Tetrahydro-ϵ-methylmorphimethine (Phenolic) Methyl Ether (V).—This base was prepared in quantitative yield from III-methiodide by the thallium hydroxide degradation described under base VII. It crystallizes as rectangular scales from acetone, m. p. 156.5–157° (corr.); $[\alpha]_D^{25}$ +199° (alcohol, c = 0.80).

Anal. Calcd. for $C_{20}H_{29}O_3N$: C, 72.45; H, 8.82. Found: C, 72.49; H, 8.85.

Base V took up one mole of hydrogen to give a quantitative yield of hexahydro-ϵ-methylmorphimethine methyl ether (VIII).

Hexahydro-ϵ-methylmorphimethine Methyl Ether (VIII).—Hydrogenation of ϵ-methylmorphimethine methyl ether[6] resulted in absorption of three moles of hydrogen, and formation of the same hexahydro base (VIII) as was obtained by hydrogenation of V or VII. It was purified from ethyl acetate, m. p. 138° (corr.); $[\alpha]_D^{25}$ +17.4° (alcohol, c = 0.98). No crystalline salts could be obtained.

(6) Pschorr and Dickhäuser, *Ber.*, **45**, 1567 (1912).

Anal. Calcd. for $C_{20}H_{31}O_3N$: C, 72.02; H, 9.38. Found: C, 72.02; H, 9.37.

Summary

1. Pseudocodeine methyl ether can be hydrogenated to give, according to the conditions, principally dihydropseudocodeine-A methyl ether or tetrahydropseudocodeine methyl ether. The (alcoholic) methoxyl group is not eliminated.

2. Reduction of pseudocodeine methyl ether with sodium and alcohol proceeds like the reduction of pseudocodeine and allopseudocodeine except that reductive loss of the group on carbon-8 is greatly diminished.

3. The ϵ-methylmorphimethine derivatives of the hydrogenated methyl ether series are described.

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Reduction Studies in the Morphine Series. VI. Hydrogenation of Alpha- and Beta-Isomorphines[1]

BY LYNDON SMALL AND BURT F. FARIS[2]

In the third paper of this series[3] it was shown that the hydrogenation of γ-isomorphine can be so controlled that the principal product is the normal dihydro derivative. The same dihydro-γ-isomorphine can be obtained in excellent yield by demethylation of dihydropseudocodeine-A. It has long been known that dihydrocodeine can be demethylated to dihydromorphine,[4] and this preparative method, if generally applicable, would constitute the most practicable way to the pharmacologically interesting dihydro-α- and dihydro-β-isomorphines, since the dihydrogenated isomers of codeine are more accessible than the isomers of morphine. Dihydroisocodeine can indeed be demethylated, but the product is apparently exceedingly sensitive to the agents employed (hydriodic or hydrobromic acids), and only resinous material is obtained. Dihydroallopseudocodeine resists demethylation; when the reaction is forced, tar-like substances, apparently of high molecular weight, are formed. The preparation of the desired derivatives must therefore start with the isomers of morphine.

α-Isomorphine (I) is a diastereomer of morphine, and can be obtained by hydrolysis of bromomorphide[5] but not in appreciable quantities from the hydrolysis of α-chloromorphide as claimed by Oppé.[6] As would be expected, α-isomorphine behaves like morphine in respect to catalytic hydrogenation, and yields exclusively dihydro-α-isomorphine. Methylation of this new base with diazomethane results in the known dihydroisocodeine.[7]

β-Isomorphine (II) is a minor product from the hydrolysis of either α-chloromorphide or bromomorphide. It is a diastereomer of γ-isomorphine, and therefore carries the alcoholic hydroxyl group on carbon-8, and has its unsaturation in the β,γ-position to the ether linkage at C-5. Like γ-isomorphine, pseudocodeine, and allopseudocodeine, β-isomorphine takes up two moles of hydrogen when hydrogenated in alcohol solution. The product is tetrahydro-β-isomorphine (IV), a sensitive diphenolic base. In the same reac-

(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

(2) Squibb Fellow in Alkaloid Chemistry.

(3) Small and Lutz, THIS JOURNAL, **56**, 1928 (1934).

