Tetrahedron, 1960, Vol. 10, pp. 175 to 181. Pergamon Press Ltd. Printed in Northern Ireland

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

SYNTHESIS OF 3-HYDROXY-N-METHYL-8-AZA-DES-N-MORPHINAN. (4-METHYL-9-HYDROXY-5·10b-TRIMETHYLENE-1,2,3,4,4a,5,6,10b-OCTAHYDROBENZO [F] QUINOLINE)

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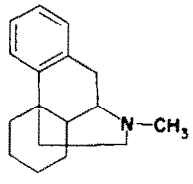
(*Received* 22 *March* 1960)

Abstract—The introduction of a hydroxy group into N-methyl-8-aza-des-N-morphinan at the 3-position was achieved through nitration of the parent compound, followed by reduction and diazocization. The position of the substituent was determined by the spectral evidence from 3-methoxy-10-oxo-8-aza-des-N-morphinan which was derived from 3-hydroxy-8-aza-des-N-morphinan via the oxidation of 3-methoxy-derivative. A pharmacological study of the compound is also presented.

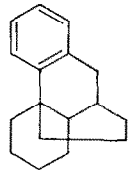
IT is a well known fact that the introduction of a hydroxy group into N-methylmorphinan at the 3-position produces a marked increase in its analgesic properties.[2]

With respect to this fact, Sugimoto *et al.* have introduced the hydroxy group at the 3-position of their N-shifted morphinan isomers, e.g. 9, 15, 16, 6 and 7-aza-des-N-morphinan for possible pharmacological benefits.[3]

The present author reports consecutively the introduction of a hydroxy group into



N—methyl—morphinan



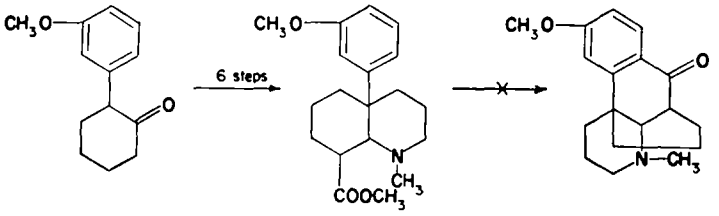
des—N—morphinan

N-methyl-8-aza-des-N-morphinan and the pharmacological testing of the resulting 3-hydroxy compounds.

Sugimoto and the present author reported the synthesis of a preliminary compound, N-methyl-8-aza-des-N-morphinan, starting with 2-phenylcyclohexanone. In the present study 2-(*m*-methoxyphenyl)-cyclohexanone(I) was utilized as the starting material and 1-methyl-8-methoxycarbonyl-10-(*m*-methoxyphenyl)-decahydroquinoline(II) was synthesized by a route analogous to that used for the corresponding desmethoxy compound. After the hydroxylis of the methyl ester ring closure of the resulting carboxy compound with polyphosphoric acid was attempted. Intractable

[1] Part XVII: S. Ohshiro, *Tetrahedron* **8**, 304 (1960).
[2] O. Schneider and A. Grüssner, *Helv. Chim. Acta* **32**, 821 (1949); O. Schneider and J. Hellerbach *Ibid.* **33**, 1437 (1950).
[3] N. Sugimoto and H. Kugita, *Pharm. Bull. Tokyo* **3**, 11 (1955); E. Ochiai and K. Harasawa, *J. Pharm. Soc. Japan* **77**, 168, 172 (1957); N. Sugimoto and S. Ohshiro, *Pharm. Bull. Tokyo* **4**, 357 (1956); N. Sugimoto and S. Ohshiro, *Ibid.* **5**, 316 (1957); N. Sugimoto and H. Kugita, *Ibid.* **6**, 427 (1958).

material resulted instead of the ketonic compound III probably due to the production of phenolic material by the demethylation that would take place during the reaction. No further attempt of ring closure has been conducted.

