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THE REDUCTION OF THEBAINE. NEOPINE METHYL ETHER

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In a brief investigation of the hydrogenation of thebaine, Small, Fitch, and Smith (1) announced the intention of examining the products other than the well-known di- and tetra-hydrothebaines and dihydrothebainone. The opportunity to do this was presented in 1947, in the large-scale hydrogenation of thebaine involved in the commercial production of metopon (methyldihydromorphinone). This communication deals with the concentrated extract from the reduction of 89 kg. of thebaine, after removal of dihydrothebaine and before precipitation of dihydrothebainone with ammonium chloride. This extract was made available through the courtesy of Merck and Co., Rahway, N. J.

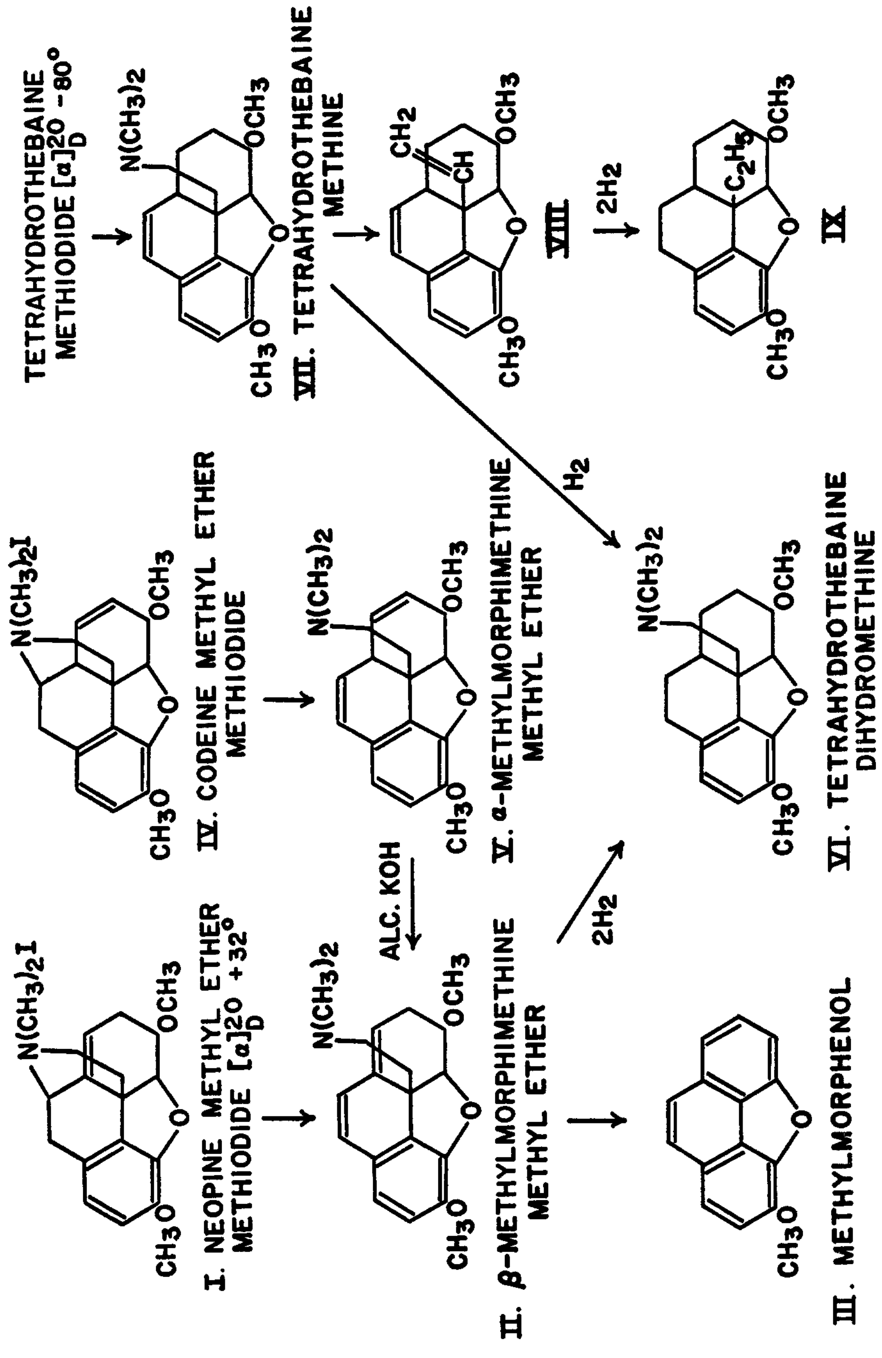
The entire alkaloidal content was first removed from the viscous dark ethereal concentrate with dilute hydrochloric acid, from which the major portion of the tetrahydrothebaine rapidly crystallized as the hydrochloride trihydrate. From the basified mother liquors there was obtained by vacuum distillation a colorless resin which was shown to consist of approximately 40% tetrahydrothebaine, and 60% of the new derivative, neopine methyl ether. These were separated readily through the methiodides, and from optical rotatory data, it appears that neopine methyl ether constitutes roughly 1% of the total reduction products.