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

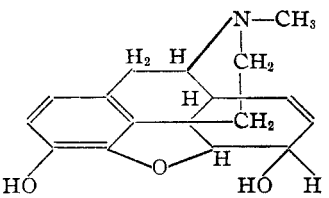
(5) Schryver and Lees, *J. Chem. Soc.*, **77**, 1024 (1900).

(6) Oppé, *Ber.*, **41**, 975 (1908).

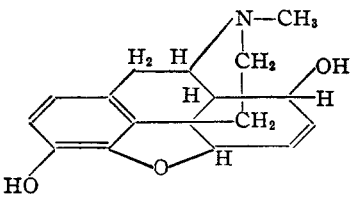
(7) Speyer and Krauss, *Ann.*, **432**, 233 (1923).

tion, a trace of tetrahydrodesoxymorphine is formed by reductive elimination of the alcoholic hydroxyl group, a process which has already been shown to operate in the hydrogenation of allopseudocodeine.[8] Tetrahydro-β-isomorphine can be converted to tetrahydroallopseudocodeine by treatment with diazomethane. The exclusive methylation of the phenolic hydroxyl group in the 3-position is in accord with our observation that the weakly phenolic 4-hydroxyl in tetrahydroallopseudocodeine is completely indifferent toward diazomethane.

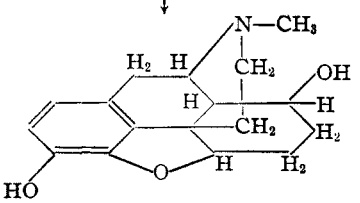
The hydrogenation of β-isomorphine hydrochloride in glacial acetic acid is complicated by the extremely low solubility of the hydrochloride in this medium, but proceeds nevertheless in the same way as the hydrogenation of other pseudocodeine types under similar conditions. Absorption stops after about one and one-third moles of hydrogen has been taken up, and the product consists of nearly equal amounts of dihydro-β-isomorphine (III) and tetrahydro-β-isomorphine.



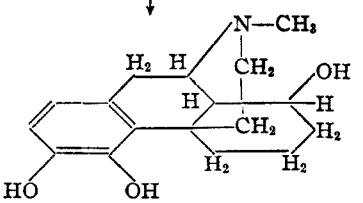
I. α-Isomorphine



II. β-Isomorphine



III. Dihydro-β-isomorphine



IV. Tetrahydro-β-isomorphine

The effect of excess acid in suppressing abnormal hydrogenation noted in an earlier publication[9] is also seen with β-isomorphine; whereas β-isomorphine hydrochloride in neutral aqueous solution takes up two moles of hydrogen and gives the tetrahydro derivative in quantitative yield, a solution of β-isomorphine in excess of dilute hydrochloric acid behaves like the above-mentioned suspension of the hydrochloride in glacial acetic acid, and yields the dihydro and tetrahydro derivatives in equal quantities.

(8) Lutz and Small, THIS JOURNAL, **56**, 2466 (1934).

(9) Lutz and Small, *ibid.*, **54**, 4719 (1932).

Dihydro-α-isomorphine and dihydro-β-isomorphine complete the series of sixteen members in the groups morphine, codeine, dihydromorphine, dihydrocodeine, and their isomers, now under pharmacological study at the University of Michigan. Their physiological action will be described in communications from that Institution.

Experimental

Dihydro-α-isomorphine.—A suspension of 5 g. of α-isomorphine (of m. p. 248° $[\alpha]_D^{23}$ −164°) in 175 cc. of alcohol with 0.2 g. of palladium–barium sulfate absorbed 450 cc. of hydrogen in five hours (calculated for one mole, 440 cc.). After removal of the catalyst the solution was concentrated to 50 cc., and dihydro-α-isomorphine separated crystalline in nearly quantitative yield. The base was purified from ethanol or ethyl acetate, very fine needles, m. p. 224–226°, $[\alpha]_D^{19}$ −125.8° (methanol, c = 1.017).

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.04; H, 7.37. Found: C, 70.85; H, 7.54.