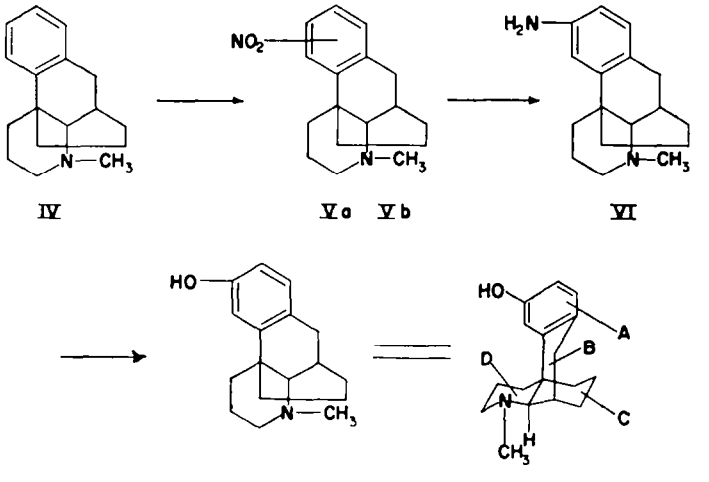


I II III

The most feasible alternative approach to the title compound appeared to be through the nitration of N-methyl-8-aza-des-N-morphinan(IV).[1] Nitration[2,4] of IV in acetic acid with fuming nitric acid gave a mixture of two isomers, from which an isomer Va separated slowly, on standing, as pale yellow crystals m.p. 94–96° in a yield of 57 per cent. The rest was converted to picrate; repeated recrystallizations finally gave two pure picrates of m.p. 227–229° and 221–223°. The higher-melting picrate gave the free base Va m.p. 94–96°, while an isomer of the free base Vb m.p. 83–85° in a poor yield, was obtained from the other. These two bases were proved by their analytical values and I.R. spectra to be isomeric with respect to the position at which the nitro group was attached.

It can be assumed that the nitration of this type of compound would take place at the 2 and/or 3 positions and it is probably the case in the present study that the 3-position would be favoured due to less steric hindrance and the reactivity which is induced by hyperconjugation at the *p*-position.

From the above considerations the nitro compound of higher yield was tentatively designated as 3-nitro-N-methyl-8-aza-des-N-morphinan and used for the further



IV Va Vb VI VII

[4] M. Gates and W. G. Webb, *J. Amer. Chem. Soc.* **80**, 1186 (1958).

studies, while the other product of lower yield—not more than 5 per cent yield—as 2-nitro-8-aza-des-N-morphinan, which consistently showed the out-of-plane vibration of a 1,3,4-trisubstituted benzene in its I.R. spectrum.

The 3-nitro compound (Va) was reduced catalytically to the 3-amino compound (VI) from which 3-hydroxy-8-aza-N-morphinan was obtained through the intermediate diazo compound. The 3-hydroxy compound(VII) is soluble in alkali hydroxide- and insoluble in alkali carbonate and with ferric chloride it gave an orange-yellow colour. The I.R. spectrum is presented in Fig. 1.

VII was converted to the 3-methoxy compound(VIII) by the action of diazo-

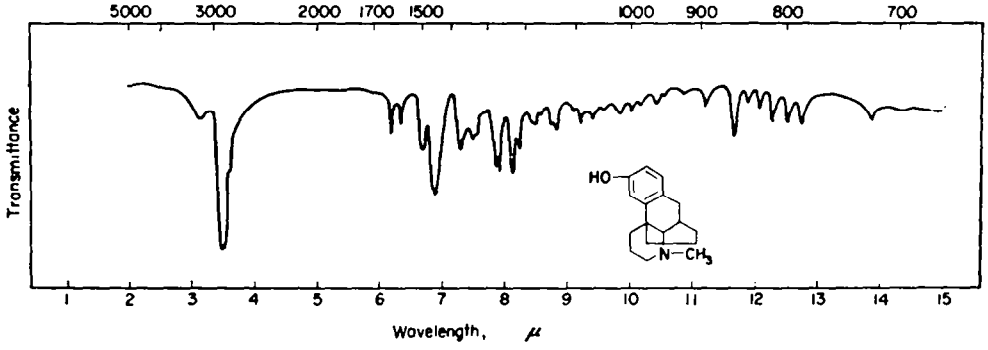


FIG. 1.

