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STUDIES ON THE SYNTHESES OF HYDROGENATED QUINOLINES AND ISOQUINOLINES AS ANALGESICS—XVI*

SYNTHESIS OF N-METHYL-8-AZA-DES-N-MORPHINAN (4-METHYL-5:10b-TRIMETHYLENE-1:2:3:4:4a:5:6:10b-OCTAHYDROBENZO [*f*] QUINOLINE)

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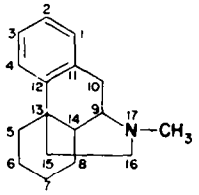
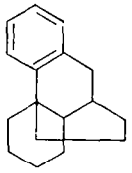
Abstract—N-Methyl-8-aza-des-N-morphinan (X) was obtained by reducing N-methyl-10-oxo-8-aza-des-N-morphinan (X) prepared by cyclizing 1-methyl-8-hydroxycarbonyl-10-phenyl-decahydroquinoline (VIII). Recent studies[1] on the synthesis of isomeric morphinans in which the nitrogen in N-methyl-morphinan (A) has migrated to positions other than 17.



A



des – N – Morphinan

OF the nine possible isomers (nitrogen in 5, 6, 7, 8, 9, 10, 14, 15, or 16 position), Sugimoto *et al.* have prepared those with nitrogen in position 6, 7, 9, or 16,[1] and Ochiai *et al.* prepared 15-aza-des-N-morphinan.[2] Pharmacological examination of these compounds was carried out. With the exception of 9-aza-des-N-morphinan, the isomers were all synthesized by formation of the B-ring, by rearrangement-cyclization of benzyloctahydro-isoquinoline or quinoline. It had been shown that the steric configurations of these synthetic compounds is the same as that of morphinan with B/C *cis* and C/D *trans*. Of these five compounds, the one with hydroxyl in 3-position and nitrogen in 9-position was found to have analgesic action equally strong as morphine, and 7-aza-des-N-morphinan was found to have analgesic activity, though weak, but 6, 15, and 16-aza-des-N-morphinans were entirely devoid of any physiological activity.

In the present work, attempted synthesis of N-methyl-8-aza-des-N-morphinan (X), was carried out by the route indicated in Chart 1. Boekelheide,[3] Backmann,[4] and

* Part XV. N. Sugimoto, *Chem. Pharm. Bull.* **6**, 429 (1958).

[1] N. Sugimoto and H. Kugita, *Pharm. Bull. Japan* **3**, 11 (1955); N. Sugimoto and S. Ohshiro, *Ibid.* **4**, 353, 357 (1956); N. Sugimoto, S. Ohshiro, H. Kugita, and S. Saito, *Ibid.* **5**, 62 (1957); N. Sugimoto and H. Kugita, *Ibid.* **5**, 67 (1957); N. Sugimoto and S. Ohshiro, *Ibid.* **5**, 316 (1957); N. Sugimoto and H. Kugita, *Ibid.* **5**, 378 (1957); N. Sugimoto and H. Kugita, *Ibid.* **6**, 429 (1958).

