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STUDIES ON THE SYNTHESES OF HYDROGENATED QUINOLINES AND ISOQUINOLINES AS ANALGESICS—XVII[1]

THE STERIC STRUCTURE OF N-METHYL-8-AZA-DES-N-MORPHINAN

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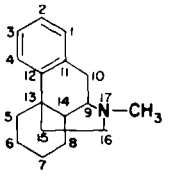
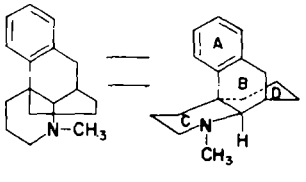
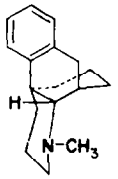
Abstract—The configuration of positions 13 and 14 in N-methyl-8-aza-des-N-morphinan[1] has been investigated. Potassium t-but-oxide in t-butanol converts N-acetyl-10-oxo-8-aza-des-N-morphinan (XVI) into 10-hydroxy-8,10-(α-oxo-ethano)-8-aza-des-N-morphinan (XVII). Formation of these new lactams is possible only when rings B and C are *cis*. It follows, therefore, that 8-aza-des-N-morphinan synthesized in this investigation has B/C in *cis* and C/D in *trans* positions the same as the steric structure of morphinan (M).



M



XIII a

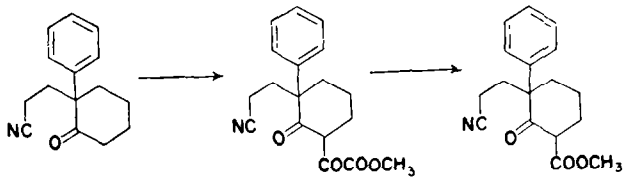


XIII b

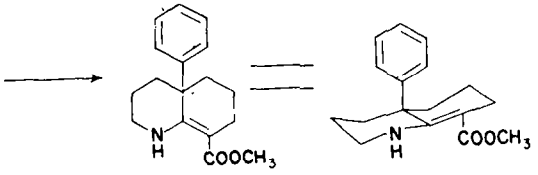
THE series of des-N-morphinan compounds with nitrogen shifted to position 6, 7, 9, 15, or 16 reported since 1955 are all compounds of morphinan type.

Condensation of 2-(β-cyanoethyl)-2-phenylcyclohexanone (I) with methyl oxalate, in the presence of sodium methoxide, and subsequent decarbonylation yielded the keto ester (III) which on reduction give methyl octahydroquinol-inecarboxylate (IV). In this case, only one ester was obtained and no isomers were detected. Heating of IV with dilute hydrochloric acid effects demethoxy-carbonylation to form octahydroquinoline (V) whose infra-red spectral analysis indicates absorptions for —NH— at 3250 cm^{-1} and for —C=CH— at 1660 cm^{-1} in neutral medium, and an absorption for $-C=\overset{+}{N}H-$ of ketimine at 1692 cm^{-1} in acid medium (V'), showing V to be an α,β-unsaturated amine.[2] Catalytic reduction of V' at ordinary pressure, using platinum oxide, results in rapid absorption of one mole of hydrogen to form decahydroquinoline (VI). The infra-red spectrum of VI failed to show the absorption of an α,β-unsaturated amine and that this compound is represented by the structure VI was proved by mixed m.p. of its picrate with that of 10-phenyldecahydroquinoline previously synthesized by Sugimoto *et al.*[3]

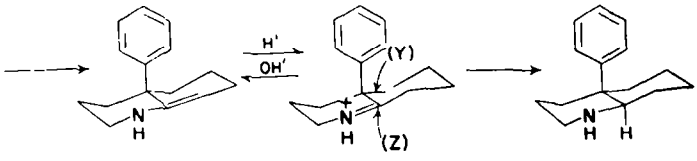
[1] Part XVI: N. Sugimoto and S. Ohshiro, *Tetrahedron* **8**, 296 (1960).
[2] N. J. Leonard, *J. Amer. Chem. Soc.* **78**, 3463 (1956).
[3] N. Sugimoto, H. Kugita and T. Fujita, *J. Pharm. Soc. Japan* **75**, 177 (1955); N. Sugimoto and H. Kungita, *Pharm. Bull. Tokyo* **5**, 378 (1957).