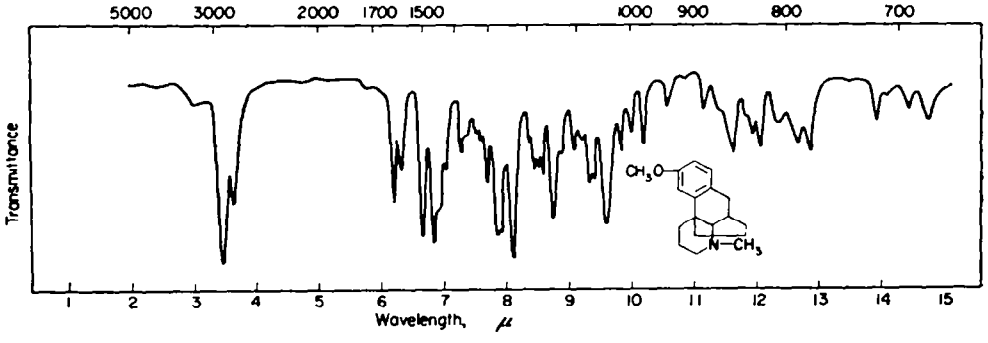


FIG. 2.

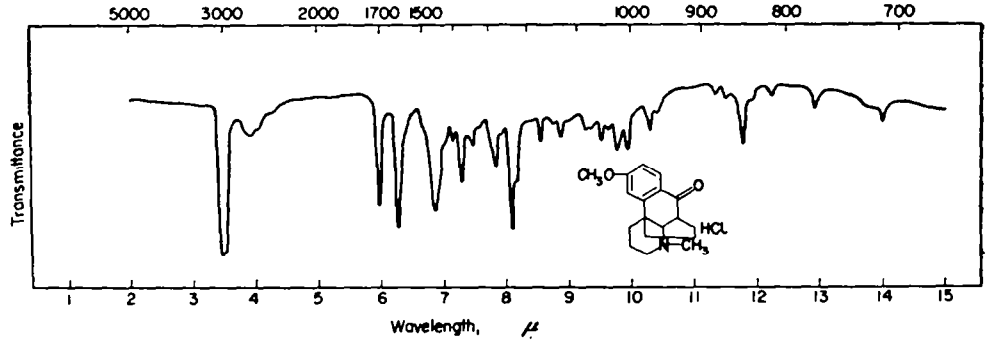
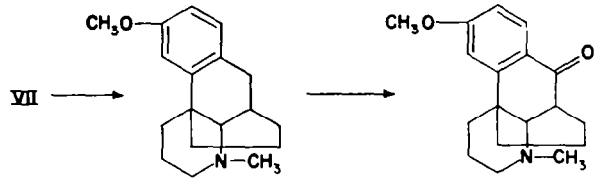


FIG. 3.

methane. Chromic acid oxidation[5] of VIII furnished the 10-oxo-compound IX. The presence of a carbonyl group in IX at the 10-position was clearly indicated by the spectral evidence; The I.R. spectrum (Fig. 3) has a strong band at 1680 cm^{-1} characteristic of aryl ketones.



