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STRUCTURES RELATED TO MORPHINE. II. AN ISOMER OF N-METHYLMORPHINAN

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In the preceding paper (1) we reported the synthesis of 2-(2-dimethylaminoethyl)-2-phenylcyclohexanone (I) and several derivatives. Of these derivatives the deoxy compound, although slightly convulsant at double the analgesic dose was about half as effective as Meperidine in mice. The present communication describes further syntheses with I leading to structures more closely related to morphine and ultimately to a position isomer (with respect to nitrogen ring closure) of N-methylmorphinan (IX).

A logical first-step in such syntheses appeared to be the conversion of I to a bicyclic system in which the nitrogen would be part of a piperidine ring. This was accomplished by applying a reaction sequence reported by Barltrop (2) in 1947 and recently extended by Blicke and Krapcho (3) to the preparation of 3-piperidones from methadone and analogs. Thus cyclization of the bromo ketone (II) produced the methobromide of III which, on dry distillation, yielded the base (III) in an over-all yield of 80%. Wolff-Kishner reduction of III gave the deoxy compound (VI).

In order to proceed from III to a substance amenable to ring closure to a phenanthrene system, we chose to introduce a carboxymethyl grouping (or potential one) at the site of the carbonyl function. Of the several well-known methods for achieving this, the Knoevenagel reaction, or a modification thereof, seemed most feasible. Accordingly, malononitrile[1] was brought to reaction with III by the procedure devised by McElvain and Lyle (4) for 4-piperidones, to give the α,β-unsaturated dinitrile (V) in a yield of 90%.[2]

Hydrogenation (platinum oxide) of V followed by acid hydrolysis-decarboxylation[3] of the crude reduction mixture afforded the amino acid (IV) in an over-all yield of 45%. Treatment of IV with polyphosphoric acid effected ring closure to the ketophenanthrene derivative (VII) which was reduced (Wolff-Kishner) to the iminoethanophenanthrene (VIII), an isomer of N-methylmorphinan (IX).

Exhaustive methylation of VIII (methiodide) and hydrogenation of the resultant olefinic material gave principally[4] the methine (X) identical with that

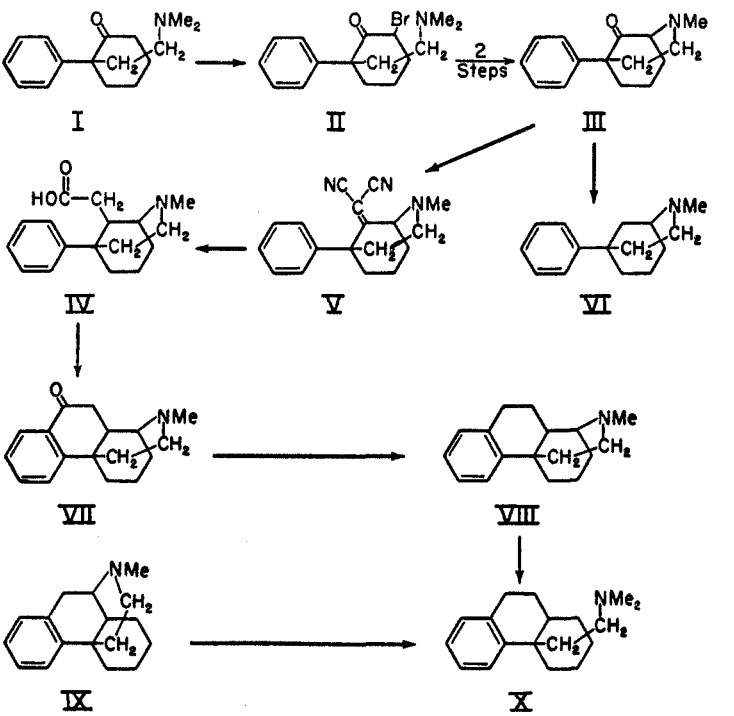
[1] Neither methyl nor ethyl cyanoacetate could be induced to react with III.

