than an additive effect. In other words, when the inhibitors tend to combine with different groups on the enzyme, each exerts a greater inhibition in the presence of the other than would be true if they were competing for the same group and therefore complying with the decreasing slope of the inhibition curve. The fact that divergence from a simple additive effect may begin at relatively low concentrations and then either remain constant or vary in degree with rising concentration, provides strong evidence for there being two or more reactive groups in the so-called active center (which is directly involved in competitive inhibitors).

Summary

A relatively simple procedure has been described for purifying liver esterase to twelve times the activity of a liver powder extract. The product obtained in repeated experiments had the characteristics of a typical albumin.

By checking the activity of the enzyme at different stages of purification on a number of ester-type substrates, it was shown clearly that the ethyl butyrase was entirely distinct from a lecithinase, sulfatase, tannase or phytase. Beta-glycero phosphatase and hexose diphosphatase activity followed ethyl butyrase activity up to the dialysis stage in the purification procedure, but then decreased, indicating their association with the albumin fraction, but also indicating their separate identity from the butyrase.

Inhibition studies with amyl alcohol, amyl chloride, 2-octanol, 2-octanone, phenol, hexylresorcinol, 2-octyl hydrogen phthalate, and sodium fluoride, showed that there was a characteristic tendency for the competitive inhibition type curve to undergo a gradual transition to a non-competitive inhibition type curve at higher concentrations.

With two inhibitors of similar chemical type present in equivalent amount, the inhibition exerted was a simple additive effect, but when the two inhibitors were of different chemical types, the inhibition exerted was greater than an additive effect, indicating their attachment to different groups on the enzyme, and hence offsetting the declining slope of the inhibition curve, with higher concentrations.

PITTSBURGH, PA. RECEIVED NOVEMBER 26, 1934

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, NO. 149]

Reduction Studies in the Morphine Series. V. Dihydro- and Tetrahydro-pseudocodeine Methyl Ethers[1]

BY LYNDON SMALL AND ROBERT E. LUTZ

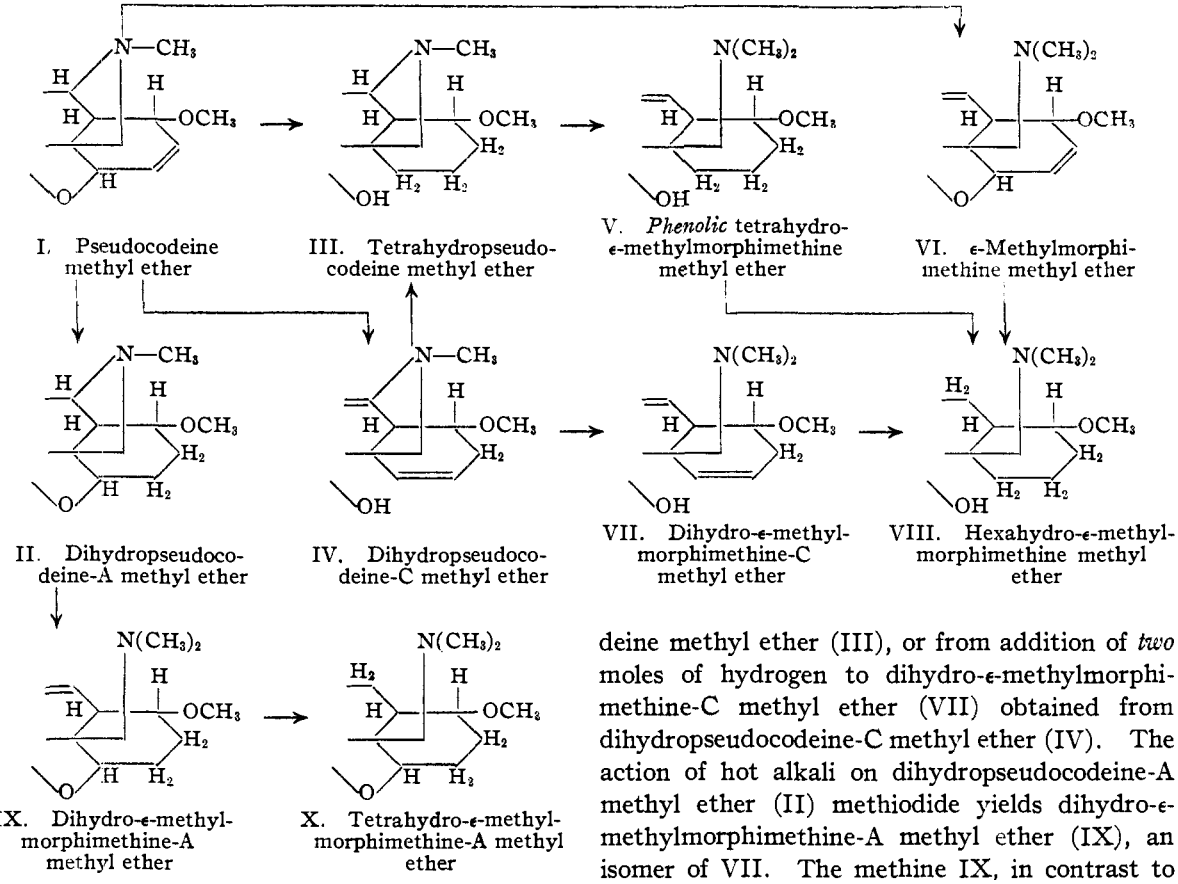
In the previous papers of this series[2] we have shown that reduction of pseudocodeine types may result in at least seven different products, namely, the dihydro isomers -A, -B, and -C, the tetrahydro derivative, dihydrodesoxycodeines-B and -C, and tetrahydrodesoxycodeine. The relative amounts of these compounds formed depend upon the reduction conditions, and to some extent upon the pseudocodeine analog selected. The direct reductive elimination of the alcoholic hydroxyl group by which the desoxycodeine derivatives are formed is a new type of reaction in the morphine series, and reduction experiments have been extended to the methyl ether series to determine whether a methoxyl group can be similarly removed. Pseudocodeine methyl ether was selected for this purpose because of its relative accessibility and because its reduction should lead to new derivatives for study of the interesting physiological effects associated with the covering of the alcoholic hydroxyl group in the morphine and codeine series.[3]

