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STRUCTURE STUDIES IN THE MORPHINE SERIES. DEGRADATION OF DIHYDROTHEBAINE TO A DIMETHOXYTRIALKYLTETRAHYDRONAPHTHALENE[1]

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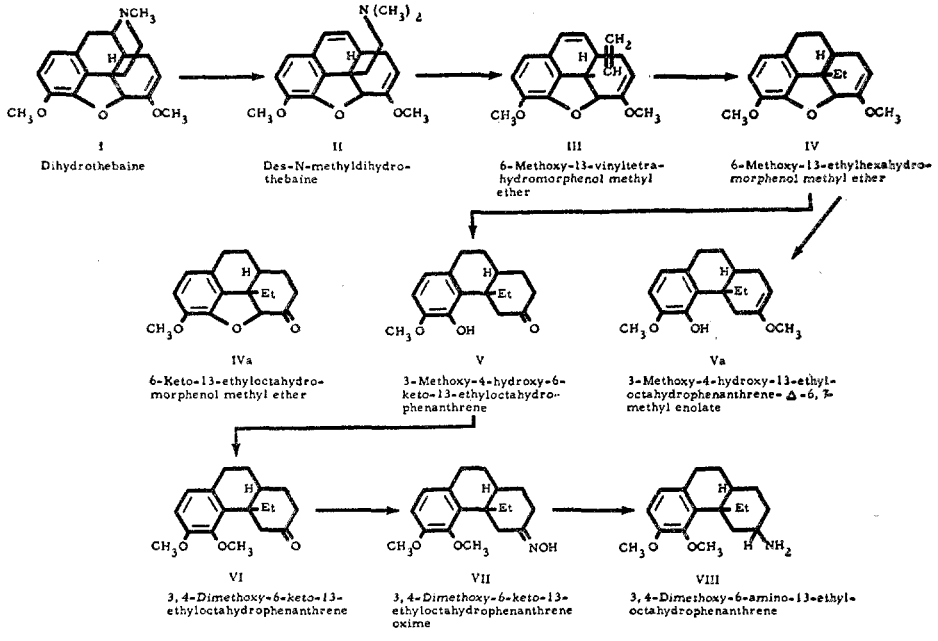
The first known nuclear-alkylated morphine derivatives, methyldihydrocodeinone and methyldihydromorphinone (Metopon) were prepared some 15 years ago (1) but in spite of the fact that the latter has been for several years in limited commercial production, there is still no definite evidence concerning the location of the new methyl group. Any attempt to ascertain this through the usual degradative procedure to a dimethoxy-x-methylphenanthrene must inevitably pass through a nuclear methyl derivative of the type of 3-methoxy-4-hydroxy-6-keto-13-ethyloctahydrophenanthrene (2) (V), with subsequent transformation to a completely aromatic system. Because of the probability of rearrangement or loss of methoxyl or alkyl groups in this process (3), it cannot come in consideration for the problem presented. On the other hand, suitable opening of ring 3 in a derivative such as VI (parent series) would lead to a substituted tetrahydronaphthalene derivative amenable to unequivocal synthesis. This could at the same time serve as final proof of the point of attachment of



[1] Presented at the American Chemical Society meeting in Chicago, Illinois, in September, 1950, and the 2nd Summer Seminar on the chemistry of Natural Products, University of New Brunswick, Fredericton, N.B., August 25, 1950.

the ethanamine chain [*cf.* synthetic evidence of Grewe, Gates, Horning, and others (4)].

The nuclear-alkylated morphine types are obtained in laborious ways, and a model experiment was essential before risking these rare compounds. Since methyldihydrocodeinone can be converted to the 6-methyl enolate (metho-methylsulfate) with potassium *tert*-butoxide and methyl sulfate,[2] *i.e.*, to a nuclear-methylated dihydrothebaine, the readily accessible dihydrothebaine (I) was chosen as the model. This fulfills two important requirements: (a) the ether bridge must be kept closed until the vinyl group at C-13 is saturated, else cyclization to a stable cyclic ether takes place with the oxygen function at C-4; this tendency is so strong as to split a 4-methoxyl group (5); (b) an activating group, such as carbonyl or double bond must be present at C-6 to permit subsequent facile opening of the ether bridge (IV → V or Va). [Dihydrocodeinone meets these requirements, but gives poor yields of heterogeneous material on degradation (5)].