[2] Efforts to apply the Knoevenagel reaction to I under various conditions failed possibly because of interference of the dimethylamino group. There was also evidence pointing to the instability of the desired product as a probable cause for this failure. If such a reaction had been successful it could have opened a pathway to another practicable synthesis of N-methylmorphinan and perhaps the potent analgesic, Dromoran.

[3] Attempts to hydrolyze-decarboxylate V to the corresponding unsaturated acid gave III (15% recovery) and ammonium chloride (70% yield only after prolonged refluxing in 20% HCl) as the only isolable products. Corson and Stoughton (5) state that "the nitrile groups in such compounds are very resistant to hydrolysis."

[4] In addition some VIII was recovered as the picrate.

obtained from IX (6). This result afforded proof of a phenanthrene structure and additionally that VIII and IX have the same configuration at carbon atoms 13 and 14, if it is assumed that Hofmann's rule (7) has been followed in the ring-cleavage of VIII. The total synthesis of tetrahydrodesoxycodeine by Grewe, *et al.* (8) has related the morphinan series to morphine, and the recent investigations of Rapoport and Lavigne (9) have demonstrated a *cis*-relationship between the hydrogen of carbon 14 and the ethanamine system. It follows, therefore, that the substituents of carbons 13 and 14 of VIII are also probably in *cis*-formation.



The stereochemistry of the reactions and intermediates leading to VIII is of some interest. Apparently the bromination of I and subsequent ring-formation are stereospecific[5] inasmuch as a single entity (III methobromide) was obtained in an over-all yield of 82%.[6] Moreover, platinum oxide hydrogenation of the dinitrile V, the step which determines the steric relationship of carbon 14 to 13 also gave only one diastereoisomer;[7] repeated attempts to isolate an amino acid isomeric with IV were unfruitful.

Compounds III, VI, VII, and VIII were screened in mice for analgesic po-

[5] In the cyclization of methadone and isomethadone, in this manner, Blicke and Krapcho (3) report excellent yields of a single product.

[6] Examination of molecular models indicated that only a *cis* ring formation would be possible in III.

[7] Platinum oxide-catalyzed hydrogenations are generally stereospecific.

tency. Only VI was significantly active, being slightly less effective than Meperidine. It was, however, somewhat toxic at approximately twice the analgesic dose.[8] In future studies we plan to deal with phenolic compounds analogous to those reported in this and the foregoing communication.

EXPERIMENTAL[9]

6-Bromo-2-(2-dimethylaminoethyl)-2-phenylcyclohexanone (II) *hydrobromide.* The base from 1.4 g. (0.005 mole) of I hydrochloride was converted to the hydrobromide, which, in 10 ml. of acetic acid (stirring, refluxing) was treated with 0.26 ml. (0.005 mole) of bromine in 10 ml. of acetic acid during 15 minutes. After refluxing for an additional 15 minutes the solution was concentrated and diluted with ethyl acetate to give 1.8 g. (88%) of II hydrobromide; tiny needles, m.p. 181–181.5°, from acetone.[10]

Anal. Calc'd for $C_{16}H_{23}Br_2NO$: C, 47.4; H, 5.7.
Found: C, 47.3; H, 5.8.

9-Keto-2-methyl-5-phenylmorphan (III) *methobromide.*[11] To 34.6 g. of II hydrobromide in 86 ml. of water was added (stirring, ice-cooling) 13 ml. of conc'd NH_4OH. The oil that separated gradually solidified. After one hour the solid was filtered and the filtrate was concentrated to give a second crop of methobromide (total yield 25.3 g., 91%, m.p. 237–240°). It crystallized from ethanol in square plates of m.p. 238–238.5°.

Anal. Calc'd for $C_{16}H_{22}BrNO$: C, 59.3; H, 6.8.
Found: C, 58.9; H, 6.8.

The *hydrochloride* of III was prepared in 88% yield by dry distillation (0.1 mm.) of III methobromide at an air-bath temperature of 225–230°, and alcoholic HCl acidification of the distillate in ether. It crystallized from acetone[10] as the hemihydrate;[12] needles, m.p. 214–215°.