I II III



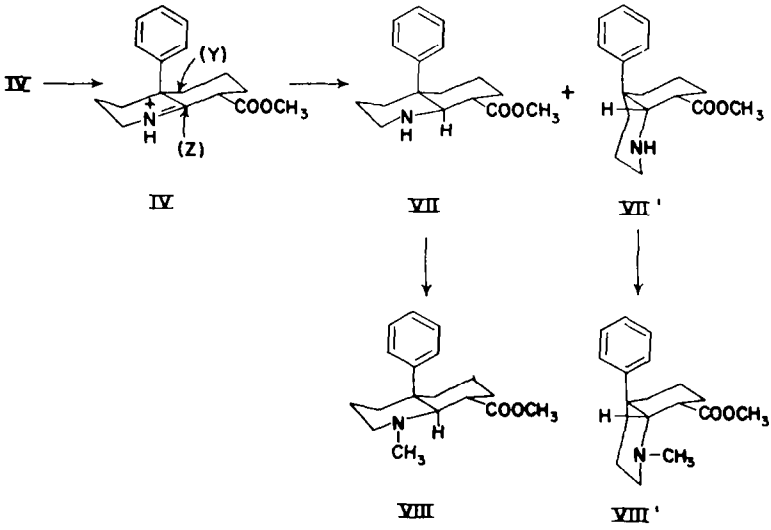
IV



V V' VI

In the catalytic reduction of octahydroquinoline (V'), addition of hydrogen could take place from the direction of either Y or Z but the addition of hydrogen from direction Z with less steric hindrance seems theoretically more probable. The fact that only one product has been obtained makes it certain that VI is a *trans* compound.

Examination of molecular a model has shown that the conformation of compound IV has the 10-phenyl group axial to octahydroquinoline and the methoxycarbonyl



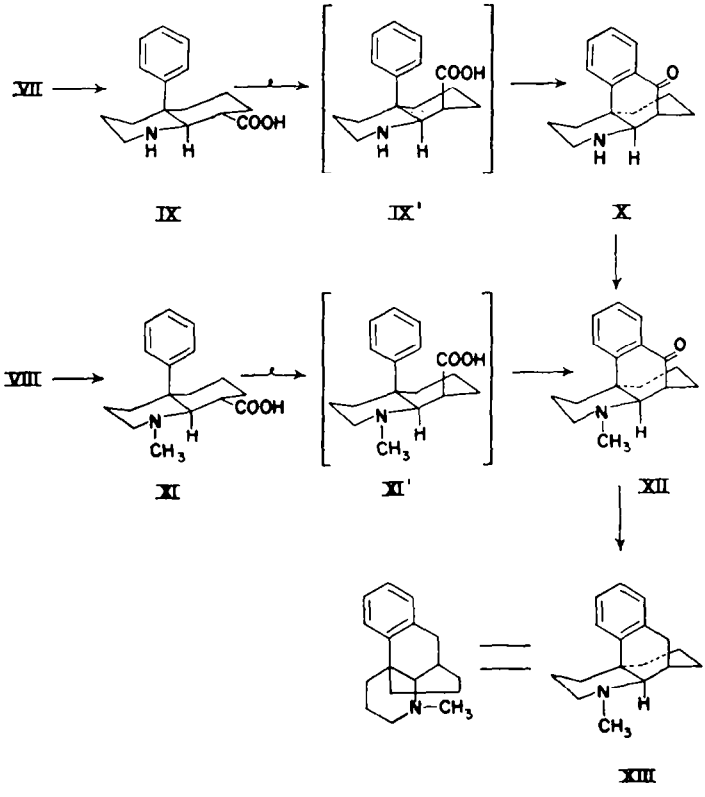
IV VII VII'

VIII VIII'

group on the same plane as the octahydroquinoline. In acid medium, the double bond in conjugation with methoxycarbonyl would form ketimine (IV) by prototropy with the imino group and excluded from conjugation with the methoxycarbonyl group,[1] and the configuration of the latter on the same plane as octahydroquinoline, would be shifted to *trans* (equatorial) position with regard to the axial phenyl group because it is assumed that the methoxycarbonyl group cannot take a *meta*-diaxial conformation in relation to the large molecule of phenyl in the axial position.