The degradation of dihydrothebaine (I) methiodide proceeded smoothly to des-N-methyldihydrothebaine (II) (6). The second step, elimination of nitrogen, to 6-methoxy-13-vinyltetrahydromorphenol methyl ether (III), which had heretofore given difficulty (2, 6), was accomplished by high-vacuum dry-distillation of II-methohydroxide, in 60% yield (without regard to appreciable recovery of II).

Hydrogenation of two double bonds went cleanly (III → IV) with Pd-$CaCO_3$, whereas with Pd-Norit concomitant partial hydrolysis of the 6-methyl enolate invariably occurred. This was found to result from traces of acid stubbornly retained by even the best-washed catalyst.

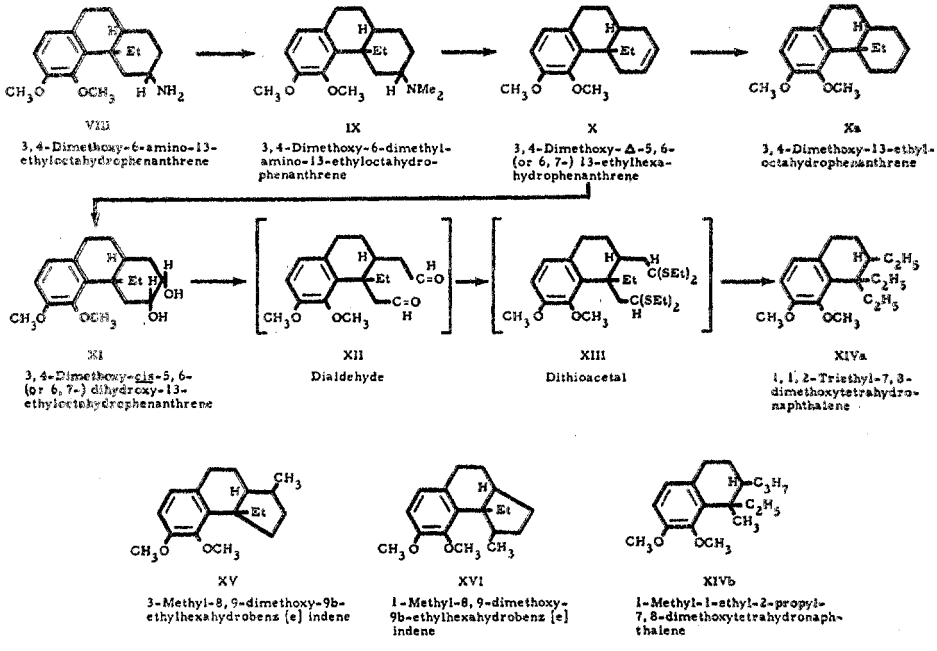
Reductive scission of the 4,5-ether bridge was accomplished by the sodium-alcohol reduction procedure used in the parallel preparation of phenolic dihydrothebaine (7). At this point the sodium-liquid ammonia method recently described by Robinson (8) probably would have been superior. According to the conditions of neutralization in the sodium-alcohol method (HCl or CO_2), V or Va was obtained. The phenolic hydroxyl of V was etherified (VI) with methyl sulfate and alkali.

Experiments directed towards opening ring 3 of VI and Va (methyl ether) were not successful. Subjecting VI-oxime (VII) to the Beckmann rearrangement did not lead to the expected 7-membered cyclic lactam, but to IVa (identified by mixture m.p. and x-ray powder-pattern). This unexpected but irrelevant phenomenon will be investigated further.

The action of cold persulfuric acid on VI (9) gave a clean liquid product whose analysis corresponded to VI plus one additional oxygen. This is probably a mixture, since ring enlargement might take place on either side of the carbonyl group. Ozonolysis of Va methyl ether by the procedure of Wieland and Small (10) was unsuccessful. Attempts to open ring 3 with hydrazoic acid (11) or selenium dioxide (12) also gave intractable products.

[2] We are indebted to Dr. A. H. Homeyer of the Mallinckrodt Chemical Works, St. Louis, Mo., for suggesting this procedure which he developed for converting dihydrocodeinone to dihydrothebaine using sodium *tert*-butoxide and methyl sulfate.