Anal. Calc'd for $C_{15}H_{20}ClNO \cdot 1/2H_2O$: C, 65.6; H, 7.7.
Found: C, 65.3; H, 7.8.

2-Methyl-5-phenylmorphan (VI) *hydrochloride.* A mixture of 2.2 g. of III hydrochloride, 0.8 ml. of 95% hydrazine, 1.6 g. of KOH, and 8.0 ml. of triethylene glycol was heated at 170–180° (bath temperature) for 6 hours, cooled, and diluted with water. The resultant oil was dried in ether and converted to the hydrochloride to give, after recrystallization from acetone,[10] 1.5 g. (75%) of slender prisms, m.p. 239–240°.

Anal. Calc'd for $C_{15}H_{22}ClN$: C, 71.5; H, 8.8.
Found: C, 71.5; H, 8.8.

9-Dicyanomethylene-2-methyl-5-phenylmorphan (V) *hydrochloride.* A mixture of III from 5.6 g. of hydrochloride, 1.4 g. of malononitrile, 0.4 g. of ammonium acetate, 0.9 ml. of acetic acid, and 7 ml. of benzene was refluxed for one hour, the water formed being collected in a Stark-Dean trap. After ether dilution and alcoholic-HCl acidification, there was obtained 5.6 g. (87%) of the hydrochloride. It crystallized from absolute ethanol in slim prisms, m.p. 210–213° (dec.)[13] in a bath preheated to 205°.

Anal. Calc'd for $C_{18}H_{20}ClN_3$: C, 68.9; H, 6.4.
Found: C, 69.0; H, 6.5.

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[8] We are indebted to Dr. Nathan B. Eddy for these results (unpublished).

[9] Melting points are corrected. Microanalyses are from the Institutes service analytical laboratory under the direction of Dr. William C. Alford.

[10] It was necessary to use a large volume of refluxing solvent, to concentrate the solution to a small volume, and occasionally to seed the supersaturated solution so obtained.

[11] The nomenclature used for this and the two following compounds was proposed by Barltrop (2).

[12] The hydrate water was indeterminate by weight-loss, probably due to sublimation.

[13] If the m.p. is taken in the usual way, the compound decomposes from 185–213°.

9-Carboxymethyl-2-methyl-5-phenylmorphan (IV) *hydrochloride.* The hydrochloride of V (2.0 g.), 0.1 g. of platinum oxide, and 50 ml. of methanol absorbed one mole of hydrogen during 1.5 hours (room temperature, atmospheric pressure) at which point the rate of absorption slowed markedly.[14] The reduction was interrupted, and catalyst was filtered (Norit, Filter-Cel). The filtrate was evaporated to dryness *in vacuo*. The residue, and 20 ml. of 20% HCl were refluxed for six hours and evaporated to dryness. After trituration with acetone the dried precipitate was digested with butanol and the mixture filtered hot to remove ammonium chloride. The filtrate deposited 0.9 g. (46%) of IV hydrochloride, m.p. 275–276° (dec.). Further recrystallization (butanol)[10] gave minute prisms, m.p. 280° (dec.).

Anal. Calc'd for $C_{17}H_{24}ClNO_2$: C, 65.9; H, 7.8.
Found: C, 65.9; H, 7.6.

1,2,3,9,10,10a-Hexahydro-9-keto-11-methyl-1,4a(4H)-iminoethanophenanthrene (VII) *hydrochloride.* Polyphosphoric acid[15] (30 g.) and 2.8 g. of IV hydrochloride were kept on the steam-bath (stirring until homogeneity was attained) for 3 hours. Excessive frothing was prevented by addition of a few drops of ether. The sirup was diluted with ice-water and poured with stirring into 45 g. of KOH in ice-water. The base was recovered by 2 ether extractions; the extracts were dried and evaporated to give 2.2 g. (93%) of almost pure VII. It was converted to the hygroscopic hydrochloride which crystallized from acetone[10] as the hemihydrate of m.p. 192–194°; blades.

