381. *Syntheses in the Morphine Series. Part VII.*[1] *A New Synthesis of 3-Methoxy-N-methylmorphinan.*

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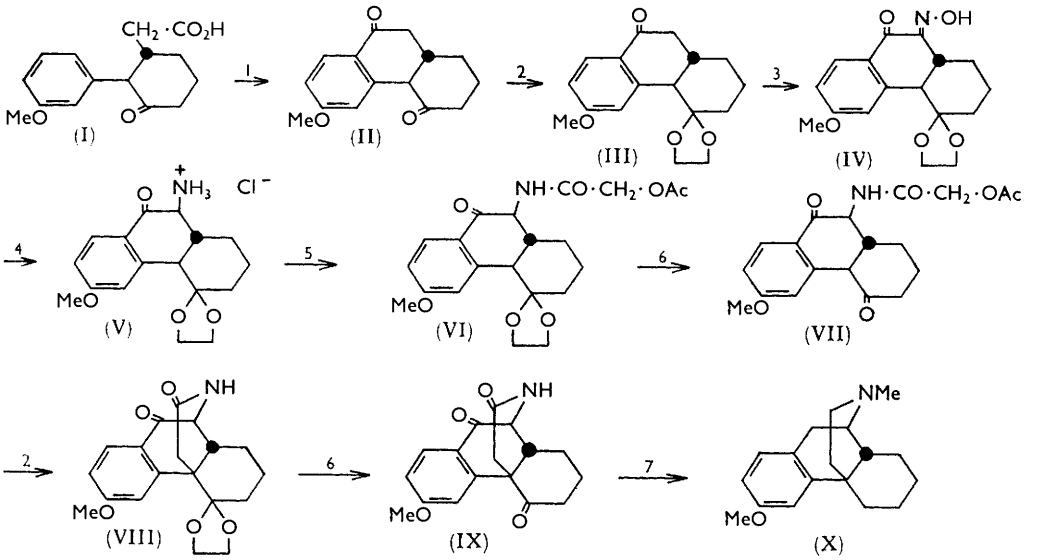
3-Methoxy-*N*-methylmorphinan (X) has been prepared by a route similar to that used [1] for the synthesis of morphine.

The synthesis of morphine in which substituted hydrophenanthrenes were used as intermediates was reported several years ago by Elad and Ginsburg.[1] Since 2-*m*-methoxyphenyl-3-oxocyclohexylacetic acid (I) was available in this Laboratory,[2] it was decided to follow earlier synthetic lines with the view of testing again the efficacy of cyclisation of the " ethanamine bridge," the ultimate goal being 3-methoxy-*N*-methylmorphinan (X). The reactions carried out are summarised in the accompanying scheme.



Reagents: 1, HF. 2, $(CH_2{\cdot}OH)_2$–*p*-$C_6H_4Me{\cdot}SO_3H$. 3, n-$C_5H_{11}{\cdot}O{\cdot}NO$–NaOEt. 4, H_2–Pd–C–HCl. 5, $AcO{\cdot}CH_2{\cdot}COCl$–$NEt_3$. 6, Aq. AcOH. 7, Huang-Minlon, $LiAlH_4$, $H{\cdot}CO_2H$–CH_2O.

Cyclisation of the keto-acid (I) with anhydrous hydrogen fluoride gave the diketone (II). The latter was selectively ketalised and the resulting ketal (III) was then treated with n-pentyl nitrite and sodium ethoxide to introduce a nitrogen function at a position adjacent to the acetophenone-type carbonyl group rather than adjacent to the alicyclic carbonyl group whose activation was blocked. The hydroxyimino-ketone (IV) thus obtained was catalytically reduced in the presence of acid to give the amino-ketone hydrochloride (V). Treatment of the latter with acetylglycollyl chloride in the presence of triethylamine gave the acetoxy-amide (VI) and at this point the ketal blocking group was removed by treatment with aqueous acetic acid in order to permit subsequent intramolecular cyclisation of the diketo-amide (VII) thus obtained. The conditions used for this cyclisation were analogous to those used previously in this series.[1] The product of cyclisation (VIII) was a lactam having an alicyclic carbonyl group blocked as a ketal and a free carbonyl group adjacent to the aromatic ring. The diketo-lactam (IX) was obtained by treatment of this ketal (VIII) with aqueous acetic acid. It was then subjected to a

[1] Part VI, Elad and Ginsburg, *J.*, 1954, 3052; cf. Ginsburg and Pappo, *J.*, 1953, 1524.
[2] Bien and Boazi, *J.*, 1959, 1727.

series of reactions without isolation of intermediates. Huang-Minlon reduction of (IX) removed the ketonic carbonyl functions. The product was further reduced, to the secondary amine, by means of lithium aluminium hydride, and methylation with formaldehyde–formic acid gave racemic 3-methoxy-*N*-methylmorphinan, m. p. 81—83° (Schnider and Hellerbach [3] report the same m. p.). The hydrobromide had m. p. 92—93·6° and did not depress the m. p. of a specimen, m. p. 92—93·5° (reported [3] m. p. 91—93°), kindly supplied by Hofmann La Roche A.G. of Basle, and the infrared spectra of the two specimens were superimposable.