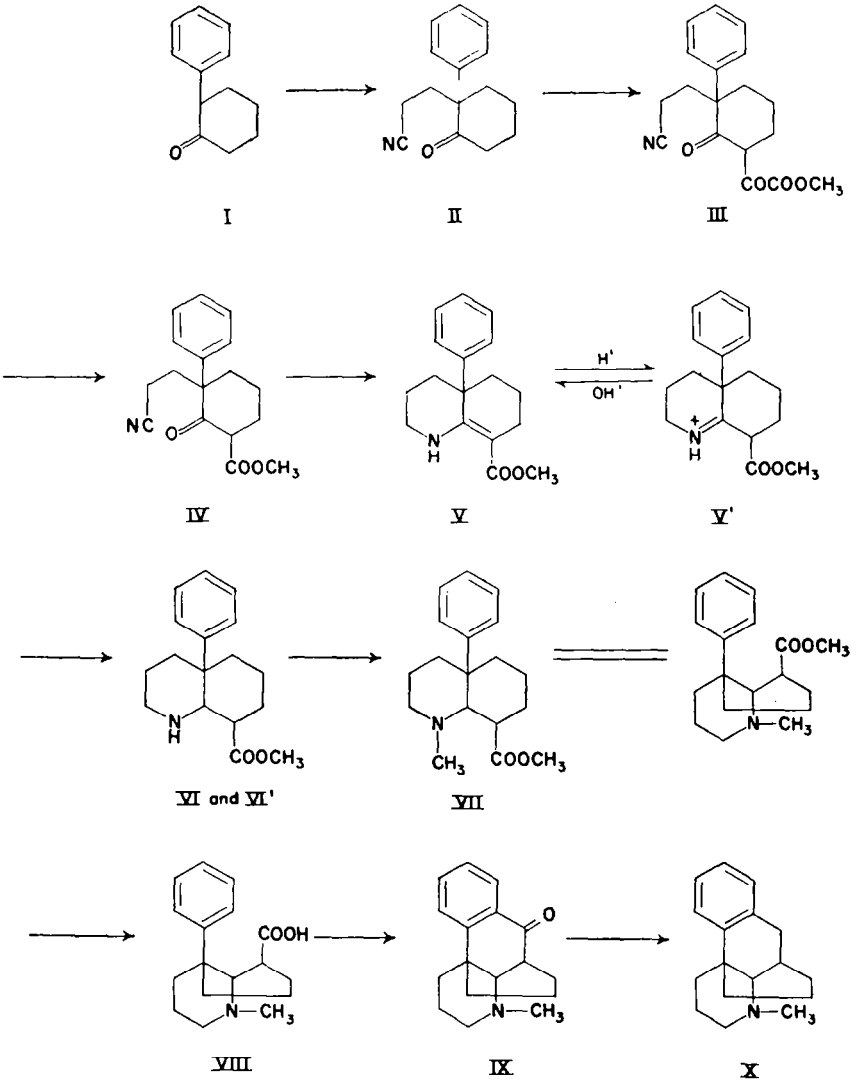
[2] E. Ochiai and K. Harasawa, *Pharm. Bull. Japan* **3**, 369 (1955).

[3] V. Boekelheide, *J. Amer. Chem. Soc.* **69**, 790 (1947).

[4] V. B. Backmann, *J. Amer. Chem. Soc.* **72**, 3388 (1950).

Sugimoto[5] had obtained 2-(β-cyanoethyl)-2-phenyl-cyclohexanone (II) by cyanoethylation of 2-phenylcyclohexanone (I). Condensation of II with methyl oxalate[6] yielded (III), which on pyrolysis gave the ketoester (IV), showing characteristic absorptions for a nitrile and β-keto-ester at 2252, 1755, 1720, 1660, and 1625 cm^{-1} (Fig. 1). Catalytic reduction of IV with Raney nickel gave the ester (V).

The structure of the ester (V) was confirmed chemically as well as by analysis and infra-red absorption spectrum.[7] In the infra-red spectrum (Fig. 2) of V, the absorption for C≡N had disappeared and instead showed absorption for —NH at 3250 cm^{-1} and for an α,β-unsaturated ester at 1650 and 1600 cm^{-1}. The infra-red spectrum of



[5] N. Sugimoto, H. Kungita and T. Fujita, *J. Pharm. Soc. Japan* **75**, 177 (1955).
[6] W. B. Backmann and L. B. Wick, *J. Amer. Chem. Soc.* **72**, 1995 (1950).
[7] K. Ohsugi, *J. Pharm. Soc. Japan* **79**, 1313 (1958).