The path which ultimately led to the successful completion of the proposed degradation is outlined in the formulas VII to XIV. The oxime mixture VII,



on catalytic hydrogenation, afforded a mixture of diastereoisomeric amines, VIII α and β, which were separable through their hydrochlorides in approximately 2:1 ratio respectively and in total combined yield of 83%. Methylation of either amine with formaldehyde and formic acid gave the corresponding tertiary amine (IX); that derived from the α-base was crystalline, while the β-tertiary base appeared as a thick syrup.[3] Decomposition of their respective quaternary hydroxides (*via* the methiodide and thallous hydroxide) in a high vacuum at moderate temperatures resulted in the *same* unsaturated substance (X) in 31% yield. A quantity of tertiary amine equivalent to 60% of that originally taken was generally recovered, thereby increasing the effective yield of X to 88%. The non-basic product proved to be *chromatographically homogeneous*. It is not possible at this time to assign, with certainty, the position of the newly generated unsaturated center. Whether it is Δ-5,6 or -6,7 will be established only when the final degradation product is ultimately shown to be identical with either XIVa or XIVb.

In the presence of platinum X absorbed one mole of hydrogen to give Xa,

[3] It is worthy of note that both forms of the tertiary base IX exhibited analgesic properties. Using codeine as a standard, the β-form was found to be half as active while the α-isomer was somewhat less active than the β-form. In view of the known lack of analgesic properties of the methylmorphimethines, congeners of codeine, the discovery of analgesic powers in IX is of interest, and it is planned to synthesize and examine analogs of this substance.

which was crystalline and optically active. An inactive liquid product assumed to have the structure Xa was synthesized by Ghosh and Robinson (13).

The addition of osmium tetroxide to X gave a mixture of glycols (56%) from which two homogeneous, optically active, isomeric substances were isolated by fractional crystallization in a ratio of 1.5:1 (XI α and β). This result seems to be in accord with stereochemical considerations. Since the configurations at C-13 and -14 are already fixed in the source material, there can be generated only four isomers, two *cis* and two *trans*. As has been shown, addition of osmium tetroxide leads principally to *cis*-glycols (14), and for our purpose the possible *trans* isomers can be disregarded.

The respective glycols were cleaved by lead tetraacetate (15) to the, presumably, same dialdehyde (XII). Because of the reported instability of such substances (16), they were immediately condensed with ethyl mercaptan (17) and the resulting dithioacetals (XIII) reduced with Raney nickel. Both glycols afforded the *same* (XIVa or b) optically active, substituted tetrahydronaphthalene (?) derivative (infrared spectra identical).

We have not overlooked the possibility of XII undergoing an internal aldol condensation (in either direction) to yield, after conversion to the thioacetal and reduction, XV or XVI. Physical as well as analytical data, however, appear to favor structures XIVa or b. Admittedly, this question will not be satisfactorily answered until the degradation product has been compared with the synthetic material.

Examination of formula XIVa or b reveals that, regardless of which isomer ultimately proves to be the final degradation product, *at least* one ethyl radical will always form part of the geminal group on C-1 (formula XIV). It will be seen that this particular ethyl group stems from the ethanamine system originally present in dihydrothebaine (I), where C-1 first existed as C-13 in the alkaloid. Demonstration of identity of the degradation product XIVa or b with its synthetic counterpart should therefore constitute unequivocal proof (from the degradation view) that the carbon end of the heterocyclic nitrogen system in dihydrothebaine, and therefore in all morphine derivatives as well, is attached to C-13. Since it has been demonstrated that Metopon may be converted to a methyl substituted dihydrothebaine, degradation of the latter according to the methods developed in this investigation should lead to one of the two possible methyl homologs of the dimethoxytrialkyltetrahydronaphthalene described above.

The synthesis of the isomers of XIV is in progress.

Acknowledgment. The dihydrothebaine used in this work was supplied in part by the Mallinckrodt Chemical Works, St. Louis, Mo., and in part by Merck and Co., Rahway, N. J. We are indebted to Dr. Robert A. Spurr, Department of Chemistry, University of Maryland for the infrared absorption spectra, and to H. George Latham, of this laboratory, for assistance in degrading large quantities of dihydrothebaine. Analyses are by the Analytical Service Laboratory, of this Institute, W. C. Alford in charge. The x-ray powder patterns were taken by Mr. William C. White.

EXPERIMENTAL

The melting points reported herein are uncorrected.