Experimental

1,2,3,4,4a,9,10,10a-*Octahydro*-6-*methoxy*-4,9-*dioxophenanthrene* (II).—Crude 2-*m*-methoxyphenyl-3-oxocyclohexylacetic acid [2] (55 g.) was treated with anhydrous hydrogen fluoride (*ca.* 900 ml.). After 4 hr. most of the hydrogen fluoride was removed by a stream of dry air. The residual oil slowly crystallised. The mixture was made alkaline with dilute sodium hydrogen carbonate solution, and the crude crystalline diketone (50 g.) was removed and washed with water. Recrystallisation gave the pure *diketone* (II), m. p. 142·5—143·5° (from benzene) (Found: C, 73·8; H, 6·8; O, 19·5. $C_{15}H_{16}O_3$ requires C, 73·75; H, 6·6; O, 19·65%). The red *bis*-2,4-*dinitrophenylhydrazone* had m. p. 253° (decomp.) (from dimethyl sulphoxide) (Found: C, 53·15; H, 4·1; N, 18·2; O, 24·4. $C_{27}H_{24}N_8O_9$ requires C, 53·7; H, 4·0; N, 18·5; O, 23·8%).

Proof of Structure (II).—The diketone (II) (1·5 g.) was reduced by the Huang-Minlon procedure with 95% hydrazine hydrate (5·6 ml.), potassium hydroxide (3 g.), and diethylene glycol (37·5 ml.). After nitrogen evolution had ceased and the usual working up, the product was extracted with benzene. Removal of the benzene from the dried ($MgSO_4$) extract afforded an oily, partially demethylated residue. Methylation was therefore carried out by treatment of the residue (1·0 g.) in acetone (10 ml.) with methyl sulphate (2·4 ml. in 3 ml. of acetone) and sodium hydroxide solution (4·5 g. in 3 ml. of water) at 50°, with stirring. After the usual working up [2] the oil obtained (1·0 g.) was dissolved in light petroleum and was percolated through a column of acid-washed alumina (Merck; 30 g.). The oil obtained (0·9 g.) after removal of solvent from the eluate was dehydrogenated with 30% palladised carbon (0·1 g.) at 300° for 50 min. Chloroform-extraction, filtration, and evaporation gave a semi-solid product (0·7 g.) which was dissolved in a minimal volume of light petroleum and chromatographed on acid-washed alumina (Merck; 25 g.). Elution with light petroleum gave, in the first fractions, colourless crystals (0·15 g.), m. p. 99—100° (from methanol), identified as phenanthrene by mixed m. p. and infrared spectrum. Later fractions gave 3-methoxyphenanthrene (0·5 g.), m. p. 62° (from methanol), with no depression on admixture with an authentic specimen and with an identical infrared spectrum.

4-(*Ethylene Ketal*) *of* 1,2,3,4,4a,9,10,10a-*Octahydro*-6-*methoxy*-4,9-*dioxophenanthrene* (III).—A mixture of the diketone (II) (10 g.), ethylene glycol (21 ml.), benzene (43 ml.), and toluene-*p*-sulphonic acid (0·5 g.) was refluxed for 3 hr., the water formed being removed azeotropically. The mixture was cooled, then neutralised with sodium methoxide, the benzene layer was separated, and the glycol layer was diluted with water and extracted with benzene. The combined benzene solutions were washed with water, dried ($MgSO_4$), and evaporated. Trituration of the residue with methanol gave the crude ketal (11 g.), m. p. 104°. Three recrystallisations gave the pure *ketal*, m. p. 108—108·5° (from methanol) (Found: C, 70·7; H, 7·0; O, 22·2. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0; O, 22·2%). The *oxime* had m. p. 218° (from propan-2-ol) (Found: C, 67·4; H, 6·9; N, 4·7. $C_{17}H_{21}NO_4$ requires C, 67·3; H, 7·0; N, 4·6%).