In respect to catalytic hydrogenation, pseudocodeine methyl ether (I) behaves like pseudocodeine, yielding principally either dihydropseudocodeine-A methyl ether (II) or tetrahydropseudocodeine methyl ether (III) by the different methods of hydrogenation previously described. As in the case of pseudocodeine, no tetrahydro desoxycodeine was found; in contrast to allo

(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) THIS JOURNAL, (a) **54**, 4715 (1932); (b) **56**, 1741, (c) **56**, 1928, (d) **56**, 2466 (1934).

(3) N. B. Eddy and co-workers, University of Michigan, unpublished results.



pseudocodeine[2d] (and β-isomorphine), compounds with the pseudocodeine configuration show no detectable tendency to lose the group at C-8 with catalytic hydrogen.

Reduction of pseudocodeine methyl ether with sodium and alcohol gives the phenolic dihydropseudocodeine-C methyl ether (IV) in nearly quantitative yield, and only a trace of the dihydrodesoxycodeines. That phase of the reduction which involves the simultaneous scission of the oxygen–carbon linkages at C-5 and C-8 in pseudocodeine and allopseudocodeine is almost entirely suppressed in the case of pseudocodeine methyl ether.

Pseudocodeine methyl ether methiodide is converted by hot alkali into ϵ-methylmorphimethine methyl ether (VI). This compound adds three moles of hydrogen by the catalytic methods, to yield hexahydro-ϵ-methylmorphimethine methyl ether (VIII). The same end-product (VIII) results from the addition of *one* mole of hydrogen to the phenolic tetrahydro-ϵ-methylmorphimethine methyl ether (V) obtained by partial degradation of tetrahydropseudocodeine methyl ether (III), or from addition of *two* moles of hydrogen to dihydro-ϵ-methylmorphimethine-C methyl ether (VII) obtained from dihydropseudocodeine-C methyl ether (IV). The action of hot alkali on dihydropseudocodeine-A methyl ether (II) methiodide yields dihydro-ϵ-methylmorphimethine-A methyl ether (IX), an isomer of VII. The methine IX, in contrast to VII, will add only one mole of hydrogen, giving as end-product a non-phenolic tetrahydro-ϵ-methylmorphimethine methyl ether (X) which is isomeric with V.

Experimental

Reduction of Pseudocodeine Methyl Ether.—Pseudocodeine methyl ether was prepared from α-chlorocodide and methanol by a modification of Knorr and Hartmann's[4] procedure. Like pseudocodeine, it proved to be unaffected by prolonged boiling with zinc dust in alcohol.

