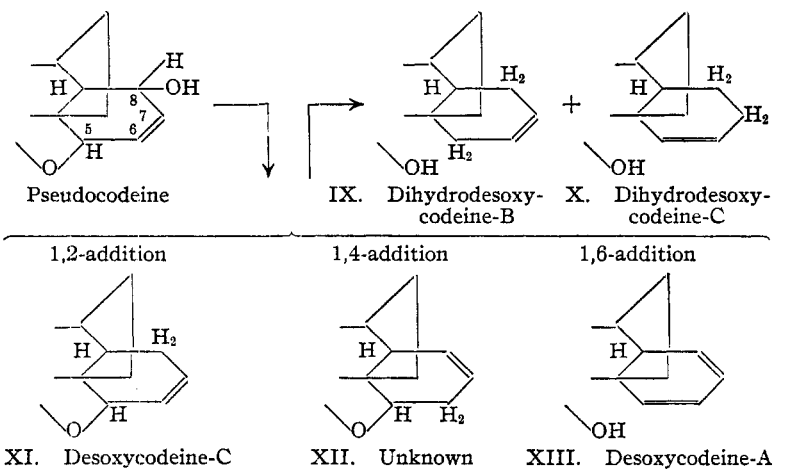
(1) This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc., and the Rockefeller Foundation.

(2) Lutz and Small, THIS JOURNAL, **54**, 4715 (1932).

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

gen to the allyl ether system present[4] which would lead to a product of formula III, and (b) 1,2-addition of hydrogen at the ether oxygen and C-5, giving II. A decision as to which of the two mechanisms applies in each case must rest on the location of the double linkage in the phenolic dihydropseudocodeines-B and -C; these have been tentatively assigned positions as in II and III on the following basis. The formation of dihydropseudocodeine-C by sodium and alcohol reduction seems most reasonably explained as a 1,4-process, since the tendency for this type of reagent to add hydrogen at the ends of conjugated systems is well known;[5] this assumption would, moreover, be in accord with the parallel reduction of desoxycodeine-C to dihydrodesoxycodeine-C. The formation of phenolic dihydropseudocodeine-B by the electrolytic reduction of pseudocodeine, if it follows the course of the analogous reduction of desoxycodeine-C, must involve the 1,2-mechanism, yielding a product of structure II.

If the above conclusions are valid, it follows that catalytic hydrogenation of pseudocodeine




takes place by 1,2-addition to the O,C-5 linkage without involving the C-6, C-7 double bond, which must therefore contribute to the reaction only an activating influence.

The formation of the two dihydrodesoxycodeines-B and -C (IX and X) during sodium and alcohol reduction of pseudocodeine involves the loss of the alcoholic hydroxyl group before or simultaneous with the opening of the ether bridge, but not afterward, since the two phenolic dihydropseudocodeines II and III are not reducible under these conditions. The alcoholic hydroxyl group must be eliminated in one of three ways, involving initial 1,2-, 1,4- or 1,6-addition, one hydrogen in each case attaching itself to the oxygen of the hydroxyl group which is thereby removed.

The first mechanism would lead to XI, which can be reduced further under these conditions; this hypothesis implies, however, an activating influence of the $\alpha,\beta$-double bond on the hydroxyl which has no parallel in the codeine series. The second mechanism is improbable because it would lead to XII in which the double bond is so located as to preclude further reduction. The 1,6-mechanism, however, would lead to XIII (which is known to be reduced with ease) and is consistent with other related reduction phenomena which have been interpreted in a similar way.[6] The assumption of XIII as an intermediate is supported by the fact that the ratio of dihydrodesoxycodeine-B to -C is the same in the pseudocodeine as in the desoxycodeine-A reduction.

## Experimental

**Dihydropseudocodeine-B (II).**—A suspension of 28 g. of pseudocodeine in 70 cc. of 80% ethanol with 1.4 g. of palladium–calcium carbonate showed an initial rapid absorption of hydrogen, the pseudocodeine dissolving and granular crystals of the reduction products separating as the reaction proceeded. At about 1640 cc. absorption (standard conditions) the reduction slowed markedly, and was interrupted. The products were brought into solution with hot alcohol, catalyst removed, the residue from evaporation of the alcohol taken up in acetic acid, and excess 40% sodium hydroxide added. The crystalline precipitate of pseudocodeine and dihydropseudocodeine-A weighed 7.6 g. The alkaline solution was acidified, made ammoniacal, and extracted with ether, yielding 19.6 g. of tetrahydropseudocodeine and dihydropseudocodeine-B, crystallized from 60% alcohol. Further hydrogenation of the 7.6 g. of non-phenolic material showed it to contain only 5% of isomer-A, whence the phenolic fraction corresponded to 1550 cc. (1.1 moles) absorption and was largely dihydropseudocodeine-B.