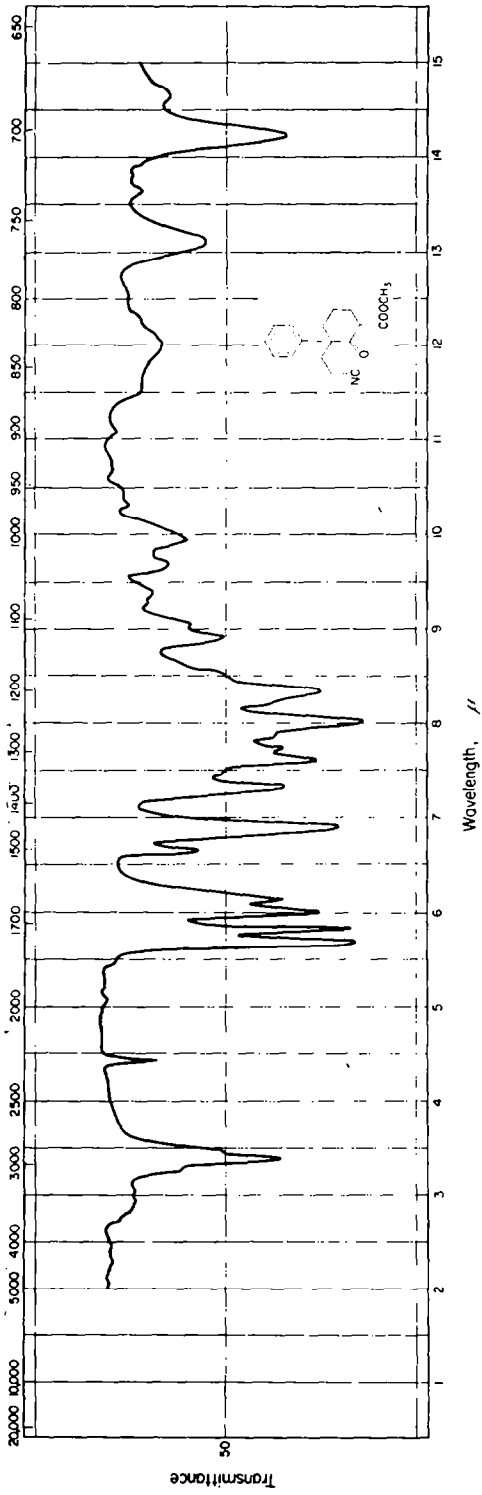

Transmittance
50
Wavelength, μ
COOCH3
NC
O

FIG. 1.