Since analytical data do not distinguish sharply the difference of two hydrogen atoms in a compound of such molecular weight as the methiodide, the new product was at first suspected to be an isomer of tetrahydrothebaine, formed by reduction of the enol methyl ether group of thebaine in the other possible (unnatural) configuration at C-6. This possibility was eliminated through preparation of dihydroisocodeine methyl ether, by reduction of α-isomorphine-6-methyl ether (2), methylation with diazomethane, and conversion to a different, strongly *levorotatory* methiodide.

The key to the structure of the new methiodide (I) was found in the first stage of the Hofmann degradation, whereby the methiodide of specific rotation $+32°$ was converted to a methine base of rotation $+433°$, which is comparable to the change of neopine methiodide, $+23°$ to β-methylmorphimethine, $+414°$ (3). The validity of this deduction was shown by comparison with β-methylmorphimethine methyl ether (II), prepared by the method of Pschorr (4) from codeine methyl ether methiodide (IV) $\rightarrow$ α-methylmorphimethine methyl ether (V) $\rightarrow$ β-methylmorphimethine methyl ether.

The "neopine methyl ether methine" was converted by hydrogenation (2 moles) to the hitherto uncharacterized tetrahydrothebaine dihydromethine (VI) (5, 6) (tetrahydromethylmorphimethine methyl ether), or by completion of the degradation, to methylmorphenol (III).

Even after the nature of the new component from thebaine reduction seemed certain, its isolation was long delayed. Attempts to convert neopine methyl



I. NEOPINE METHYL ETHER METHIODIDE $[\alpha]^{20}_{D}$ +32°

IV. CODEINE METHYL ETHER METHIODIDE

VII. TETRAHYDROTHEBAINE METHINE

II. β-METHYLMORPHIMETHINE METHYL ETHER

V. α-METHYLMORPHIMETHINE METHYL ETHER

VIII

III. METHYLMORPHENOL

VI. TETRAHYDROTHEBAINE DIHYDROMETHINE

IX

FIGURE 1.

ether methiodide back to the tertiary base by the usual (methochloride) method failed, as did the methylation of the 6-hydroxyl of neopine by the method of Mannich (7), which works so well in the series having the 7,8-double bond (2). Separation by salts during eight years of occasional trials resulted in a crystalline picrate mixture of which neopine methyl ether picrate was the more soluble component. From the end fractions the pure crystalline base of m.p. 82° was obtained in poor yield.

The appearance of neopine methyl ether in the hydrogenation of thebaine presents a new aspect of a reaction which has already been the subject of considerable speculation [Wieland (8), Schöpf (9), Small (10), Stork (11, 12)]. All mechanisms offered have neglected the possibility of a primary saturation of the 6,7-double bond alone, principally because of the known indifference of the enol ether, Δ^6-dihydrothebaine, to further catalytic reduction. In the present instance, it seems evident that the 8,14-double bond of thebaine activates the 6,7-enol ether bond enough to cause some reduction, perhaps much more than that represented by the neopine derivative isolated. Since the 8,14-unsaturation of the neopine series is reduced about as rapidly (3, 13) as the 7,8-bond of the codeine type (possible intermediate), or the conjugated system of thebaine, it is probable that considerable of the initially formed neopine methyl ether had been reduced to tetrahydrothebaine before the hydrogenation was interrupted.

Although neopine is a normal constituent of opium in small amount (13), the existence of neopine methyl ether as an unrecognized impurity of commercial thebaine does not seem possible. If present in opium, it should, like neopine, appear in the codeine fraction; its physical properties, and its failure to form a crystalline bitartrate (commercial thebaine isolation), preclude its presence in thebaine.

EXPERIMENTAL

Isolation of neopine methyl ether methiodide (I). The material utilized consisted of the concentrate of 304 liters of ether extract obtained from the hydrogenation solution of 89 kg. of thebaine, after removal of dihydrothebaine with alkali, and before precipitation of the by-product dihydrothebainone with ammonium chloride. The hydrogenation and work-up had been carried out essentially as described by Small, Fitch, and Smith (1), excepting that hydrogenation was interrupted at the point where a sensitive color-test showed no more thebaine present. The nature of this test is property of the manufacturer.