Des-N-methyldihydrothebaine (II). The following modified procedure gave results consistently superior to those previously reported (2, 6). A solution of 150 g. of dihydrothebaine (I) in 1400 ml. of methanol was gently refluxed for 45 min. with 86 g. (excess) of methyl iodide, then concentrated to *ca.* 500 ml. on the steam-bath. Water (600 ml.) and 10% aqueous sodium hydroxide (800 ml.) were added and the system heated for 2 hours longer (steam-bath). After cooling in ice, the colorless, crystalline methine was thoroughly washed with cold water; yield 135 g. (87%), m.p. 136.5–138°; lit. m.p. 135° (6).

The *methine methiodide* was obtained by cautiously adding 21 ml. of methyl iodide to a solution of 90 g. of methine in 750 ml. of acetone and gently warming the resulting magma for 30 min. The colorless salt, 122 g. (95%), had m.p. 241–243°; lit. m.p. 243° (6).

The *methohydroxide*. A stirred suspension of 50 g. of finely powdered methiodide in 200 ml. of water was gradually treated during 30 min. with 600 ml. (slight excess) of 0.18 *N* thallous hydroxide, digested on the steam-bath for 30 min. and filtered from thallous iodide. The clear, straw-colored filtrate was concentrated to dryness (*vacuo*) and gave 40 g. of crude methohydroxide, which was powdered and preserved in a well-stoppered bottle.

Degradation. 6-Methoxy-13-vinyltetrahydromorphenol methyl ether (III). The methohydroxide was decomposed in 10 g.-lots by dry distillation at 120°/0.6 mm. ("cold-finger"). The combined colorless, crystalline sublimates (23.5 g.), consisting principally of nitrogen-free material, mixed with a little methine, was dissolved in 900 ml. of ether and extracted with 50-ml. portions of 0.25 *N* HCl until the Mayer's test was negative. The water-washed dried ether solution yielded 20 g. of crystalline material. After leaching with petroleum ether (b.p. 28–38°), 17.5 g. (60%) of cream-colored prisms, m.p. 123–124.5° (lit. m.p. 120–121°), (2) remained.

Basification of the combined aqueous acid extracts with concentrated NH_4OH and extraction with ether afforded 4 g. of crystalline methine, m.p. 134–136°.

6-Methoxy-13-ethylhexahydromorphenol methyl ether (IV). A solution of 17.5 g. of III in 500 ml. of 95% ethanol absorbed 3350 ml. (2.15 moles) of hydrogen in 2.5 hours in the presence of 1.8 g. of Pd-$CaCO_3$ (2% Pd). After concentration *in vacuo*, there remained 17.3 g. (98%) of an amber syrup which crystallized when seeded; m.p. 64–66°; massive prisms from petroleum ether (b.p. 28–38°). The analytical sample was purified by sublimation at 130°/0.4 mm., m.p. 65–66.5°; $[\alpha]_D^{20}$ −134° (*c*, 0.41 in alcohol).

Anal. Calc'd for: $C_{18}H_{22}O_3$: C, 75.5; H, 7.75.
Found: C, 75.6; H, 7.72.

3-Methoxy-4-hydroxy-6-keto-13-ethyloctahydrophenanthrene (V). To a boiling and rapidly-stirred solution of 17.7 g. of IV in 250 ml. of alcohol (nitrogen atm.), 60 g. of sodium was added during 50 min. An additional 550 ml. of ethanol added intermittently, in 50-ml. portions, was required to prevent the separation of sodium ethoxide. After heating and stirring for another hour, the system was cautiously diluted with 300 ml. of ice-water and concentrated on the steam-bath (*vacuo*). The oily residue was taken up in ether and successively washed with water and a solution of sodium hydrosulfite to remove colored oxidation products. The yield was 16.6 g. of oily crystals, which were covered with 250 ml. of warm ethanol and treated with 45 ml. of concentrated HCl. The resulting solution was kept at 20° for 1 hour and then concentrated to incipient crystallization (*in vacuo*). The residue was covered with 1500 ml. of water and, after keeping overnight, was recrystallized from a concentrated solution in methanol (Norit). The crystalline product was rendered colorless by leaching the finely powdered material with a little ice-cold methanol; yield 8.9 g. (53%), m.p. 151–153° (lit. m.p. 148–150°), (2); intense blue-green color with ferric chloride (in alcohol).

A specimen was sublimed at 160–170°/0.5 mm.; m.p. 154–155.5°; $[\alpha]_D^{20}$ −48° (*c*, 0.25 in alcohol).

Anal. Calc'd for: $C_{17}H_{22}O_3$: C, 74.4; H, 8.09.
Found: C, 74.8; H, 8.36.