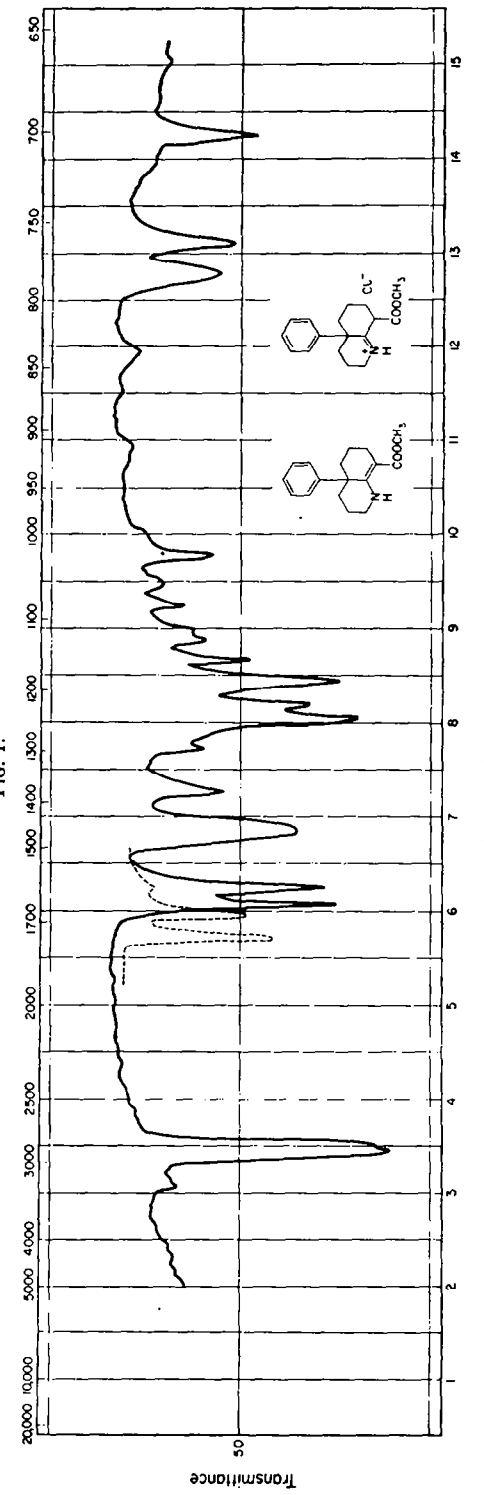

Transmittance
50
Wavelength, μ
COOCH3
CL⁻
N
H

FIG. 2.

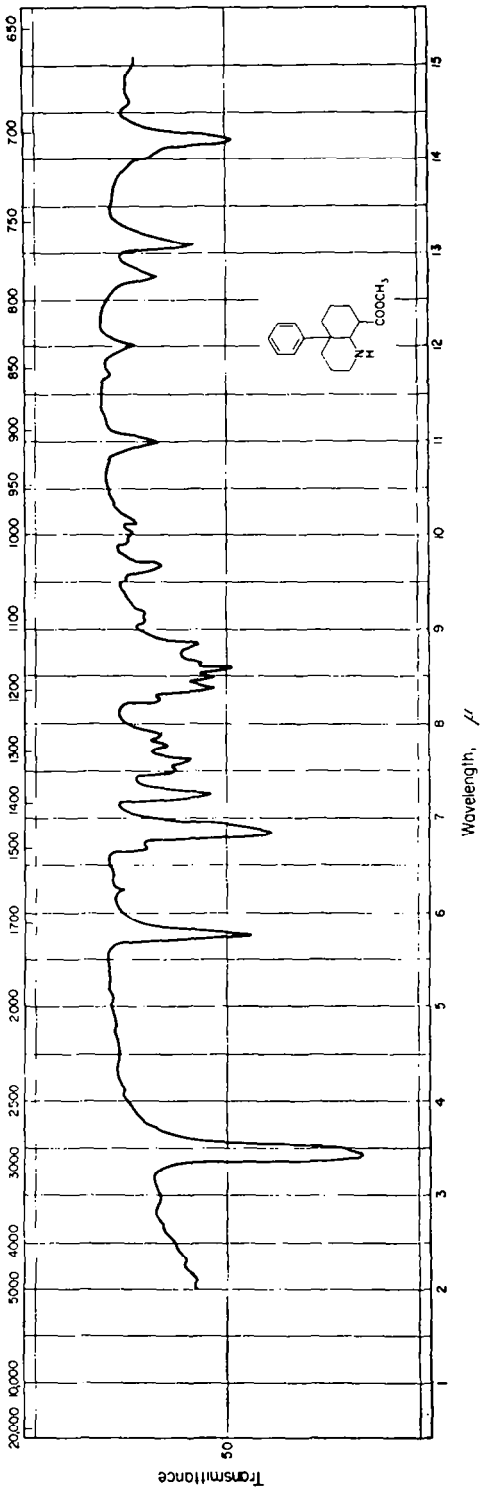

Transmittance
Wavelength, μ
COOCH3
N
H

FIG. 3.