A suspension of 5 g. of pseudocodeine methyl ether hydrochloride in 50 cc. of glacial acetic acid with 60 mg. of platinum oxide absorbed 374 cc. of hydrogen (1.1 moles). The excess of acetic acid was removed from the filtered solution under diminished pressure, and an excess of 25% sodium hydroxide was added. The amorphous precipitate consisted of nearly pure dihydropseudocodeine-A methyl ether, yield 3.7 g. (77%). From the alkaline filtrate 0.7 g. (15% yield) of tetrahydropseudocodeine methyl ether was isolated in the way usual for phenolic bases.

Hydrogenation of 8 g. of pseudocodeine methyl ether hydrochloride in 40 cc. of water with 0.7 g. of palladium–barium sulfate gave 4.5 g. of the dihydro and 3 g. of the tetrahydro derivative. From hydrogenation of pseudocodeine methyl ether base in 10% acetic acid principa tetrahydro derivative was obtained.

(4) Knorr and Hartmann, *Ber.*, **45**, 1354 (1912).

Dihydropseudocodeine-A methyl ether (II) crystallizes from ethyl acetate–ligroin mixture as short thick prisms, or from dilute alcohol as square plates. It has the melting point 127° (corr.), and shows in ethanol $[\alpha]_D^{25}$ +35° (c = 1.37).

Anal. Calcd. for $C_{19}H_{25}O_3N$: C, 72.33; H, 7.99. Found: C, 72.01; H, 8.01.

The only crystalline salt obtainable was the perchlorate; six-sided plates or prisms from water; m. p. 243–244° (corr., decomp.); $[\alpha]_D^{27}$ −6.5° (water, c = 0.53).

Anal. Calcd. for $C_{19}H_{26}O_7NCl$: Cl, 8.56. Found: Cl, 8.73.

Dihydro-ε-methylmorphimethine-A Methyl Ether (IX).—The amorphous methiodide from 5 g. of dihydropseudocodeine-A methyl ether was degraded in the usual way with 25% sodium hydroxide. The oily precipitate was extracted into ether and yielded 4.5 g. of the methine base. It crystallizes as six-sided plates or thin needles from 40% alcohol; m. p. 102.5° (corr.); $[\alpha]_D^{27}$ +202° (ethanol, c = 0.95).

Anal. Calcd. for $C_{20}H_{27}O_3N$: C, 72.90; H, 8.26. Found: C, 72.84; H, 8.15.

IX-Hydrochloride crystallizes from absolute ethanol, m. p. 219–220°, $[\alpha]_D^{27}$ +157° (water, c = 0.60).

Anal. Calcd. for $C_{20}H_{28}O_3NCl + H_2O$: H_2O, 4.7. Found: H_2O, 3.6. Calcd. for $C_{20}H_{28}O_3NCl$: Cl, 9.70. Found (dried at 120°): Cl, 9.73.

IX-Perchlorate is sparingly soluble in water and forms thick crystals melting at 85–87°, solidifying and remelting at 155–156° (corr.); $[\alpha]_D^{27}$ +136° (water, c = 0.86).

Anal. Calcd. for $C_{20}H_{28}O_7NCl + H_2O$: H_2O, 4.0. Found: H_2O, 3.6. Calcd. for $C_{20}H_{28}O_7NCl$: Cl, 8.28. Found (dried at 120°): Cl, 8.23.

Tetrahydro-ε-methylmorphimethine-A Methyl Ether (X).—Hydrogenation of 2 g. of IX in 15 cc. of 7.5% acetic acid with 20 mg. of platinum oxide resulted in absorption of 1 mole of hydrogen. Two grams of crystalline product was obtained; purified from 50% alcohol it formed six-sided plates of m. p. 98.5°, $[\alpha]_D^{27}$ +54° (alcohol, c = 0.70).

Anal. Calcd. for $C_{20}H_{29}O_3N$: C, 72.45; H, 8.82. Found: C, 72.37; H, 8.87.

X-Hydrochloride crystallizes from alcohol as thin square-ended needles of m. p. 251–252° (corr., decomp.), $[\alpha]_D^{27}$ +42° (water, c = 0.62).

Anal. Calcd. for $C_{20}H_{30}O_3NCl$: Cl, 9.64. Found: Cl, 9.37.