3-Methoxy-4-hydroxy-13-ethyloctahydrophenanthrene-Δ-6,7-methyl enolate (Va). The reduction of 8 g. of IV in 175 ml. of ethanol with 32.5 g. of sodium (nitrogen atm.) was carried out as described immediately above. The resulting amber solution was diluted with 200 ml. of ethanol and saturated with CO_2, stirring mechanically during the procedure. After collecting the sodium carbonate, the red filtrate was again treated with CO_2 and filtered. The sodium carbonate precipitates were combined, digested with warm ethanol and filtered. The combined ethanol filtrates were concentrated *in vacuo* (under nitrogen) and the residue taken up and recrystallized from a concentrated solution in methyl acetate. Colorless prisms, 2.5 g.; emerald-green color with ferric chloride in ethanol. The analytical sample was sublimed at 140–150°/0.5 mm.; m.p. 171–173°; $[\alpha]_D^{20}$ + 23.8° (*c*, 0.34 in alcohol).

Anal. Calc'd for: $C_{18}H_{24}O_3$: C, 75.0; H, 8.39.
Found: C, 75.1; H, 8.43.

The combined mother liquors were concentrated and the residue evaporatively distilled at 150–155°/0.5 mm. Trituration of the oily distillate with boiling petroleum ether (b.p. 28–38°) afforded an additional 0.75 g. of crystalline product, m.p. 163–166°; total yield, 3.25 g. (40%).

The substance (Va) is rapidly hydrolyzed by mineral acids at room temperature to form V.

3,4-Dimethoxy-6-keto-13-ethyloctahydrophenanthrene (VI). Compound V (11.3 g.) was dissolved in 22 g. of KOH in 350 ml. of 60% ethanol (N_2 atm., stirring), treated during 10 min. with 49 ml. (excess) of methyl sulfate, and refluxed for 18 hours. Excess methyl sulfate was destroyed by treating the stirred mixture with 58 g. of KOH in 75 ml. of water and refluxing 30 min. The crude product was taken up in ether and the solution washed successively with 2 *N* NaOH, 2 *N* HCl, and water. The ether yielded 11 g. of cream-colored crystals, m.p. 109–111°. Ferric chloride test negative. After sublimation at 115–120°/0.5 mm. it had m.p. 114–116° and $[\alpha]_D^{20}$ − 54.2° (*c*, 0.5 in alcohol).

Anal. Calc'd for: $C_{18}H_{24}O_3$: C, 75.0; H, 8.39.
Found: C, 74.9; H, 8.48.

The *semicarbazone*, prepared in the usual way, crystallized in needles from acetone, m.p. 203.5–205°.

Anal. Calc'd for: $C_{19}H_{27}N_3O_3$: C, 66.1; H, 7.88.
Found: C, 65.9; H, 7.83.

3,4-Dimethoxy-6-keto-13-ethyloctahydrophenanthrene oxime (*mixture of diastereoisomers*) (VII). A mixture of 55 g. of VI, 42 g. of hydroxylamine hydrochloride, 48 g. of sodium acetate, 260 ml. of methanol, and 50 ml. of water was heated on the steam-bath for 5.5 hours. After partial concentration (*in vacuo*) 750 ml. of water was added and the product extracted with ether. This was washed with dilute salt solution, dried, and concentrated (*in vacuo*); yield, 60 g. of clear, amber syrup.

α- and β-3,4-Dimethoxy-6-amino-13-ethyloctahydrophenanthrene hydrochlorides (VIII). A solution of the above oxime mixture (60 g.) in 500 ml. of glacial acetic acid took up slightly more than the calculated amount of hydrogen in 3.25 hours with 4.5 g. of platinum oxide. The filtrate was cooled to 0°, basified with concentrated NH_4OH, and extracted with ether. The dried ether solution yielded 58 g. of oil (mixture of amines). Treatment at 0° with a slight excess of ethanolic HCl (Congo Red) afforded a colorless, crystalline magma which was diluted with ether; yield 40 g. (crop I). The filtrate was concentrated to small volume (*vacuo*) and strongly diluted with alcohol-free ether; 16 g. (crop II) of crystalline hydrochloride resulted.