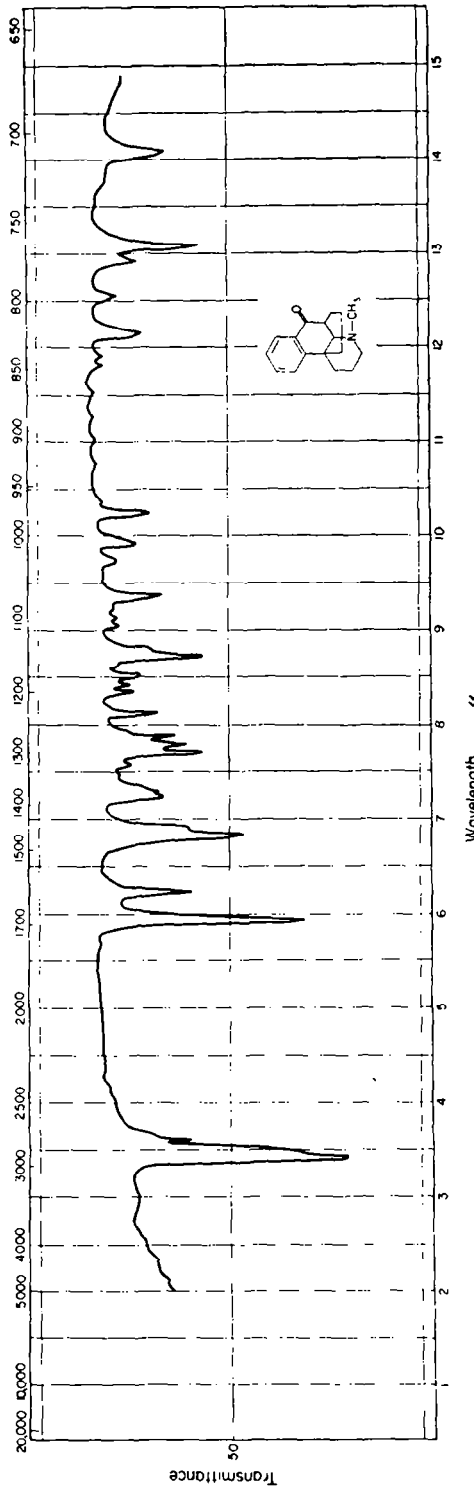

Transmittance
Wavelength, μ
N—CH3

FIG. 4.

its hydrochloride (Fig. 2) exhibits absorption for non-conjugated ester at 1745 cm^{-1} and ketimine $-C=\overset{+}{N}(H)-$ at 1685 cm^{-1}. Ferric chloride gives no reaction with V but on heating V with dilute hydrochloric acid demethoxycarbonylation takes place with evolution of carbon dioxide.

Hydrogenation of V in neutral medium, over platinum oxide, failed to effect reduction, but in acid medium, catalytic reduction of V was effected quite easily at ordinary temperature and pressure, and 1 mole of hydrogen was absorbed smoothly

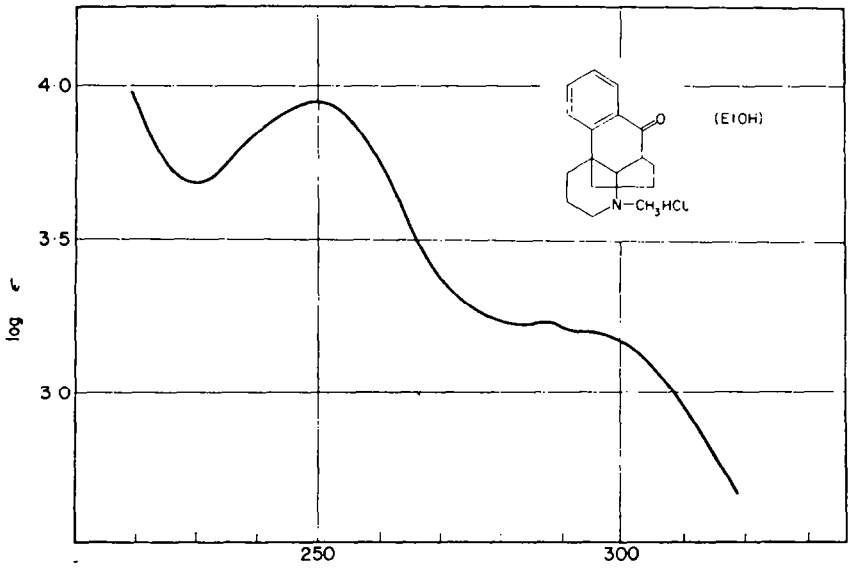


FIG. 5.