The ether concentrate (20 kg.) was extracted with successive portions of 3 *N* HCl until an acidic extract resulted; the fractions were combined, and brought to Congo acidity with 3 *N* HCl. Slow cooling to 0° resulted in 7.3 kg. of tetrahydrothebaine hydrochloride trihydrate, faintly brown crystals. This was best purified from acetone containing 10% water (Schöpf, 14), m.p. 114–116° (gas). Liberation of the base and recrystallization from U.S.P. ether gave tetrahydrothebaine of m.p. 82.5–83°.

The acidic liquors from above were made ammoniacal and extracted with ether, which yielded a black, viscous tar. After de-gassing in a vacuum, this was distilled from a stirred pot-still at bath-t. 125–150°, 0.02 mm. About 90% of it came over as a colorless sirup, yield 1.5 kg. From this no crystalline salts with acids could be obtained, excepting a picrate, which is discussed below. Fractional extraction, and adsorption on alumina were also unsuccessful. The methiodide was obtained in practically quantitative yield by warming the components in methanol, m.p. crude, in vac., 196–210°; $[\alpha]_D^{20}$ −11.9° methanol, *c*, 1.9. From the final rotatory values of tetrahydrothebaine methiodide −80°, and of neopine methyl ether methiodide +32°, it may be assumed that the mixture contains these in the proportion of 39:61 respectively. From this it may be estimated that there is an approximate yield of one per cent neopine methyl ether from the hydrogenation of thebaine.

The separation of the mixed methiodides was achieved through their different solubilities in methanol. Five crystallizations brought the less-soluble fraction to the constant value $[\alpha]_D^{20}$ +32°, while the more-soluble fractions approached the end value $[\alpha]_D^{20}$ −80° for tetrahydrothebaine methiodide. From 95 g. of crude mixed methiodides, 35 g. of pure neopine methyl ether methiodide was obtained, without recovery from the more soluble fractions. The new methiodide had the m.p. 234° (vac.) and $[\alpha]_D^{20}$ +32° (methanol, *c*, 2.0).

Anal. Calc'd for $C_{20}H_{26}INO_3$ (455.3): C, 52.7; H, 5.76.

Found: C, 52.5; H, 5.93.

Neopine methyl ether methine. (*β-Methylmorphimethine methyl ether*) (II). A suspension of 20 g. of neopine methyl ether methiodide [of $(\alpha)_D^{20}$ +32°] in 100 ml. of 30% NaOH with 100 ml. of alcohol was boiled vigorously (mech. stirring) until the alcohol was gone (*ca.* 15 min.), then for 20 min. longer. The pale yellow oil, extracted into ether, washed with alkali and water, and dried with sodium sulfate, yielded faintly tan crystals. These were sublimed in a vacuum between 80–100° bath-t., giving 13.1 g. of glassy crystals (91%); m.p. 81–82°, also when mixed with β-methylmorphimethine methyl ether. In absol. alcohol, $[\alpha]_D^{20}$ +443° (*c*, 2.0).

Anal. Calc'd for $C_{20}H_{25}NO_3$ (327.4): OCH_3, 18.9. Found: OCH_3, 18.9.

The *hydrochloride* was prepared with alcoholic HCl and absol. ether. It had the m.p. 199–200° (vac.) and showed in methanol $[\alpha]_D^{20}$ +354° (*c*, 2.0); in water, $[\alpha]_D^{20}$ +352° (*c*, 2.0).

Anal. Calc'd for $C_{20}H_{26}ClNO_3$ (363.8): Cl, 9.7. Found: Cl, 9.8.

The *methiodide* was prepared in methanol and purified from water, glassy square ended prisms; unmelted at 250°. Aniline (n_D^{20} 1.5855) was the only practicable organic solvent found for rotation: $[\alpha]_D^{20}$ +326° (*c*, 1.0).

Anal. Calc'd for $C_{21}H_{28}INO_3$ (469.3): C, 53.7; H, 6.01.

Found: C, 53.8; H, 6.05.

Degradation of II to methylmorphenol. A suspension of 2 g. of neopine methyl ether methine methiodide in 25 ml. of water was shaken for 3 hours with the fresh oxide from 2.2 g. of silver nitrate and separated by centrifugation. The pale yellow liquid (which gives a crystalline methonitrate with dil. HNO_3) was evaporated to dryness *in vacuo* on steam [trimethylamine evolution, *cf.* Mosettig and Meitzner (15)], and sublimed at 85–100° at 0.1 mm. The sublimate, in ether, was washed with dil. HCl and resublimed at 75–80°. Yield 1 g., m.p. 65°, in mixture with authentic methylmorphenol the same.