VIII IX

The comparison of the U.V. spectra (Fig. 5) of 6-methoxy and 7-methoxy-α-tetralone with that of the present methoxy compound appeared to provide most valuable information supporting structure IX for the methoxy compound. There is some

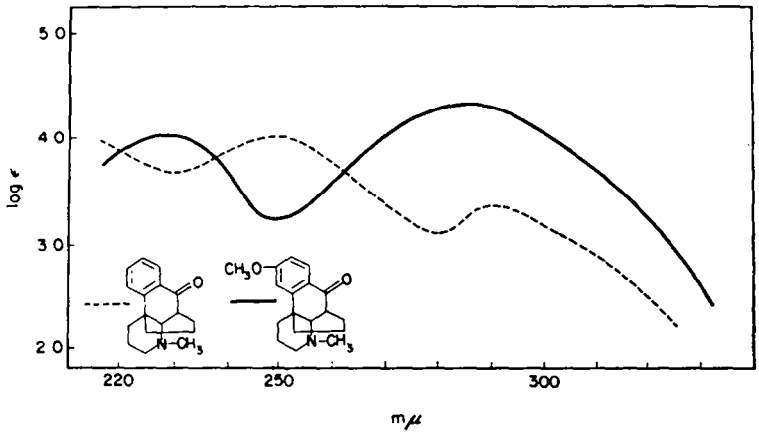


FIG. 4.

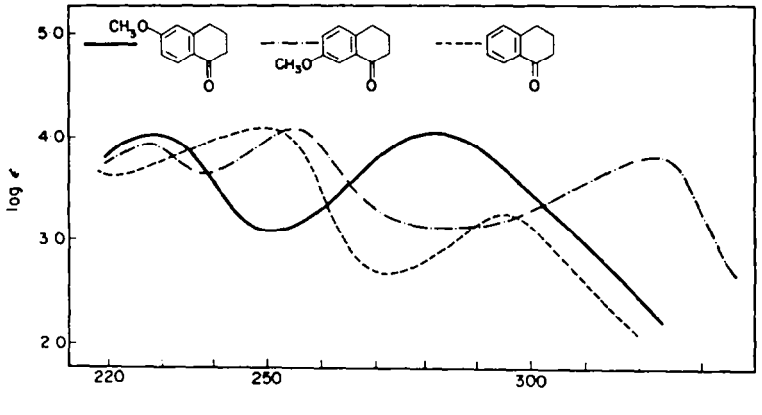


FIG. 5.

[5] O. Schneider, M. Walter and A. Brossi, *Helv. Chim. Acta* **39**, 2053 (1956).

relationships between α-tetralone and methoxy-substituted α-tetralones in their U.V. spectra.[6,7]

(1) Introduction of a methoxy group at the 5 or 7-position of α-tetralone produces a marked bathochromic shift from 293 mμ to 325 mμ of its first band, but does not change the second band at 248 mμ. (2). Introduction of a methoxy group at the 6-position of α-tetralone leaves its first band unchanged, contrary to the above observation, while it shifts the second band bathochromically from its normal position to 277 mμ, so that it falls almost on the first band. As can be seen in Fig. 4 this same relation can be found between the U.V. spectrum of N-methyl-10-oxo-8-aza-des-N-morphinan and that of the methoxy derivative(IX). It is therefore most likely that the present methoxy derivative is 3-methoxy-10-oxo-8-aza-des-N-morphinan(IX) and consequently the nitro compound (Va) is 3-nitro-8-aza-des-N-morphinan.

As for the stereochemical nature of 3-hydroxy-N-methyl-8-aza-N-morphinan (VII) it can be safely concluded that the compound has the same ring configuration (B/c:*cis*) as that of starting material, N-methyl-8-aza-des-N-morphinan which was proved to be the same as morphine in its ring structure.

Pharmacological tests of the compound VII were made by Dr. H. Fujimura in the Pharmacological Department, University of Kyoto, for analgesic activity in mice. Its toxicity was 0·79 mg/10 g by intraperitoneal injection, showing it to be somewhat stronger than that of codeine. Analgesic action measured by the Haffner, D'Amour-Smith method, and inhibiting effect of stretching gave the following results.