to form (VI). The infra-red spectrum of VI no longer exhibited absorption of an α,β-unsaturated ester but absorption of a non-conjugated ester was observed at 1740 cm^{-1} (Fig. 3). A crystalline hydrochloride (VI–HCl) is readily formed together with a small amount of non-crystalline hydrochloride (VI'–HCl). Methylation of VI–HCl by the conventional method yielded the N-methyl compound VII. Attempted cyclization of VII with polyphosphoric acid failed with recovery of the starting compound and VII also resisted saponification with ethanolic potassium hydroxide. Saponification was finally effected by heating with concentrated hydrochloric acid for 20 hours. The hydrochloride of (VIII) obtained was heated with polyphosphoric acid 10 hours and the cyclized product (IX) obtained. Its infra-red spectrum no longer showed characteristics of the ester but exhibited the absorption of an aromatic ketone at 1690 cm^{-1} (Fig. 4).[8] The UV spectrum of IX showed absorption maxima at 250 mμ (log ε 3·945) and at 287 mμ (log ε 3·228).[8] These facts indicated that IX is N-methyl-10-oxo-8-aza-des-N-morphinan (Fig. 5).

The Huang-Minlon reduction of the hydrazone of IX resulted in the formation of N-methyl-8-aza-des-N-morphinan (X) whose infra-red spectrum no longer showed

[8] C. D. Gutsche, *J. Amer. Chem. Soc.* 73, 786 (1951).

absorption for an aromatic ketone (Fig. 6). Analysis also proved the formation N-methyl-8-aza-des-N-morphinan.

Structure and steric configuration of X will be described in detail in the following report.

EXPERIMENTAL

2-(β-Cyanoethyl)-2-phenyl-6-methoxycarbonyl-cyclohexanone (IV). Methanol free sodium methylate prepared from sodium (2·3 g) and methanol, was suspended in benzene (60 cc) and to this solution methyl oxalate (11·8 g) was added. Phenyl-cyclohexanone-nitrile (II, 11·3 g) in benzene (70 cc) was added dropwise to the above homogeneous mixture. The mixture was kept below 5° during the addition, which required about 2 hr. The mixture was allowed to stand overnight at room temp, and then decomposed with ice-water. The aqueous layer was separated, acidified to congo red with hydrochloric acid and extracted with ether. After removal of the solvent, a red brown oil remained which was heated with finely powdered glass in an oil-bath at 160–170° under nitrogen. Evolution of carbon monoxide was complete after 10 min, and heating continued for further 15 min.

After cooling, the reaction mixture was extracted with benzene, washed with water and dried. After evaporation of the solvent, the residue was distilled giving the keto ester (IV, 8·2 g, 58%) as a pale yellow viscous oil, b.p. 195–198°/0·9 mm.

Ethanol solution of IV gave an orange yellow colour for enol test with $FeCl_3$.

8-Methoxycarbonyl-10-phenyl-1,2,3,4,5,6,7,10-octahydroquinoline (V). A mixture of keto ester (IV, 3·0 g), Raney-Ni (5·0 g), liq. ammonia (2 g) and ethanol (200 ml) sealed in a stainless steel bomb was hydrogenated in 76 atm at 150°. Absorption of hydrogen was completed after 6 hr and after cooling, the filtrate was evaporated under diminished pressure and the residue recrystallized from methanol. Methl octahydroquinoline-carboxylate (V, 1·8 g 66·2%) was obtained as colorless plates, m.p. 106–107·5.

The ethanol solution of V gave negative enol test with $FeCl_3$.