Methylation of dihydro-α-isomorphine with diazomethane gave dihydroisocodeine of m. p. 198–199° (after sublimation in high vacuum) which did not depress the melting point of a known specimen. The relationship of α-isomorphine to isocodeine, previously demonstrated by Schryver and Lees only through the methyl ether methiodide, was likewise verified. α-Isomorphine methyl ether melts at 169–171°, and does not depress the melting point of pure isocodeine.

Dihydro-α-isomorphine hydrochloride was prepared in absolute alcohol with alcoholic hydrogen chloride. The salt separated as minute needles, insoluble in alcohol, very soluble in water, having $[\alpha]_D^{23}$ −112° (water, c = 1.021).

Anal. Calcd. for $C_{17}H_{22}O_3NCl$: Cl, 10.95. Found: Cl, 10.76.

The hydrobromide was prepared with aqueous 20% hydrobromic acid and purified from water. In aqueous solution $[\alpha]_D$ −97.9° (c = 0.986).

Anal. Calcd. for $C_{17}H_{22}O_3NBr$: Br, 21.71. Found: Br, 21.54.

The methiodide separated amorphous from an alcoholic solution of the base when methyl iodide was added, and rapidly became crystalline; yield, 90%. It was purified from water, and showed $[\alpha]_D^{23}$ −80.4° (water, c = 1.114).

Anal. Calcd. for $C_{18}H_{24}O_3NI$: I, 29.58. Found: I, 29.36.

Dihydro-α-isomorphine binoxalate was prepared with alcoholic oxalic acid and recrystallized from alcohol; in water, $[\alpha]_D^{22}$ −91.9° (c = 1.056).

Anal. Calcd. for $C_{19}H_{23}O_7N$: C, 60.45; H, 6.15. Found: C, 60.61; H, 6.24.

Tetrahydro-β-isomorphine.—Two grams of β-isomorphine (having the melting point 182° and $[\alpha]_D^{23}$ −216°) suspended in 75 cc. of ethanol was hydrogenated in the

presence of 50 mg. of platinum oxide. Two moles of hydrogen was absorbed in less than an hour, and a suspension of the tetrahydro base resulted. This base is very sensitive toward oxygen in the presence of alcohol, and was filtered out, together with the catalyst, as rapidly as possible. The crystalline base was dissolved in dilute hydrochloric acid, the catalyst removed, and the base precipitated by slow addition of sodium carbonate. Tetrahydro-β-isomorphine is sparingly soluble in ethanol, methanol or water, and turns red rapidly in these solvents; it is practically insoluble in other organic solvents. The perchlorate is the only crystalline salt, and was obtained by treating the base with 20% aqueous perchloric acid. The salt was purified from water, and has $[\alpha]_D^{19}$ −76° (water, c = 0.974).

Anal. Calcd. for $C_{17}H_{24}O_7NCl$: Cl, 9.10. Found: Cl, 9.14.

The pure perchlorate in aqueous solution with a trace of sodium hydrosulfite was treated slowly with a concentrated solution of sodium carbonate. Tetrahydro-β-isomorphine base separated crystalline and nearly white. It melts at 245–247° (decomp.) and has $[\alpha]_D^{22}$ −60.4° (10% acetic acid, c = 0.910).

Anal. Calcd. for $C_{17}H_{23}O_3N$: C, 70.54; H, 8.02. Found: C, 70.38; H, 8.20.

The preparation of the tetrahydro derivative may also be accomplished advantageously by hydrogenation of β-isomorphine hydrochloride in aqueous solution. The base precipitates in quantitative yield as pure white crystals when sodium carbonate containing a trace of sodium hydrosulfite is added to the filtered hydrogenation solution. The solid base turns red rapidly unless dried in an oxygen-free atmosphere.

Methylation of tetrahydro-β-isomorphine with diazomethane gave tetrahydroallopseudocodeine, m. p. (after vacuum sublimation) 145°, no depression in mixed melting point with a known sample.