Dihydropseudocodeine-C Methyl Ether (Phenolic, IV).—Five grams of pseudocodeine methyl ether was reduced in absolute alcohol with 25 g. of sodium as described in the preparation of dihydropseudocodeine-C.[2b] The reaction mixture was diluted with water, and alcohol removed under diminished pressure. Excess of acid, then excess of ammonia, were added, and the product extracted into ether. The base is liquid and was converted to the hydriodide; yield, 6.5 g. or 92%. The base regenerated from the pure hydriodide was distilled in high vacuum for analysis.

Anal. Calcd. for $C_{19}H_{25}O_3N$: C, 72.33; H, 7.99. Found: C, 71.95; H, 7.95.

IV-Hydriodide crystallizes from water as short prisms of m. p. 161–162° (corr., decomp.); $[\alpha]_D^{27}$ +48° (water, c = 0.48).

Anal. Calcd. for $C_{19}H_{26}O_3NI$: C, 51.45; H, 5.91. Found: C, 51.20; H, 6.04.

The mother liquors from the hydriodide preparation yielded 0.2 g. of the characteristic mixture of dihydrodesoxycodeines-B and -C, identified through the mixed hydrochloride and the methine of m. p. 174° as previously described.[5]

IV-perchlorate crystallizes from water in boat-shaped Plates of m. p. 252–255° (corr., decomp.); $[\alpha]_D^{27}$ +38.7° (water, c = 0.74).

Anal. Calcd. for $C_{19}H_{26}O_7NCl$: Cl, 8.56. Found (dried at 120°): Cl, 8.91.

IV-Methiodide crystallizes as rectangular scales from methanol or water, m. p. 230–232° (corr., decomp.); $[\alpha]_D^{30}$ + 43° (water, c = 0.78).

Anal. Calcd. for $C_{20}H_{28}O_3NI + 0.5\ H_2O$: H_2O, 1.9. Found: H_2O, 1.8. Calcd. for $C_{20}H_{28}O_3NI$: I, 27.8. Found: I, 27.9.

Dihydro-ε-methylmorphimethine-C Methyl Ether (VII).—An aqueous solution of 4 g. of IV-methiodide was treated with the calculated amount of thallous hydroxide and evaporated to dryness after removal of thallous iodide. The residue was heated to 180° for thirty minutes, and was crystallized from ethyl acetate–ligroin, yield 1.6 g. Purified from acetone, the base had the m. p. 140–140.5° (corr.); $[\alpha]_D^{25}$ +138.5° (alcohol, c = 0.98).

Anal. Calcd. for $C_{20}H_{27}O_3N$: C, 72.90; H, 8.26. Found: C, 73.06; H, 8.21.

The base VII absorbed two moles of hydrogen in 10% acetic acid with platinum oxide yielding hexahydro-ε-methylmorphimethine methyl ether (VIII).

Tetrahydropseudocodeine Methyl Ether (III).—This phenolic base was isolated from hydrogenations of pseudocodeine methyl ether as described under the preparation of II, or more advantageously by hydrogenation of IV. A solution of 4.8 g. of dihydropseudocodeine-C methyl ether in 6 cc. of 5% acetic acid with 20 mg. of platinum oxide absorbed one mole of hydrogen and yielded 4.6 g. of crystalline tetrahydro derivative. The hydrated base crystallizes from 60% alcohol as thin scales of m. p. 125–130°; $[\alpha]_D^{30}$ −5° (alcohol, c = 0.59). It dissolves in alkali and is reprecipitated by ammonium chloride; ether extracts it partly from the alkaline solution.

Anal. Calcd. for $C_{19}H_{27}O_3N + 0.5\ H_2O$: H_2O, 2.76. Found: H_2O, 2.73. Calcd. for $C_{19}H_{27}O_3N$: C, 71.88; H, 8.57. Found: C, 71.64; H, 8.47.

III-Hydriodide is sparingly soluble in water, and crystallizes as six-sided needles, m. p. 251–252° (corr., decomp.); $[\alpha]_D^{27}$ +6° (water, c = 0.49).

Anal. Calcd. for $C_{19}H_{28}O_3NI + 0.5\ H_2O$: H_2O, 1.98. Found: H_2O, 2.02. Calcd. for $C_{19}H_{28}O_3NI$: I, 28.5. Found: I, 28.3.

III-Methiodide crystallizes from water, m. p. 250–255° (corr., decomp.); $[\alpha]_D^{27}$ +25.5° (water, c = 0.59).

Anal. Calcd. for $C_{20}H_{30}O_3NI$: I, 27.6. Found: I, 27.2.

(5) Small and Lutz, THIS JOURNAL, **56**, 1738 (1934).

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).