Hydrogenation of the ketimine (IV') yielded two isomers VII and VII' indicated by analyses and infra-red spectral analyses. It is clear that in this case, hydrogenation is more likely to be made on the Z side of the equatorial methoxycarbonyl group and not on the Y side of the axial phenyl group. It is assumed that crystalline VII obtained in a larger quantity is the 9,10-*trans* compound and liquid VII' obtained in a smaller amount is the 9,10-*cis* compound.

Methylation of VII and VII' gave the methylated compound VIII, m.p. 106–108°, and VIII' of m.p. 95–96° respectively. A mixture of the two showed a m.p. depression.



Cyclization of ester (VIII) with polyphosphoric acid and saponification by heating with ethanolic or aqueous sodium hydroxide failed,[1] indicating that VIII is a stable compound which does not undergo steric rearrangement.

Saponification of VIII was finally effected with hydrochloric acid and heating of N-methyl-decahydroquinolinecarboxylic acid (XI) so formed with polyphosphoric acid

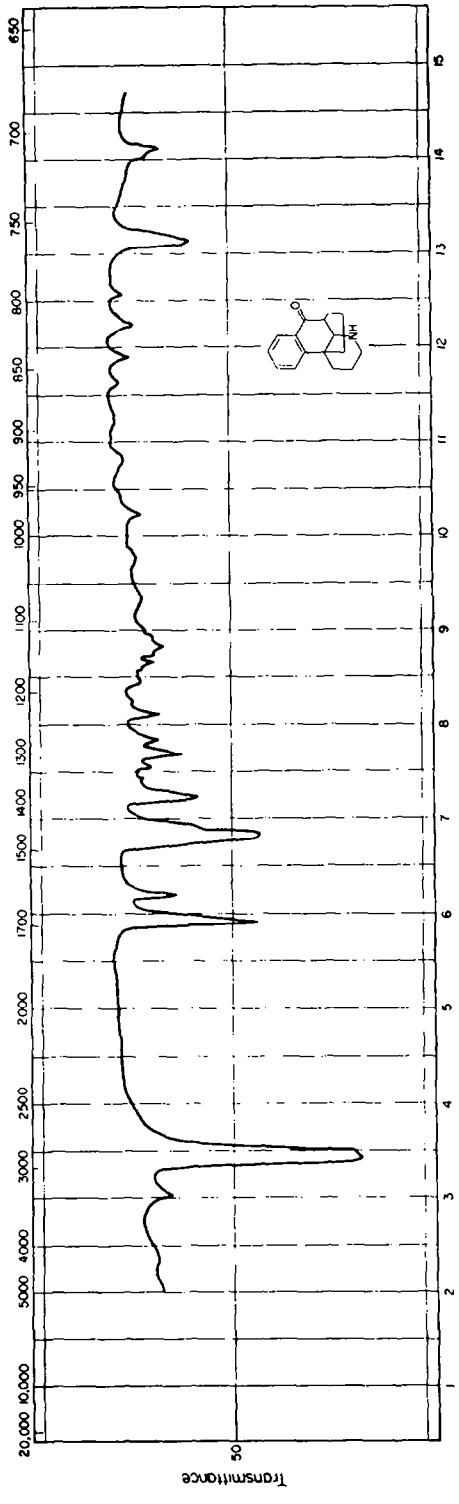

Transmittance
50
Wavelength, μ
20,000 10,000 5000 4000 3000 2500 2000 1700 1500 1400 1330 1200 1100 1000 950 900 850 800 750 700 650
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
NH
O

FIG. 1.

gave N-methyl-10-oxo-des-N-morphinan (XII).[1] It is assumed that, in this case, the carboxyl group of XI undergoes epimerisation by heating, and assumes *meta*-diaxial conformation with the phenyl group, forming XI′ with subsequent cyclization-condensation with the phenyl group to form XII. As stated above, this reaction does not involve rearrangement of the configuration in the decahydroquinoline ring, its *trans* nature being maintained throughout these reactions.

On the other hand, the compound IX was prepared from VII by the same reaction route, and 10-oxo-des-N-morphinan (X) was prepared via the epimer IX′ of IX.