Separation of α- and β-hydrochlorides. The above hydrochloride mixture, crop I, was dissolved in hot propanol-2, filtered, and concentrated to incipient crystallization (separation of α-hydrochloride). After 15 hours (20°), the solvated salt (slender prisms) amounted to 34.7 g., m.p. 138–144°, resolidifying and melting again at 211–213°; $[\alpha]_D^{20}$ +12.4° (*c*, 0.8 in water).

The *perchlorate* of the *α-amine*, prepared in ethanol with ethanolic perchloric acid,

crystallized from methyl acetate-ether in colorless plates, m.p. 197.5–199°; $[\alpha]_D^{20}$ +8.4° (*c*, 0.36 in alcohol).

Anal. Calc'd for: $C_{18}H_{23}ClNO_3$: C, 55.5; H, 7.24.

Found: C, 55.1; H, 7.46.

Concentration of the propanol-2 mother liquor to small volume followed by dilution with 6 volumes of acetone and seeding gave 4.6 g. of fine needles (*β*-hydrochloride), m.p. 253–255°; $[\alpha]_D^{20}$ −56.3° (*c*, 0.74 in water).

Recrystallization of crop II (16 g. above) was effected by solution in hot propanol-2 (Norit) and concentrating to small volume. The addition of 5 volumes of acetone and seeding gave fine needles (*β*-hydrochloride), 11.5 g., m.p. 251–253°, $[\alpha]_D^{20}$ −58.9° (*c*, 0.74 in water).

The *perchlorate* of the *β-amine* (liberated from its hydrochloride and evaporatively distilled at 145–150°/0.6 mm.) was formed in dry ether solution with ethereal $HClO_4$ (prepared by shaking 60% aq. $HClO_4$ with alcohol-free ether). Recrystallization from diethyl ketone-ether gave small prisms, m.p. 238–239.5°; $[\alpha]_D^{20}$ −63.8° (*c*, 0.92 in alcohol).

Anal. Calc'd for: $C_{18}H_{23}ClNO_6$: C, 55.5; H, 7.24.

Found: C, 55.7; H, 7.13.

α-3,4-Dimethoxy-6-dimethylamino-13-ethyloctahydrophenanthrene (IX). The amine, 27.4 g., regenerated from 34.7 g. of *α*-hydrochloride (NH_4OH-ether), was methylated by heating with 18.8 ml. of 98% formic acid and 17.7 ml. of aqueous formaldehyde (36% solution) for 4.5 hours on the steam-bath. Dilution of the reaction mixture with water and acidification with 100 ml. of 2 *N* HCl gave a small amount of flocculent material, which was removed by ether extraction. Recovery of the amine from the ice-cooled aqueous acid solution (NH_4OH-ether) gave 25 g. of a yellow syrup which slowly crystallized.

In order to remove any primary or secondary bases present, the above product (in 300 ml. of ether) was shaken for 1 hour with 15 ml. of benzoyl chloride and 275 ml. of 2 *N* NaOH. The ether solution was washed twice with cold water, and extracted with 50-ml. portions of 0.2 *N* HCl until no more amine was removed. The acid extracts were washed twice with alcohol-free ether, cooled, the amine liberated (NH_4OH) and taken up in ether, which yielded 23.3 g. (85%) of tertiary amine. The analytical sample was sublimed three times at 120–130°/0.4 mm., m.p. 76.5–78°.

Anal. Calc'd for: $C_{20}H_{31}NO_2$: C, 75.7; H, 9.84.

Found: C, 75.9; H, 10.44.

The *perchlorate*, prepared in ethanol, crystallized in prismatic needles from acetone-ether, m.p. 224–225.5°; $[\alpha]_D^{20}$ +18.8° (*c*, 0.93 in alcohol).

Anal. Calc'd for: $C_{20}H_{32}ClNO_6$: C, 57.5; H, 7.72.

Found: C, 57.6; H, 7.48.

The *methiodide* of the above base was obtained by treating a cooled solution of 23.3 g. of the amine in 50 ml. of acetone with 8.5 ml. of methyl iodide and refluxing for 30 min. Dilution with alcohol-free ether gave 35 g. of the colorless salt, m.p. 242–244°.

β-3,4-Dimethoxy-6-dimethylamino-13-ethyloctahydrophenanthrene perchlorate. Methylation of the *β*-6-amino derivative was carried out as described above. From 6.8 g. of amine, 4.6 ml. of 98% formic acid, and 4.4 ml. of 35% aq. formaldehyde, there resulted 6.3 g. of tertiary amine (viscous yellow oil). It was evaporatively distilled at 140–150°/0.6 mm. and converted to the perchlorate with alcoholic $HClO_4$. Small flat prisms from acetone-ether, m.p. 230–231.5°; $[\alpha]_D^{20}$ −64.3° (*c*, 0.9 in alcohol).