Anal. Calc'd for $C_{15}H_{10}O_2$ (222.2): C, 81.1; H, 4.53.

Found: C, 81.3; H, 4.65.

Neopine methyl ether tetrahydromethine, prepared from the methine (II) plus two moles of hydrogen (methanol, platinum oxide) was purified like tetrahydrothebaine dihydromethine (see below), m.p. 45–46°, no depression in mixture; $[\alpha]_D^{20}$ −51° (alc., *c*, 2.1).

β-Methylmorphimethine methyl ether. This was prepared essentially as described by Pschorr (4), by degradation of codeine methyl ether and rearrangement of α-methylmorphimethine methyl ether. It was best purified by vacuum sublimation; over-all yield, 77%. It had the m.p. 81–82°, and $[\alpha]_D^{20}$ +443° (absol. alc., *c*, 2.0). Pschorr gives $[\alpha]_D^{27}$ +432°.

Attempted regeneration of neopine methyl ether. Neopine methyl ether methiodide was converted to the methochloride with silver chloride in aqueous suspension; by evaporation, the methochloride was obtained as soft white crystals, purified from methanol by addition of ether or acetone, thick, glassy prisms, $[\alpha]_D^{20}$ +39.6° (methanol, *c*, 2.2). In the oil-pump vacuum it was unaffected at 200°, with a free flame (*in vacuo*) it distilled amorphous but unchanged. Its hygroscopic nature made analysis difficult.

Anal. Calc'd for $C_{20}H_{28}ClNO_3$ (365.9): Cl, 9.7. Found: Cl, 9.3.

Neopine methyl ether. Separation through the picrate. Initial experiments on separation of the reduction mixture of tetrahydrothebaine and neopine methyl ether through salts were fruitless, but after eight years of intermittent trials it was found that an inefficient separation of the components was possible through the picrates. Tetrahydrothebaine picrate (14) is much less soluble in alcohol than neopine methyl ether picrate, and in such a separation all the incidental impurities accumulate in the desired fractions.

A solution of 0.1 mole (31.5 g.) of the crude mixed resinous bases in 100 ml. of boiling alcohol was treated with 0.1 mole +10% of picric acid in 200 ml. of boiling alcohol. The resulting crystalline precipitate was principally that of tetrahydrothebaine picrate. Imposed on this in 24 hrs. was a brittle resinous mass which was separated mechanically, and consisted mainly of neopine methyl ether picrate. By five fractional crystallizations from alcohol, in each of which the less-soluble portion was discarded, an end-fraction of picrate of constant m.p. 179–180° (decomp.) was obtained; yield about 10% of that calculated from the methiodide data. The picrate was treated with N NaOH and absol. ether, and the product was distilled at the oil-pump, bath-t. 150°, giving a sparkling viscous liquid of n_D^{20} 1.5832 and $[\alpha]_D^{20}$ $-18°$ (alcohol). This still contained traces of tetrahydrothebaine. On long standing in 30° petroleum ether it gave soft white crystals of m.p. 82–83°; a mixture with tetrahydrothebaine (m.p. 82.5–83°) melted at 59–64°. The specific rotation in alcohol was $[\alpha]_D^{20}$ 0.0° ± 0.1°; in 0.1 N HCl, $[\alpha]_D^{20}$ +19° (c, 1.0). The compound is extremely soluble excepting in petroleum ether, moderately soluble in water.

Anal. Calc'd for $C_{19}H_{23}NO_3$ (313.4): C, 72.8; H, 7.40; OCH_3, 19.8.

Found: C, 72.7; H, 7.52; OCH_3, 19.7.

Dihydroisocodeine methyl ether. For the preparation of this derivative, α-isomorphine-6-methyl ether was available from a previous investigation (2). A solution of 2.9 g. of this compound in 40 ml. of 0.25 N HCl with platinum oxide absorbed one mole of hydrogen in 60 min. The product was precipitated crystalline with dil. ammonia, 2.8 g., m.p. 204–205°, and was methylated with excess diazomethane in abs. ether-methanol, 2.7 g., diazosulfanilic acid test negative. The product was purified from methanol and sublimed at the oil-pump, bath-t. 110°, 1.9 g., m.p. 126° $[\alpha]_D^{20}$ $-111.7°$ (methanol, c, 1.2).

Anal. Calc'd for $C_{19}H_{25}NO_3$ (315.4): C, 72.3; H, 7.99; OCH_3, 19.6.

Found: C, 72.2; H, 7.87; OCH_3, 19.7.