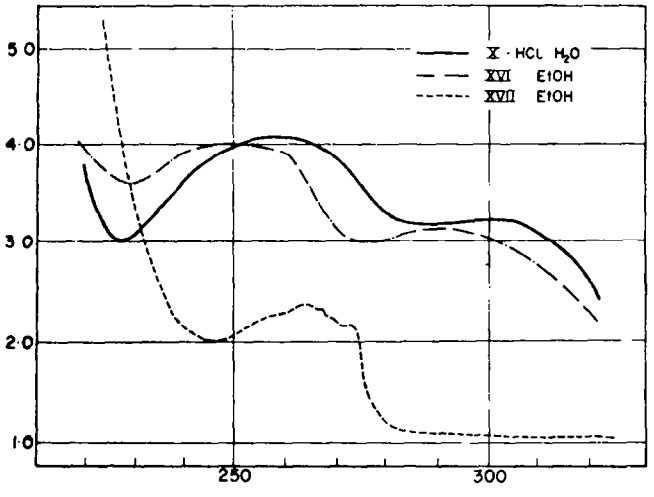
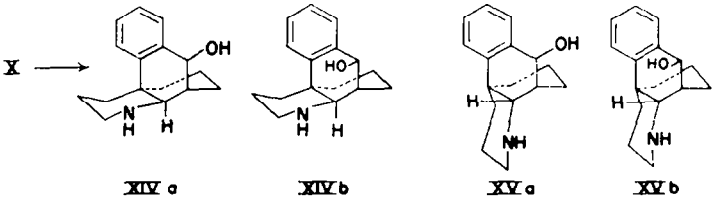


FIG. 2.

Infra-red spectrum of this compound (X) indicated absorptions of =NH at 3300 cm^{-1}, of an aromatic ketone at 1690 cm^{-1}, and an out-of-plane vibration of *ortho*-substituted benzene at 760 cm^{-1} (Fig. 1). The U.V. spectral curve of X exhibits characteristic absorptions of an aromatic ketone (Fig. 2).[4] Methylation of X gives a compound identical with N-methyl-10-oxo-8-aza-des-N-morphinan (XII) previously synthesized.

The preparation of N-methyl-8-aza-des-N-morphinan (XIII) by the Huang-Minlon reduction of XII has been described.[1]

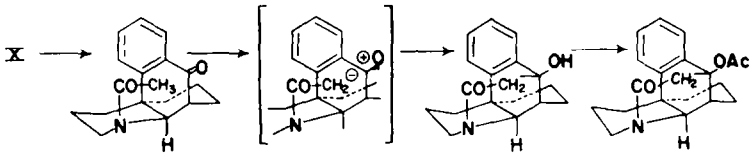


XIV a XIV b XV a XV b

Catalytic reduction of the hydrochloride of X gave 10-hydroxy-8-aza-des-N-morphinan (XIVa m.p. 137–139°), and no isomer was detected. There is a possibility of two isomers, by reduction of the ketone group in quasi-equatorial form (XIVa) and in quasi-axial form (XIVb).

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

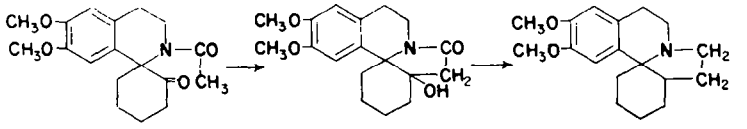
In the morphinan-type (XIVa), C^{14}—C^{8} lies axial to the B-ring with hydroxyl in quasi-equatorial conformation, while in XIVb C^{14}—C^{8} lies axial to the B-ring with hydroxyl in quasi-axial conformation. In the isomorphinan-type (XVa), this C^{14}—C^{8} bond lies equatorial to the B-ring, with hydroxyl in quasi-equatorial conformation, and in XVb, the C^{14}—C^{8} is equatorial to the B-ring with hydroxyl in quasi-axial conformation. That XIVb should be the most unstable of all the four possible isomers, is self-explanatory from the fact that it assumes *meta*-diaxial conformation. If XIV is a morphinan type, there is a possibility of the formation of XIVa alone, while if it is an isomorphinan type, it would be possible to expect formation of a mixture of XVa and XVb. Since only one kind of hydroxy compound had been obtained, it is likely that this compound (XIV) is in morphinan-type configuration.