Tetrahydrodesoxymorphine.—The mother liquors from the preparation and purification of tetrahydro-β-isomorphine perchlorate were made ammoniacal and extracted with ethyl acetate (in which tetrahydro-β-isomorphine is not detectably soluble). The residue from evaporation of the ethyl acetate yielded a crystalline salicylate of m. p. 224–227° and $[\alpha]_D^{24}$ −30.1°. The mixed melting point with an authentic sample of m. p. 236° and $[\alpha]_D$ −31° was 230–233°.

Dihydro-β-isomorphine.—Two grams of β-isomorphine hydrochloride (of $[\alpha]_D^{23}$ −200°) suspended in 75 cc. of glacial acetic acid with 50 mg. of platinum oxide absorbed no hydrogen. When the mixture was warmed to 60°, slow absorption began, and was complete in six hours; hydrogen absorbed, 200 cc.; calcd. for one mole 155 cc. Sufficient water was added to dissolve the hydrochlorides present, the catalyst removed and the solution was evaporated to dryness in vacuum at 60°. Separation of the two hydrochlorides was accomplished by triturating the residue with absolute alcohol, from which dihydro-β-isomorphine hydrochloride crystallized immediately, tetrahydro-β-isomorphine hydrochloride remaining in solution.

Hydrogenation of 2 g. of β-isomorphine hydrochloride suspended in 60 cc. of normal hydrochloric acid with 50 mg. of platinum oxide was complete after twenty minutes, absorption 1.4 moles. The mixture was warmed to dissolve the dihydro-β-isomorphine hydrochloride, freed from platinum, and worked up as described above. The yield of dihydro-β-isomorphine hydrochloride was 1.2 g. The base was precipitated crystalline from an aqueous solution of the hydrochloride on addition of sodium carbonate; some of the product remains in solution, and can be recovered by extraction with chloroform. The crude base was purified from absolute alcohol, from which it crystallized as the monohydrate, m. p. 202–203°. In methanol an anhydrous sample showed $[\alpha]_D^{22}$ −104° (c = 1.048).

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.04; H, 7.37. Found (sample dried at 100° in vacuum): C, 70.88; H, 7.33.

Dihydro-β-isomorphine in ether solution was methylated with excess of diazomethane. After twenty-four hours, the methylation solution was extracted with normal sodium hydroxide, and the ether distilled off. The oily residue on treatment with aqueous tartaric acid yielded dihydroallopseudocodeine acid tartrate of m. p. 124–125°; the salt did not depress the melting point of an authentic sample.[8]

Dihydro-β-isomorphine hydrochloride may be obtained directly from the hydrogenation of β-isomorphine described above, or by treating the purified dihydro base with alcoholic hydrogen chloride. It was analyzed without further purification. In water, $[\alpha]_D^{23}$ −98.7° (c = 1.044) was found.

Anal. Calcd. for $C_{17}H_{22}O_3NCl$: Cl, 10.95. Found: Cl, 10.99.

The hydrobromide was prepared with a slight excess of 20% aqueous hydrobromic acid and was recrystallized from water. In aqueous solution, $[\alpha]_D^{23}$ −87° (c = 1.018).

Anal. Calcd. for $C_{17}H_{22}O_3NBr$: Br, 21.71. Found: Br, 21.53.

Dihydro-β-isomorphine acid fumarate is obtained when the base is treated with excess of alcoholic fumaric acid. After recrystallization from water the salt showed $[\alpha]_D^{22}$ −81.3° (water, c = 0.842).

Anal. Calcd. for $C_{21}H_{25}O_7N$: C, 62.50; H, 6.25. Found: C, 62.46; H, 6.37.

Summary

1. α-Isomorphine adds one mole of hydrogen normally to give dihydro-α-isomorphine; the latter yields dihydroisocodeine on methylation.

2. The hydrogenation of β-isomorphine proceeds ordinarily like that of other pseudocodeine types, with addition of two moles of hydrogen. By hydrogenating under certain conditions the normal product dihydro-β-isomorphine can be obtained. Dihydro-β-isomorphine and tetrahydro-β-isomorphine give on methylation dihydroallopseudocodeine and tetrahydroallopseudocodeine, respectively.

3. Catalytic addition of hydrogen to β-isomorphine involves in small degree a reductive elimination of the alcoholic hydroxyl group.

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