The *methiodide* was prepared in warm acetone, and purified from methanol. It had the m.p. 253–254° (gas-evol., evac. tube) and $[\alpha]_D^{20}$ $-71.2°$ (methanol, c, 2.0).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.8. Found: I, 28.3.

DEGRADATION OF TETRAHYDROTHEBAINE

Tetrahydrothebaine methiodide. Tetrahydrothebaine (50 g.) in 300 ml. of acetone was treated slowly with a solution of 30 g. of methyl iodide in 50 ml. of acetone. The methiodide which crystallized out was pure white, and remained so for eight years, in contrast to that prepared in methanol and precipitated with peroxide-free ether; yield quantitative. In four crystallizations from methanol-acetone, only the slight change from $[\alpha]_D^{20}$ $-79.8°$ to $-80.0°$ (methanol, c, 1.6) was observed.

Tetrahydrothebaine methine (VII). Tetrahydrothebaine methiodide was entirely unaffected by long boiling with 30% aqueous sodium hydroxide; with 6% alcoholic sodium ethoxide, a poor yield of highly colored product was obtained. Twelve grams of the methiodide were suspended in a mixture of 50 ml. of alcohol and 50 ml. of 30% sodium hydroxide, and with vigorous mechanical stirring, boiled until the alcohol was removed (15 min.), and an additional 15 min. The colorless oil was extracted with ether, which left a rapidly crystallizing residue, 8 g. (95%). It was recrystallized twice between 60° and $-10°$ from 85–100° ligroin, 6.5 g., m.p. 53°. It sublimed in a high vacuum at bath-t. 65°, m.p. 53.5–54°; $[\alpha]_D^{20}$ +50.9° (methanol, c, 2.0). It did not form a crystaline hydrochloride with aqueous or alcoholic HCl.

Anal. Calc'd for $C_{20}H_{27}NO_3$ (329.4): C, 72.9; H, 8.26.

Found: C, 73.2; H, 7.96.

6-Methoxy-13-vinylhexahydromethylmorphenol ($\Delta^{9,10}$) (6). (VIII). Tetrahydrothebaine methine methiodide was obtained in 98% yield from methanol. It evolved no trimethylamine with boiling 30% NaOH, or with alcoholic alkali. A suspension of 14 g. of the methiodide in 75 ml. of water with the fresh oxide from 8 g. of silver nitrate was shaken for 2 hours. The centrifuged liquid gave no test for iodide ion. Evaporation in a vacuum at 40° gave a white crystalline cake, which was heated in a pot-still at 90° (aspirator vacuum), and gave off trimethylamine copiously up to 120°. At 135° (bath-t., oil-pump) a clear colorless product distilled rapidly, 7.4 g. This was dissolved in benzene, and washed with 0.5 *N* HCl to a negative Mayer's test, and redistilled; yield 6.0 g. (70%), n_D^{20} 1.5890, n_D^{27} 1.5860, $[\alpha]_D^{20}$ +63.4° (alcohol, *c*, 2.3). Literature values are n_D^{27} 1.5861, $[\alpha]_D^{20}$ +61.0° for the compound obtained as a result of methyl migration in the degradation of dihydromethylmorphimethine (ref. 6, cpd. VIII).

6-Methoxy-13-ethyloctahydromethylmorphenol (IX) was formed in quantitative yield by hydrogenation (2 moles) of the liquid N-free product from degradation of tetrahydrothebaine methine, in methanol with platinum oxide. It was purified by high-vacuum sublimation, bath-t. 75–80°, long white needles, m.p. 52.5–53.5°; mixture melting point with a sample supplied by H. Rapoport, (ref. 6, cpd XII) the same.

Tetrahydrothebaine dihydromethine (VI). (Tetrahydromethylmorphimethine methyl ether). This compound was prepared by Faltis (5) and by Rapoport (6), but not characterized. Reduction of tetrahydrothebaine methine in methanol with platinum oxide gave a resin which crystallized on seeding with neopine methyl ether tetrahydromethine. It was purified from 60° ligroin between 20° and −10°, and was sublimed in a vacuum at bath-t. 85°; m.p. 45–46°, yield 80%; $[\alpha]_D^{20}$ −51° (alc., *c*, 2.2).

Anal. Calc'd for $C_{20}H_{29}NO_3$ (331.4). C, 72.5; H, 8.82.
Found: C, 72.7; H, 8.83.

SUMMARY

Investigation of the by-products of the commercial hydrogenation of thebaine shows the presence of about one per cent neopine methyl ether, evidently formed by a primary reduction of the enol ether double bond of thebaine.

The degradation of tetrahydrothebaine to nitrogen-free products is described.

BETHESDA 14, MD.

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