(Found: C, 75·24; H, 7·8; N, 5·16. $C_{17}H_{21}NO$ requires: C, 75·6; H, 7·8; N, 5·1%).

8-Methoxycarbonyl-10-phenyl-decahydroquinoline (VI). A solution of V (10 g) dissolved in ethanol (200 ml) and 26% ethanolic hydrogen chloride (17 ml) was hydrogenated at atmospheric pressure using PtO_2 (0·2 g). After 10 min, one equivalent (930 ml) of hydrogen was absorbed and further absorption was not observed. The filtrate from catalyst was evaporated under reduced pressure, and the residue was recystallized from methanol–ether to give 9·1 g of VI–HCl as colorless needles m.p. 243° (dec).

(Found: C, 65·91; H, 7·75; N, 4·52. $C_{17}H_{24}NO_2Cl$ requires; C, 65·8; H, 7·8; N, 5·1%).

Evaporation of the mother liquor left a non-crystalline hydrochloride (0·9 g) identification as isomer of VI–HCl will be reported in the following paper.

Free base VI was obtained by neutralization of its hydrochloride with aqueous potassium carbonate and recrystallized from methanol to give colorless columns m.p. 73–75°.

(Found: C, 74·69; H, 8·48; N, 5·12. $C_{17}H_{23}NO_2$ requires: C, 74·6; H, 8·6; N, 5·6%).

1-Methyl-8-methoxycarbonyl-10-phenyl-decahydroquinoline (VII). VI was methylated by the usual technique. The decahydro compound VI–HCl (0·5 g) was heated with 80 % formic acid (15 ml), 35% formaline solution (4·0 g) and sodium formate (0·68 g) at 95° for 10 hr. The mixture was evaporated to dryness under diminished pressure, and the residue was made alkaline with aqueous ammonia. The separated solid was filtered, washed with water and dried. Recrystallization of the residue from methanol gave colorless plates, m.p. 106–108°.

(Found: C, 75·22; H, 8·77; N, 4·87. $C_{18}H_{25}NO_2$ requires: C, 75·25; H, 8·7; N, 4·87%).

Hydrochloride; colorless plates (from methanol–ether), m.p. 242 (dec).

(Found: C. 66·75; H, 8·04; N, 4·33. $C_{18}H_{26}NO_2Cl$ requires: C, 66·5; H, 8·0; N, 4·5%).

N-Methyl-10-ox-8-aza-des-N-morphinan (IX). VII 5·2 g) was heated to boiling with HCl (50 ml) for 8 hr. Then, after addition of HCl (50 ml), heating was continued for 8 hr. The mixture was evaporated to dryness under reduced pressure, and the residue basified with 10 % aqueous sodium hydroxide and extracted with ether from which a small amount of starting material was recovered. The aqueous layer was again acidified with conc HCl, and evaporated to dryness.

Polyphospholic acid prepared from P_2O_5 (36 g) and 85 % H_3PO_4 (36 ml) was added to the above