4-(*Ethylene Ketal*) *of* 1,2,3,4,4a,9,10,10a-*Octahydro*-10-*hydroxyimino*-6-*methoxy*-4,9-*dioxophenanthrene* (IV).—A solution of the ketal (III) (4·2 g.) in dry tetrahydrofuran (18 ml.) was added to an ice-cold solution of sodium ethoxide (0·37 g. of sodium in 7·5 ml. of dry ethanol). The mixture was stirred for a few minutes and n-pentyl nitrite (3·4 ml.) was added in one portion. Stirring and cooling (ice–water) were continued for 1 hr. and the mixture was set aside at 0° for 48 hr. The brownish solution was then diluted with water, 10% sodium hydroxide solution (20 ml.) was added, and the whole was extracted with ether to remove dark material. Finally

[3] Schnider and Hellerbach, *Helv. Chim. Acta*, 1950, **33**, 1446.

the crude *hydroxyimino-derivative* (2·1 g.) was precipitated from the alkaline solution by saturation with carbon dioxide. It had m. p. 158—161°. Several recrystallisations from acetone raised the m. p. to 178—179° (decomp.) (Found: C, 64·5; H, 6·1; N, 4·5. $C_{17}H_{19}NO_5$ requires C, 64·3; H, 6·0; N, 4·4%).

4-(*Ethylene Ketal*) *of* 10-*Amino*-1,2,3,4,4a,9,10,10a-*octahydro*-6-*methoxy*-4,9-*dioxophenanthrene Hydrochloride* (V).—The crude hydroxyimino-compound (IV) was reduced catalytically in batches of 0·6 g., as follows. Ethanol (25 ml.), concentrated hydrochloric acid (0·8 ml.) and 10% palladised carbon (0·15 g.) were shaken under hydrogen, and the crude oxime (0·6 g.) was added in small portions; every new portion was added only after hydrogen uptake had ceased. The catalyst was removed by filtration and the solvent was removed at the water pump. Trituration of the residue with acetone gave the *amine hydrochloride* (0·36 g.), m. p. 216—218° (from methanol–acetone) (Found: C, 60·0; H, 6·3; N, 4·1; Cl, 10·7. $C_{17}H_{22}ClNO_4$ requires C, 60·25; H, 6·5; N, 4·1; Cl, 10·5%).

10-*Amino*-1,2,3,4,4a,9,10,10a-*octahydro*-6-*methoxy*-4,9-*dioxophenanthrene Hydrochloride*.—The crude ketal (V) (0·35 g.) was heated in 50% aqueous acetic acid (5 ml.) at 100° for 30 min. Evaporation of the solvent at the water pump, followed by trituration with acetone, gave the *amino-diketone hydrochloride* (0·2 g.), m. p. 209—210° (decomp.) (from propan-2-ol) (Found: C, 60·7; H, 6·2; N, 4·6; Cl, 12·1. $C_{15}H_{18}ClNO_3$ requires C, 61·0; H, 6·1; N, 4·7; Cl, 12·0%).

4-(*Ethylene Ketal*) *of* 10-*Acetoxyacetamido*-1,2,3,4,4a,9,10,10a-*octahydro*-6-*methoxy*-4,9-*dioxophenanthrene* (VI).—The crude hydrochloride (V) (2·75 g.) was dissolved with stirring in an ice-cold mixture of dry chloroform (145 ml.) and dry triethylamine (2·5 ml.). Acetylglycollyl chloride (1·31 g.) in chloroform (82 ml.) was added dropwise with stirring and cooling (ice–water) during 1 hr., and finally the mixture was refluxed for 30 min. The solution was cooled, washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water and dried ($MgSO_4$). Evaporation at the water pump gave an oil which upon trituration gave crystals (2·5 g.). Recrystallisation from methanol gave the pure *ketal* of the acetoxy-amide, m. p. 171—171·5° (Found: C, 62·1; H, 6·2; N, 3·8; O, 27·6. $C_{21}H_{25}NO_7$ requires C, 62·5; H, 6·25; N, 3·5; O, 27·75%).

10-*Acetoxyacetamido*-1,2,3,4,4a,9,10,10a-*octahydro*-6-*methoxy*-4,9-*dioxophenanthrene* (VII).—The crude ketal (VI) (2·4 g.) was heated in 50% aqueous acetic acid (30 ml.) at 100° for 30 min. The solution was cooled and poured into an excess of dilute sodium hydrogen carbonate solution and the whole was extracted with chloroform. The oil obtained on evaporation crystallised on trituration with ether–chloroform. The filtered solid (1·85 g.) gave pure *acetoxy-amide*, m. p. 153·5—154·5° (from benzene–methylcyclohexane) (Found: C, 63·3; H, 5·7; N, 4·0. $C_{19}H_{21}NO_6$ requires C, 63·5; H, 5·9; N, 3·9%).