Anal. Calc'd for: $C_{20}H_{32}ClNO_6$: C, 57.5; H, 7.72.

Found: C, 57.7; H, 7.59.

The *methiodide* was prepared in acetone, m.p. 263–264°.

3,4-Dimethoxy-Δ-5,6-(or 6,7)-13-ethylhexahydrophenanthrene (X). A finely divided suspension of 12 g. of *α*-methiodide in 50 ml. of water was gradually treated with 190 ml. (slight excess) of 0.16 *N* thallous hydroxide. After digesting for 20 min. (steam-bath) the thallous iodide was removed and the filtrate concentrated to a syrup (at 100°, *vacuo*) and decomposed with evaporative distillation, at 0.4 mm., air-bath temp. 140°. The

nearly-colorless, semi-solid distillate was taken up in ether and the solution extracted with 0.2 *N* HCl to remove unchanged basic material. The washed and dried ether solution gave 2.1 g. (31% yield; or 88% based on recovered tertiary amine), of an oil which soon crystallized. The unsaturated substance, chromatographically homogeneous, crystallized in massive, colorless prisms from petroleum ether (b.p. 28–38°), m.p. 109.5–111°. The analytical sample was sublimed three times at 135°/0.4 mm., m.p. 110.5–112°; $[\alpha]_D^{20}$ +6.8° (*c*, 0.8 in alcohol).

Anal. Calc'd for: $C_{18}H_{24}O_2$: C, 79.4; H, 8.88; OCH_3, 22.8.

Found: C, 79.5; H, 9.08; OCH_3, 22.7.

The cooled acid extracts on basification with ammonia and extraction with ether yielded 5.2 g. of IX, doubtlessly arising from the methohydroxide by elimination of the elements of methanol during degradation.

The same unsaturated compound (m.p. and mixture m.p.) resulted from degradation of the β-tertiary amine in the above manner.

3,4-Dimethoxy-13-ethyloctahydrophenanthrene (Xa). A solution of 0.4 g. of X in 20 ml. of methanol absorbed 96% of the required amount of hydrogen in 6 min. in the presence of 80 mg. of platinum oxide. The product was 0.35 g. of crystals, m.p. 78–80°, which was purified by sublimation at 135°/0.5 mm., m.p. 78.5–80°; $[\alpha]_D^{20}$ −32.3° (*c*, 0.4 in alcohol).

Anal. Calc'd for: $C_{18}H_{26}O_2$: C, 78.8; H, 9.55.

Found: C, 79.1; H, 9.48.

α- and β-3,4-Dimethoxy-cis-5,6-(or 6,7)-dihydroxy-13-ethyloctahydrophenanthrene (XI). To an ice-cold solution of 4.8 g. (0.0188 mole) of osmium tetroxide and 3.1 ml. (0.038 mole) of dry pyridine in 130 ml. of anhydrous ether, a cold solution of 5.0 g. (0.0185 mole) of X in 250 ml. of dry ether was added at one time. The solution darkened and began to deposit a brown precipitate within a few minutes. After keeping at 0° for 15 hours, 10.7 g. (83%) of adduct was collected.

The hydrolysis of the adduct was effected by shaking it in 300 ml. of cold methylene chloride with a cold solution of 3.7 g. of KOH (2.6 equivs.) and 9.6 g. of mannitol (2.6 equivs.) in 300 ml. of water for 70 min. with intermittent cooling. The aqueous layer was washed twice with small portions of methylene chloride and the combined extract was washed with six 50-ml. portions of 0.25 *N* HCl to remove pyridine, dried, and concentrated (*vacuo*). The residual amber syrup (glycol mixture) crystallized when rubbed with a few drops of ether; 4.4 g. (56%). The glycol mixture was dissolved in 500 ml. of boiling, anhydrous ether (Norit), filtered, and concentrated to incipient crystallization. After 1 hour at 20°, the crystalline material was rinsed twice with small quantities of ice-cold ether, the washings being combined with the main mother liquor. The crystalline product (α-glycol) was suspended in petroleum ether (b.p. 28–38°); yield 1.9 g., m.p. 137–142°; from dry ether, colorless prisms, m.p. 150.5–152°; $[\alpha]_D^{20}$ −47.6° (*c*, 0.6 in alcohol).