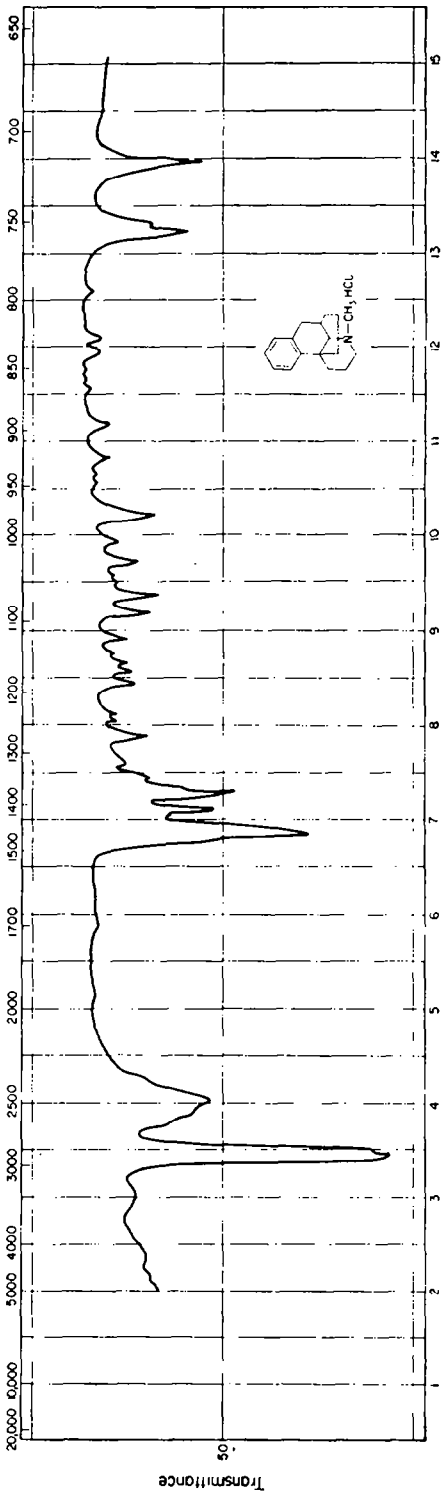


FIG. 6.

crude VIII–HCl, and the mixture was heated (oil bath) at 130–140° for 10 hr. The reaction mixture was poured on crushed ice, and basified with 30% aqueous potassium hydroxide below 10°. The alkaline mixture was extracted with ether, washed with water, and dried. After evaporation of the solvent, the residue was purified by distillation giving IX (2·9 g, 62·5%) of colorless viscous oil b.p: 170–175°/0·1 mm. The distillate solidified on treatment with methanol and recrystallization from this solvent gave colorless plates, m.p. 96–98°.

(Found: C, 79·96; H, 8·29; N, 5·49. $C_{17}H_{21}NO$ requires: C, 79·9; H, 8·2; N, 5·9%).

Hydrochloride: colorless plates (from methanol–ether), m.p. 159° (dec).

(Found: C, 65·91; H, 7·75; N, 4·52. $C_{17}H_{22}NOCl{\cdot}H_2O$ requires: C, 66·35; H, 7·85 N, 4·3%).

IX was heated with 85% hydrazine hydrate in boiling ethanol for 3 hr, to give the *hydrazone* which formed colorless plates, from aqueous ethanol, m.p. 154–156°.

(Found: C, 75·79; H, 8·61; N, 15·6. $C_{17}H_{23}N_3$ requires: C, 75·9; H, 8·25; N, 15·4%).

N-*Methyl*-8-*aza*-*des*-N-*morphinan* (X). When IX (0·5 g), and 85% hydrazine hydrate (0·3 ml) were heated (steam bath) for a few minutes, the colorless hydrazone separated. After heating for 1 hr, finely powdered potassium hydroxide (0·5 g) and propylenglycol (5 ml) were added and heating continued at 170–180° (bath temp) for 10 hr.

The mixture was cooled, diluted with water and extracted with ether, the extracts were evaporated and the residue distilled to give 0·2 g of X as a colorless viscous oil which b.p. 155–165° (bath temp)/ 0·1 mm.

Hydrochloride: colorless needles (from methanol–ether), m.p. 274–276° (dec)

(Found: C, 73·51; H, 8·6; N, 5·05. $C_{17}H_{24}NCl$ requires: C, 73·55; H, 8·55; N, 5·05%).

The *methiodide* was prepared from X and excess methyl iodide in methanol and it formed colorless columns from methanol, m.p. 267° (dec).

(Found: C, 56·2; H, 6·8; N, 3·65 $C_{18}H_{27}NI$ requires: C, 56·05; H, 6·55; N, 3·7%).

Acknowledgements—The authors are indebted to Mr. K. Kodera of this Laboratory for infra-red spectral measurement and to Mrs. F. Hisamichi and Messrs. T. Yoda and T. Kawano for elemental analyses.