XVI XVII XVIII

Acetylation of X gave XVI whose infra-red and ultra-violet spectral curves are shown in Figs. 3 and 2. Heating of XVI with potassium t-butoxide results in intramolecular proton migration, a piperidone ring being formed. This fact is proved by its infra-red spectrum (Fig. 3) showing absorptions for hydroxyl at 3240 cm^{-1} and a six-membered ring acid amide —NH—CO— at 1620 cm^{-1}, and disappearance of a carbonyl absorption. The ultra-violet spectral curve of XVII (Fig. 2) indicates the disappearance of the characteristic absorption of an aromatic ketone, leaving the absorption of a benzene ring.

Acetylation of XVII afforded the acetoxy compound (XVIII), whose infra-red spectrum (Fig. 4) indicates absorption for ester at 1725 cm^{-1}, and no hydroxy absorption. Such transfer of a proton from acetamide to a ketone with formation of a new ring-lactam is similar to the following reaction which was utilized by Sugasawa and Yoshikawa[5] for the synthesis of erythrinane.



Possibility of condensed-ring formation between the ketone at 10 and acetyl group at 8-position was examined with a model. The results clearly indicate that this reaction is possible only in the morphinan type XIIIa since the distance between the methyl in acetyl and the carbonyl is too great in the isomorphinan type XIIIb.

8-Aza-des-N-morphinan prepared by Sugimoto and Ohshiro[1] is, therefore, a morphinan type XIIIa with B/C in *cis* and C/D in *trans*. At the same time, the steric configurations assumed above for the intermediates formed during the course of these reactions are correct.

[5] S. Sugasawa and H. Yoshikawa, In press.

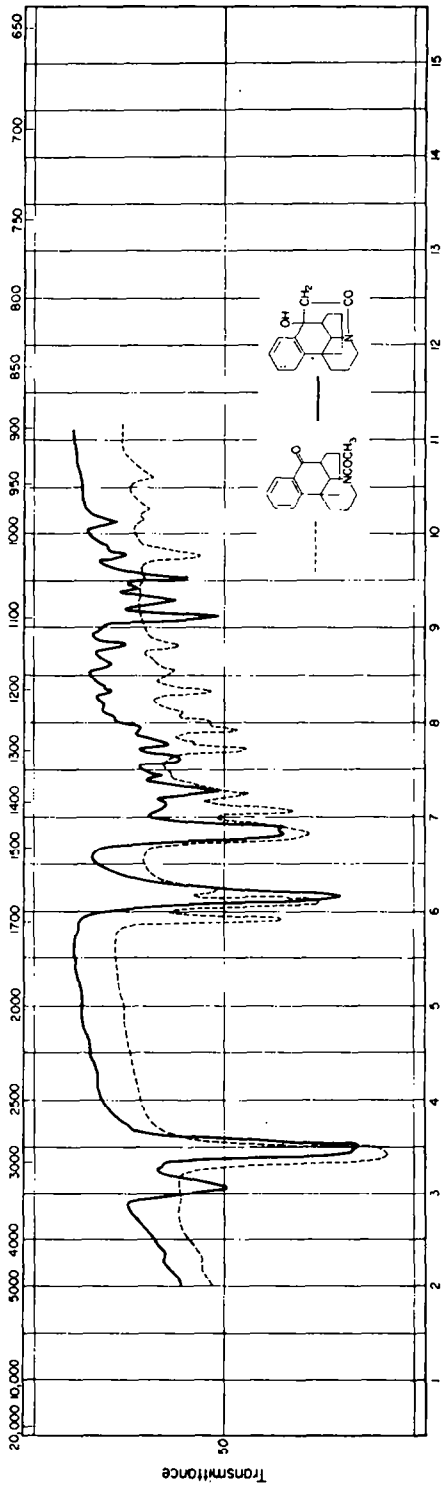


FIG. 3.