Anal. Calc'd for: $C_{18}H_{26}O_4$: C, 70.6; H, 8.56.

Found: C, 70.5; H, 8.48.

Concentration of the α-glycol mother liquor to small volume and seeding with a little of the original glycol mixture gave 1.3 g. of the β-glycol, m.p. 114.5–117°; from dry ether, colorless needles, m.p. 119–121°; $[\alpha]_D^{20}$ −11.7° (*c*, 1.0 in alcohol).

Anal. Calc'd for: $C_{18}H_{26}O_4$: C, 70.6; H, 8.56.

Found: C, 70.2; H, 8.58.

1,1,2-Triethyl-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (?) (XIV). To a rapidly-stirred solution of 0.42 g. (0.00137 mole) of α-glycol in 25 ml. of dry benzene, 0.61 g. (0.00137 mole) of powdered lead tetraacetate was added during 5 min. The very mild exothermic reaction was accompanied by the separation of a small amount of colorless material. After stirring for an additional 15 min., the suspension was filtered and the filtrate rapidly washed successively with cold 0.25% $NaHCO_3$ solution and cold water and dried over sodium sulfate. The syrupy residue resulting from concentration (*vacuo*, below 37°) of the benzene solution was taken up in 10 ml. of dry ether and cooled to 0°. The solu-

tion was then added drop-wise to an ice-cold mixture of 0.46 g. (0.0074 mole) of ethylmercaptan, 0.1 g. of freshly-fused zinc chloride, and 0.07 g. of anhydrous sodium sulfate. The system was swirled in an ice-bath for 10 min., kept at 0° for 19 hours, poured into 30 ml. of ice-water, and extracted with alcohol-free ether. The ether solution was successively washed with cold water, 2 *N* NaOH, again with water, dried, and concentrated *in vacuo*.

A solution of the residual oil in 70 ml. of 70% ethanol was refluxed with *ca.* 10 g. of Raney nickel for 2.5 hours. The nickel was extracted three times with boiling ethanol and the extracts were concentrated (*vacuo*, 50–60°). The oily suspension was diluted with cold water and extracted with alcohol-free ether; yield 0.28 g. of oily crystals which were triturated twice with a little cold ether-petroleum ether mixture (4 :1). The colorless, crystalline solid had m.p. 158–160°; after 2 crystallizations from ether, slender prisms, m.p. 162–163.5°.

Anal. Calc'd for: $C_{18}H_{26}O_4$: C, 70.6; H, 8.56; OCH_3, 20.2.
Found: C, 70.2; H, 9.05; OCH_3, 20.4.

Although the analytical values appear to fit reasonably well those calculated for the original glycol, a mixture of the two substances showed a marked m.p.-depression. Lack of material has made it necessary to lay this aside for the present.

After concentration (*vacuo*, 50°) of the ether-petroleum ether solution there remained 0.22 g. of a colorless oil. This was purified by three evaporative distillations at 96–105°/0.4 mm.; d_{20}^{20} 1.027; n_D^{20} 1.5295; $[\alpha]_D^{20}$ −53° (*c*, 0.93 in alcohol).

Anal. Calc'd for: $C_{18}H_{28}O_2$: C, 78.2; H, 10.2; OCH_3, 22.5; M.R., 82.81.
Found: C, 78.2; H, 10.2; OCH_3, 22.2; M.R., 82.98.
Calc'd for: $C_{18}H_{26}O_2$ (XV or XVI): C, 78.8; H, 9.53; OCH_3, 22.6; M.R., 80.61.

Degradation of the *β-glycol* according to the above scheme yielded a colorless oil, b.p. (evap. distillation) 95–108°/0.4 mm.; n_D^{25} 1.5288; $[\alpha]_D^{20}$ −61° (*c*, 1.0 in alcohol); infrared spectrum indistinguishable from that obtained with the α-glycol degradation product.

SUMMARY

Dihydrothebaine has been degraded in a novel manner to a dimethoxytrialkyltetrahydronaphthalene (?). The possibility that this degradation might lead to a complementary proof of the point of attachment of the ethanamine system (at C-13) in the morphine alkaloids is discussed. An unexpected finding of moderate analgesic powers in 3,4-dimethoxy-6-dimethylamino-13-ethyloctahydrophenanthrene (both isomers) is recorded.

BETHESDA 14, MD.

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