Cyclisation of the Amide (VII) *to the* 4-(*Ethylene Ketal*) *of the Dioxo-lactam* (VIII).—A mixture of the crude acetoxy-amide (VII) (1·75 g.), ethylene glycol (10 ml.), toluene (16 ml.), benzene (10 ml.), and toluene-*p*-sulphonic acid (35 mg.) was refluxed for 6 hr., under an azeotropic separator to collect volatile products. After cooling, sodium methoxide was added until a slightly alkaline reaction was obtained and the two layers were separated. The ethylene glycol layer was diluted with water and extracted with chloroform, and the combined organic layers were dried ($MgSO_4$) and evaporated. Trituration of the residue with benzene gave crystals (0·4 g.). Recrystallisation from propan-2-ol gave the pure *ketal* of the dioxo-lactam, m. p. 255° (sintering from 250°) (Found: C, 66·4; H, 6·2; N, 4·3; O, 23·5. $C_{19}H_{21}NO_5$ requires C, 66·5; H, 6·2; N, 4·1; O, 23·3%).

Evaporation of the benzene mother-liquor and trituration of the dark residue with methanol precipitated the 4-ethylene ketal of uncyclised acetoxy-amide (VI) (0·8 g.).

3-*Methoxy*-5,10,16-*trioxomorphinan* (IX).—The ketal (VIII) (0·35 g.) was heated in 50% aqueous acetic acid (30 ml.) at 100° for 1 hr. The solution was cooled, neutralised with dilute sodium hydrogen carbonate solution, and extracted with chloroform. After evaporation of the solvent the residue was triturated with ethyl acetate, giving the *dioxo-lactam* (0·1 g.), m. p. 171—172° (from ethyl acetate) (Found: C, 68·8; H, 6·1; N, 4·5; O, 21·5. $C_{17}H_{17}NO_4$ requires C, 68·2; H, 5·7; N, 4·7; O, 21·4%).

1,2,3,4,4a,9,10,10a-*Octahydro*-10-*hydroxyacetamido*-6-*methoxy*-4,9-*dioxophenanthrene*.—A suspension of the 4-ethylene ketal (VI) (0·2 g.) in ethanol (15 ml.) was saturated with gaseous ammonia and stirred at room temperature until all solid had dissolved (about 90 min.). The syrupy residue obtained on evaporation of the solvent was heated in 50% acetic acid (8 ml.) at 100° for 30 min. The solvent was evaporated at the water pump and the residue was dissolved

in a few ml. of benzene–chloroform (1 : 1) and chromatographed on acid-washed alumina (Merck; 16 g.). Elution was started with the same solvent mixture followed by benzene–chloroform (1 : 4), which eluted crystalline material (50 mg.). The pure *hydroxyacetamido-derivative* had m. p. 166—167° (from benzene) (Found: C, 64·9; H, 6·1; N, 4·6; O, 24·7. $C_{17}H_{19}NO_5$ requires C, 64·3; H, 6·0; N, 4·4; O, 25·2%).

3-*Methoxy*-N-*methylmorphinan* (X).—(*a*) A solution of the dioxo-lactam (IX) (115 mg.) was submitted to the conditions of the Huang-Minlon procedure with hydrazine hydrate (0·5 ml.), potassium hydroxide (0·2 g.), and diethylene glycol (3 ml.). After 4 hours' heating at 180° the mixture was worked up in the usual way. (*b*) The lactam thus obtained as a light brown oil (70 mg.; no ketonic absorption) was dissolved without further purification in dry tetrahydrofuran (5 ml.) and treated with an excess of lithium aluminium hydride (0·5 g.). Refluxing was continued for 8 hr. and the amine isolated in the usual way. (*c*) The oily crude basic product (52 mg.) was dissolved in formic acid (0·5 ml.), 30% aqueous formaldehyde (0·2 ml.) was added, and the mixture was refluxed for 8 hr. After the usual working up to remove the reagents and addition of an excess of sodium carbonate solution, the product was extracted with chloroform. Removal of the solvent at the water pump afforded a semi-solid residue of 3-methoxy-*N*-methylmorphinan (56 mg.). After three recrystallisations from ether–methanol it had m. p. 81—83°. The hydrobromide had m. p. 92—93·6° (from water) and did not depress the m. p. of an authentic specimen.[3]

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