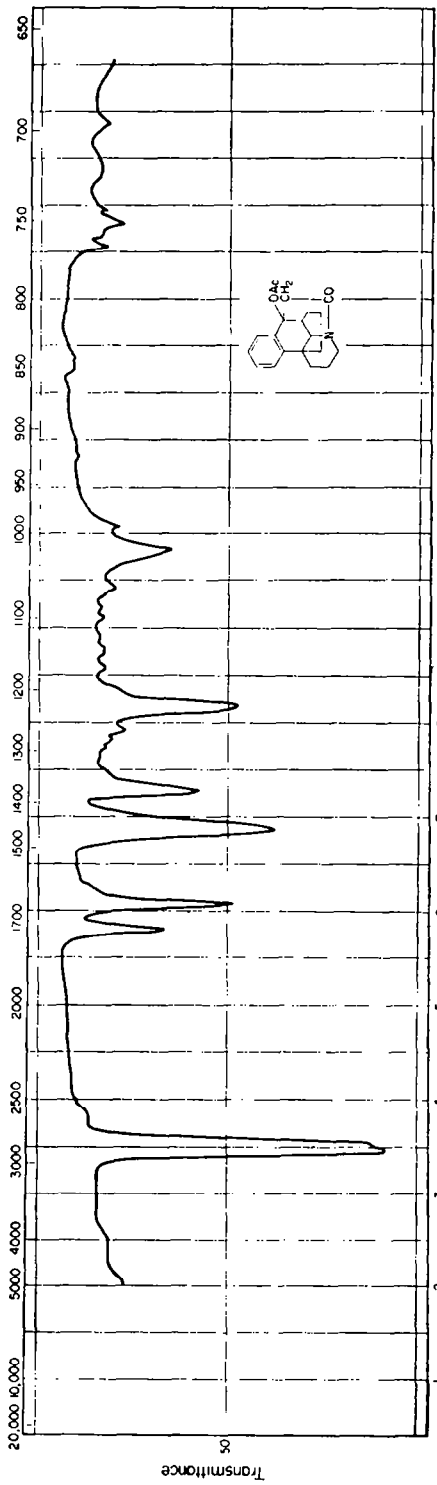


FIG. 4.

EXPERIMENTAL

10-*Phenyl*-1,2,3,4,5,6,7,10-*octahydroquinoline* (V). Methyl 10-phenyl-octahydroquinoline carbonate (IV, 1·0 g) was dissolved in 20% HCl (7 ml), and heated (steam bath) for 5 hr. The mixture was evaporated to dryness under reduced pressure, and the residue basified with aqueous potassium carbonate. The base (r) was extracted with ether, dried and evaporated and (0·8 g) was obtained as a colorless oil b.p. 115–118°/0·5 mm.

Perchlorate: Recrystallization from aqueous methanol gave colorless plates, m.p. 174–176°.

(Found: C, 57·41; H, 6·38; N, 4·46. $C_{16}H_{20}NO_4Cl$ requires: C, 57·55; H, 6·5; N, 4·4%).

Picrate: yellow needles (from acetone), m.p. 152–153°.

10-*Phenyl-decahydroquinoline* (VI). The V-$HClO_4$ (0·7 g) in ethanol (25 ml) was hydrogenated at atm press with PtO_2 (0·2 g). One equivalent hydrogen (95 ml) was absorbed in 5 min, with no further absorption. The catalyst was filtered and the filtrate concentrated under reduced pressure. Recrystallization of the residue from aqueous methanol gave decahydroquinoline (VI)-$HClO_4$ as colorless columns, m.p. 215–217: a mixed m.p. with an authentic sample[5] showed no depression.

Picrate: yellow needles (from acetone), m.p. 157–158°.

These results indicate that the product VI is identical with the product prepared by Sugimoto.[5]

Isomeric N-*methyl*-8-*methoxycarbonyl*-10-*phenyl-decahydroquinoline* (VIII'). Isomeric decahydroquinoline (VII', 0·6 g), obtained by hydrogenation of octahydroquinoline (IV) as described in the previous paper, was methylated with formic acid (5 ml) and formalin solution (1 ml). The crude decahydroquinoline (VIII') was recrystallized from methanol to give colorless plates, m.p. 95–96°. Mixed m.p. with VIII m.p. 106–108° was depressed to 75–80°.

(Found: C, 75·25; H, 8·77; N, 4·87. $C_{18}H_{25}NO_2$ requires: C, 75·2; H, 8·7; N, 5·15%).