Separation of the constituents of the phenolic fraction was accomplished by utilizing the extreme ethyl acetate solubility of the anhydrous amorphous form of tetrahydro-

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

(5) See for example Hückel, "Theoret. Grundl. d. org. Chem.," Vol. I, 1931, p. 306 (1931); Finkelstein [*Verhandl. d. Gesell. deut. Naturf. u. Ärtzte*, II, 176 (1911)] first pointed out that systems of this type may behave like conventional conjugated systems of double bonds [see Henrich, "Theories of Org. Chem.," 1922, pp. 49–50]. For examples see the reduction of cinnamyl alcohols [Klages, *Ber.*, **39**, 2587 (1906)] and of cyclic $\beta$-bromobenzoylcrotonic ester [Lutz, THIS JOURNAL, **56**, 1378 (1934)].

(6) *Cf.* Lutz, THIS JOURNAL, **51**, 3008 (1929).

pseudocodeine. A solution of the mixed bases in a large volume of ethyl acetate was boiled down to expel water, and yielded 10 g. of dihydropseudocodeine-B. It crystallizes from dry ethyl acetate as flat truncated prisms m. p. 174.5–175.5°; from alcohol it crystallizes solvated, m. p. 125–127°. Sublimation of the solvated base in high vacuum yields a second anhydrous form, which can be recrystallized from dry benzene (long, thin scales), m. p. 196–197°; this form, crystallized from alcohol, reverts to the low-melting solvated form whose rotation in alcohol is $[\alpha]^{24}_{D}$ −14.1° ($c$ = 0.65).

*Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.71; H, 7.70. Found: (sublimed base) C, 71.42; H, 7.60.

When seed for dihydropseudocodeine-B is available, it may be separated from the more soluble tetrahydropseudocodeine III directly from the concentrated ether extract. The tetrahydropseudocodeine was best identified by conversion to the corresponding methine, which gave no melting point depression with a known sample, but depressed the melting point of dihydro-ε-methylmorphimethine-B. Tetrahydropseudocodeine of m. p. 115–120° is converted to a high-melting form (179–180°) when seeded with the high-melting form of II; we have found several similar cases in the morphine series. Prolonged reduction of II or III with sodium and alcohol is without effect.

A solution of dihydropseudocodeine-B in dilute acetic acid with platinum oxide absorbed 0.96 mole of hydrogen to give a quantitative yield of tetrahydropseudocodeine, identified as such and as the corresponding methine.

**Dihydro-ε-methylmorphimethine-B (VI).**—The methiodide obtained from 2.7 g. of dihydropseudocodeine-B was boiled for fifteen minutes in 25 cc. of water with 20 g. of potassium hydroxide. The product was isolated in the usual way as crystalline crusts from ether, and purified from ethyl acetate, yield 1.8 g. It melts at 188.5–189.5° (corr.) and shows $[\alpha]^{24}_{D}$ + 28° ($CHCl_3$, $c$ = 1.00). It depressed the melting point of tetrahydro-ε-methylmorphimethine by 15°. No crystalline salts could be obtained.

*Anal.* Calcd. for $C_{19}H_{25}O_3N$: C, 72.33; H, 7.99. Found: C, 72.34; H, 8.16.

The solid methine base does not dissolve in alkali, but when an acid solution is made alkaline the base appears at the isoelectric point and goes into solution in excess alkali, from which ammonium chloride precipitates it. It is not appreciably extracted by ether from alkaline solution, in contrast to V and to phenolic tetrahydro-ε-methylmorphimethine.

A solution of VI in ethanol with palladium–calcium carbonate absorbed 1.8 moles of hydrogen, giving a quantitative yield of hexahydro-ε-methylmorphimethine, identified by m. p. 164°, mixed m. p., and rotation $[\alpha]^{24}_{D}$ +33.6°.