Anal. Calc'd for $C_{17}H_{22}ClNO + 1/2H_2O$: C, 68.0; H, 7.7.
Found: C, 67.9; H, 7.8.

The *picrate* (from alcohol-acetone) melted at 220–222° (dec.); yellow prisms.

Anal. Calc'd for $C_{23}H_{24}N_4O_8$: C, 57.0; H, 5.0.
Found: C, 56.8; H, 5.1.

1,2,3,9,10,10a-Hexahydro-11-methyl-1,4a(4H)-iminoethanophenanthrene (VIII) *hydrochloride.* Reduction of 0.5 g. of VII as described in the preparation of VI gave 0.4 g. (84%) of VIII hydrochloride, m.p. 244–245.5° (dec.); needles from acetone.[10]

Anal. Calc'd for $C_{17}H_{24}ClN$: C, 73.5; H, 8.7.
Found: C, 73.5; H, 8.6.

The *picrate*, yellow needles from alcohol-acetone or acetone, melted at 192–193° (dec.).[16]

Anal. Calc'd for $C_{23}H_{26}N_4O_7$: C, 58.7; H, 5.6.
Found: C, 58.6; H, 5.7.

4a-(2-Dimethylaminoethyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (X) *picrate.* The methiodide of VIII (0.4 g., m.p. *ca.* 320°),[17] 0.5 g. of commercial silver oxide, and 5 ml. of water were kept on the steam-bath for 45 minutes, filtered, and evaporated to dryness *in vacuo*. Dry distillation (120–130°/0.5 mm.) of the residue gave 0.25 g. of distillate which absorbed 0.8 mole of hydrogen (platinum oxide, ethanol) during 15–20 minutes. Addition of 0.2 g. of picric acid to the filtered solution gave 0.3 g. of picrate of m.p. 175–180°. Careful recrystallization from methanol gave 0.18 g. (35%)[18] of the picrate of X, m.p. 185–186° Recrystallized again (ethanol) it melted at 185–187°; yellow blades.

Anal. Calc'd for $C_{24}H_{30}N_4O_7$: C, 59.3; H, 6.2.
Found: C, 59.5; H, 6.2.

When mixed with a sample of X picrate (m.p. 185–187°) prepared from N-methylmor-

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[14] For maximum yields the reaction must be stopped at this point.

[15] For a leading reference on polyphosphoric acid cyclizations, see reference 10.

[16] Apparently this picrate is dimorphic. It crystallized from methanol in broad needles of m.p. 194–195°. A recrystallization of this form from alcohol-acetone again gave fine needles melting at 192–193°.

[17] This methiodide is unaffected by boiling, aqueous KOH or NaOH in contrast to the methiodide of N-methylmorphinan (6) or N-methylisomorphinan (11).

[18] From this filtrate a 10% yield of the picrate of VIII was recovered.

phinan (6)[19] the m.p. was unchanged, while if mixed with the "dihydrodesbase picrate" of Gates, *et al.* (11),[20] the m.p. was 170–180°.

The *hydrochloride* of X crystallized from acetone-ether in square plates, m.p. 213–214° alone or in mixture with that prepared from N-methylmorphinan.

Anal. Calc'd for $C_{18}H_{28}ClN$: C, 73.6; H, 9.6.
Found: C, 73.8; H, 9.7.

SUMMARY

Starting from 2-(2-dimethylaminoethyl)-2-phenylcyclohexanone (I), an isomer of N-methylmorphinan, 1,2,3,9,10,10a-hexahydro-11-methyl-1,4a(4H)-iminoethanophenanthrene (VIII) has been synthesized.

Exhaustive methylation of VIII followed by reduction of the olefin resulting has given the same methine (X) as that obtained by similar degradation of N-methylmorphinan.

2-Methyl-5-phenylmorphan (VI) obtained in the Wolff-Kishner reduction of the intermediate III is half as effective as Meperidine in producing analgesia in mice.

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[19] The N-methylmorphinan used was obtained through the courtesy of Hoffmann-La Roche, Basle.

[20] We are indebted to Dr. Marshall Gates for generously sending us a specimen of this picrate.