10-*Oxo*-8-*aza-des*-N-*morphina* (X). 8-Methoxycarbonyl-10-phenyl-decahydroquinoline hydrochloride (VII)-HCl (0·5 g) was heated to boiling with conc HCl (20 ml) for 10 hr, and the mixture was evaporated under reduced pressure.

The residue, amino acid–HCl (IX) was, without purification, heated (oil bath) at 130–140° for 8 hr, with polyphosphoric acid prepared from 85% H_3PO_4 (6 ml) and P_2O_5 (6 g). The mixture was cooled and diluted with ice-water, and basified with aqueous 30% KOH and chilled below 10°.

The oil was extracted with ether, the combined extracts washed with water, dried, and evaporated. The residue solidified on treatment with ether and recrystallization from this solvent yielded 10-*oxo*-8-*aza-des*-N-*morphinan* (X, 0·15 g) as colorless columns, m.p. 90–92°.

(Found: C, 79·63; H, 7·94; N, 5·80. $C_{16}H_{19}NO$ requires: C, 79·5; H, 7·9; N, 5·75%).

X (120 mg) was methylated with methyl sulfate (60 mg) and powdered potassium carbonate (110 mg) in acetone. Methylated product (from methanol, m.p. 95–97°) was identified by a mixed m.p. with an authentic sample prepared in the previous paper.

N-*Acetyl*-10-*oxo*-8-*aza-des*-N-*morphinan* (XVI). 10-Oxo-8-aza-des-N-morphinan (X, 0·3 g) was acetylated with acetic anhydride (2 ml) and pyridine (1 ml) by heating (steam bath) for 6 hr. The mixture was decomposed with ice-water, and the product recrystallized from ethanol yielding the N-*acetyl derivative* (XVI, 0·3 g) as colorless plates, m.p. 195–197°.

(Found: C, 76·29; H, 7·47; N, 4·94. $C_{18}H_{21}NO_2$ requires: C, 76·4; H, 7·3; N, 5·25%).

10-*Hydroxy*-8,10-(α-*oxo-ethano*)-8-*aza-des*-N-*morphinan* (XVII). XVI (170 mg) in t-buthanol (3 ml) was added to the solution of potassium (50 mg) in t-buthanol (3 ml), and the mixture gently refluxed (water bath) for 5 hr. The solvent was removed and the residue diluted with water repeatedly extracted with ethylacetate. The combined extracts were washed, dried and evaporated.

The residue was purified by repeated recrystallization to give 10-hydroxy-8,10-(α-oxo-ethano)-8-aza-des-N-morphinan (XVII, 130 mg) as colorless columns, m.p. 238–240°.

(Found: C, 76·29; H, 7·47; N, 4·94. $C_{18}H_{21}NO_2$ requires: C, 75·93; H, 7·47; N, 4·97%).

10-*Acetoxy*-8,10-(α-*oxo-dethano*):8-*aza-des*-N-*morphinan* (XVIII). XVII (350 mg) was heated with acetic anhydride (5 ml) and conc H_2SO_4 (0·1 ml) (steam bath) for 10 hr. The mixture was decomposed with ice-water, and the product recrystallized from ether yielding the *acetoxy derivative* (XVIII) as colorless columns, m.p. 188–190°.

(Found: C, 73·83; H, 7·12. $C_{20}H_{23}NO_3$ requires: C, 73·5; H, 7·24%).

10-*Hydroxy*-8-*aza-des*-N-*morphinan* (XIVa). X (0·3 g) was dissolved in ethanol (20 ml) and 17% ethanolic hydrogen chloride (3 ml). This solution was hydrogenated at atm press using PtO_2 (0·1 g) as catalyst. One equivalent (32 ml) of hydrogen was absorbed in 25 min, after which hydrogenation

became slow. The filtrate from the catalyst was distilled and the residue recrystallized from ethanol–ether, giving XIVa-HCl (0·3 g) as colorless needles, m.p. 264° (decom).

(Found: N, 5·01. $C_{16}H_{22}NOCl$ requires: N, 5·35%).

Neutralization of the hydrochloride with aqueous potassium carbonate gave the free base (XIV) which was recrystallized from petroleum ether to give colorless needles, m.p. 137–139°.

(Found: C, 78·96; H, 8·70; N, 5·76. $C_{16}H_{21}NO$ requires: C, 79·2; H, 8·5; H, 5·8%).

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