**Electrolytic Reduction of Pseudocodeine.**—Four grams of pseudocodeine in dilute sulfuric acid was electrolyzed for twenty-four hours on a 60 sq. cm. lead electrode with 8 amp. at 12–15°. By the usual separation method, 0.9 g. of dihydropseudocodeine-B was isolated, m. p. 130–134°, solidifying and remelting at 166–167°, showing no depression in mixed melting point with a sample from catalytic reduction. It was further identified by conversion to the methine base (50% yield) of m. p. 185–189° (no depression in mixed melting point). The remainder of the reduction product was pseudocodeine from which, however, a small fraction giving a hydrochloride of m. p. 152–155° could be separated. This material may have been "dihydrodesoxycodeine-A."

**Dihydropseudocodeine-C (III).**—Five grams of pseudocodeine in 150 cc. of absolute alcohol, mechanically stirred and cooled in ice, was treated under nitrogen with 20 g. of sodium during three hours, 100 cc. of alcohol being added and the temperature rising to 40° toward the end. After dilution with water, alcohol was removed under diminished pressure, and the dihydrodesoxycodeines present (1.6–2.2 g.) extracted from the alkaline solution with ether. The alkaline solution was treated with hydrochloric acid and ammonia, dihydropseudocodeine-C extracted with ether, and crystallized from 60% alcohol, yield 1.8 to 2 g. The base crystallizes from ethanol as hexagonal square-ended prisms melting at 100–116° with frothing. When the solid base was seeded with isomer-B it changed rapidly to a form melting at 167.5–168° (corr.), convertible to the low-melting form by recrystallization; it is soluble from the solid state in dilute alkali. In 95% alcohol $[\alpha]^{22}_{D}$ + 13° ($c$ = 0.61).

*Anal.* Calcd. for $C_{18}H_{23}O_3N + C_2H_5OH$: $C_2H_5OH$, 13.2. Found: $C_2H_5OH$, 12.8. Calcd. for $C_{18}H_{23}O_3N$: C, 71.71; H, 7.70. Found: C, 71.67; H, 7.91. High-melting form, not dried, calcd. for $C_{18}H_{23}O_3N + C_2H_5OH$: C, 69.12; H, 8.42. Found: C, 68.97; H, 8.60.

Dihydropseudocodeine-C in ethanol with platinum oxide absorbed one mole of hydrogen to give a quantitative yield of tetrahydropseudocodeine, identified by conversion to the characteristic methine. From very vigorous reduction of dihydropseudocodeine-C with alcohol and molten sodium, 7% yield of mixed dihydrodesoxycodeines-B and -C could be obtained.

**Dihydro-ε-methylmorphimethine-C (V).**—A solution of 4.3 g. of dihydropseudocodeine-C methiodide in 40 cc. of water with 35 g. of potassium hydroxide was boiled for fifteen minutes. The product, isolated as in the case of VI, weighed 2.9 g., and was purified from ethyl acetate, m. p. 150°. It is very sensitive in alcohol solution, and yields no crystalline hydrochloride. In chloroform $[\alpha]^{23}_{D}$ + 62.5° ($c$ = 1.08).

*Anal.* Calcd. for $C_{19}H_{25}O_3N$: C, 72.33; H, 7.99. Found: C, 72.35; H, 8.06.

The methine base resembles its isomer VI in its alkali solubility, but is partly extracted by ether from an alkaline solution.

Reduction of 1.1 g. of ε-methylmorphimethine with sodium and alcohol gave 0.35 g. of starting material and 0.013 g. of dihydro-ε-methylmorphimethine-C of m. p. and mixed m. p. 149.5°. The low yield is probably due to the instability of V toward alcohol.

Dihydro-ε-methylmorphimethine-C in alcohol with palladium–calcium carbonate absorbed 1.7 moles of hydrogen, giving a nearly quantitative yield of hexahydro-ε-methylmorphimethine, identified by melting point, mixed melting point, rotation $[\alpha]^{24}_{D}$ + 30.2°, and by the characteristic low-melting hydrated acid tartrate.

**The So-called Dihydrodesoxycodeine-A.**—The combined material from ether extraction of the alkaline liquors from several sodium–alcohol reductions of pseudocodeine was converted to the hydrochloride and purified by many recrystallizations from alcohol. The salt had the m. p. 156–157° (foaming) and showed $[\alpha]_D^{28}$ −38.8°, −40.2° (water, $c$ = 1.3). The base, isolated from the salt in the usual way and crystallized from ethyl acetate, melted at 155–156° as did authentic samples of dihydrodesoxycodeine-A (m. p. 134–136°) when treated in the same way (see preceding paper). The high-melting form had the specific rotation $[\alpha]_D^{28}$ −30.6° (ethanol, $c$ = 1.1).

*Anal.* (material from pseudocodeine reduction). Calcd. for $C_{18}H_{23}O_2N$ + 0.5 $H_2O$: $H_2O$, 3.06. Found: $H_2O$, 3.09. Calcd. for $C_{18}H_{23}O_2N$: C, 75.74; H, 8.12. Found: C, 75.50; H, 8.29.

## Summary

1. The stepwise nature of catalytic hydrogenation in the case of pseudocodeine is demonstrated through the isolation of a phenolic unsaturated intermediate, dihydropseudocodeine-B.

2. Electrolytic reduction of pseudocodeine takes the same course as the primary step in the catalytic process.

3. Reduction of pseudocodeine with sodium and alcohol proceeds by a mechanism different from that of electrolytic or catalytic reduction, and results in dihydropseudocodeine-C and dihydrodesoxycodeines-B and -C.

TABLE OF DERIVATIVES

| Base | Derivative | $[\alpha]_D^{\circ}$ | $t$° | $c$ | Solv. | M. p., °C. (corr.) | Formula | Calcd. | Found | Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| II | Hydrochloride[a] | − 2.5 | 26 | 0.6 | $H_2O$ | 265–266 | $C_{18}H_{24}O_3NCl$ + $H_2O$ | C, 63.97[g] $H_2O$, 5.06 | 63.74[g] 5.09 | H, 7.16[g] | 7.25[g] |
| II | Salicylate[b] | − 7.4 | 26 | .6 | EtOH | 130–132[h] 225–226 | $C_{25}H_{29}O_6N$ | C, 68.30 | 68.34 | H, 6.65 | 6.82 |
| II | Methiodide | + 4.5 | 26 | .7 | $H_2O$ | 222–223[c] | $C_{19}H_{26}O_3NI$ + $3H_2O$ | I, 25.50 | 25.56 | $H_2O$, 10.9 | 10.1 |
| III | Hydrochloride[d] | +21 | 23 | .6 | $H_2O$ | 253 | $C_{18}H_{24}O_3NCl$ + $0.5H_2O$ | Cl, 10.23 | 10.07 | $H_2O$, 2.7 | 2.3 |
| III | Salicylate[e] | +24 | 23 | 1.0 | EtOH | 232–234 | $C_{25}H_{29}O_6N$ | C, 68.30 | 68.27 | H, 6.65 | 6.85 |
| III | Methiodide | +40.6 | 24 | 0.7 | $H_2O$ | 238–239 | $C_{19}H_{26}O_3NI$ + $H_2O$ | I, 27.50 | 27.25 | $H_2O$, 3.90 | 4.18 |
| V | Hydriodide[f] | +51 | 26 | .8 | $H_2O$ | 137–138 | $C_{19}H_{26}O_3NI$ + $H_2O$ | I, 27.50 | 27.22 | $H_2O$, 3.90 | 3.83 |

[a] Prepared in absolute alcohol with alcoholic hydrogen chloride, crystallized from alcohol or water as thin plates. [b] Prepared in ether with ethereal salicylic acid, recrystallized from absolute alcohol. [c] Melts partly at 131–132°. [d] Prepared in absolute alcohol or acetone with alcoholic hydrogen chloride, thin six-sided blades or scales; darkens at 235–240°. [e] Prepared like II salicylate, crystallizes from ethanol in rectangular plates; darkens at 210°. [f] The melting point of some apparently pure samples was 128–129°; melts with frothing. [g] Anhydrous. [h] Solvated.

In view of the small amount of material available no attempt was made to separate the substance into its components, dihydrodesoxycodeines-B and -C. It absorbed one mole of hydrogen in the presence of palladium–calcium carbonate, giving a quantitative yield of tetrahydrodesoxycodeine which was sublimed and identified by its rotation and by the m. p. 156–157° and mixed m. p. of the anhydrous form.

4. Reductions in the ϵ-methylmorphimethine series are parallel to those in the pseudocodeine series.

5. The mechanism by which the various products of pseudocodeine reduction may be formed is discussed.

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