	Compound (VII)	Codeine phosphate
Haffner method	ED_{50} 0·38 mg/10 g	ED_{50} 0·50 mg/10 g
D'Amour-Smith method	ED_{50} 0·19 mg/10 g	ED_{50} 0·178 mg/10 g
Inhibiting effect of stretching	ED_{50} 0·044 mg/10 g	ED_{50} 0·048 mg/10 g

Accordingly, VII showed analgesic action about equal to that of codeine. Antitussive action was determined by Dr. Y. Kasé of the Pharmaceutical Department, University of Kumamoto, by the Kasé method,[8] using a dog and a cat.

A value of minimal antitussive dose was 2·5 mg/kg (dog) and 2·12 mg/kg (cat), while that of control codeinephosphate was 3·76 mg/kg and 2·53 mg/kg, respectively, showing VII to be somewhat stronger than codeinephosphate.

EXPERIMENTAL

3-Nitro-N-methyl-8-aza-des-N-morphinan (Va). A solution of IV (1·5 g) in glacial acetic acid (5 cc) was added dropwise with stirring to the solution of fuming nitric acid (d = 1·52, 7·5 cc) in glacial acetic acid (4·4 cc), cooled to 3° during 1½ hr, at a temp below 5°. The reaction mixture was allowed

[6] T. Momose, Y. Ohkura and S. Goya, *Pharm. Bull. Tokyo* **3**, 401 (1955).
[7] K. Miki, *J. Pharm. Soc. Japan* **61**, 272 (1941).
[8] Y. Kasé, *Pharm. Bull. Tokyo* **2**, 298 (1954); *Japan. J. Pharm.* **4**, 130 (1955).

to stand overnight at room temp and then acetic acid was removed under reduced pressure and temperature not exceeding 60°.

The residue was diluted with ice water, basified with aqueous ammonia, and the separated base extracted with ether. On evaporating the washed and dried ethereal solution a viscous pale yellow oil was obtained. This oil was purified by vacuum distillation yielding b.p. 135–140°/0·3 mm (original substance, 0·2 g), and b.p. 170–180°/0·3 mm, a mixture of Va and Vb (1·3 g). The higher boiling product was dissolved in pet ether (10 cc), and allowed to stand overnight at 0° with separation of pale yellow crystals. The crude product was recrystallized from pet ether to yield Va (1·02 g 57%) as pale yellow rods, m.p. 96–97°.

(Found: C, 71·3; H, 7·74; N, 9·78. $C_{17}H_{22}N_2D_2$ requires: C, 71·5; H, 7·7; N, 9·2%).

Picrate: Yellow plates (from acetic acid), m.p. 227–229°.

(Found: C, 53·59; H, 4·89; N, 13·59. $C_{23}H_{25}N_4O_9$ requires: C, 53·8; H, 4·8; N, 13·6%).

2-(*or* 4)-*Nitro*-N-*methyl*-8-*aza-des*-N-*morphinan* (Vb). A solution of picric acid in acetone was added to the mother liquor obtained by filtration of Va and the resulting mixture was allowed to stand overnight at 0°.

The separated picrate was filtered, and then washed with ethanol, and recrystallized from acetic acid to give yellow plates, m.p. 226–228° and identified as Va picrate by a mixed m.p.

The filtrate from the Va-picrate was concentrated until the appearance of Vb-picrate, which was collected, and recrystallized from acetone–ethanol. Vb-picrate m.p. 221–223° showed by mixed m.p. determination with Va-picrate a depression of about 10°.

The free base of Vb-picrate was recrystallized from pet ether to give pale yellow columns, m.p. 83–85°, but yielded only 5% Vb and was depressed by mixed m.p. with Va.

(Found: C, 71·3; H, 7·74; N, 9·78. $C_{17}H_{22}N_2O_2$ requires: C, 70·4; H, 7·00; N, 9·63%).

3-*Amino*-N-*methy*-8-*aza-des*-N-*morphinan*(VI). A solution of Va (0·2 g) in ethanol (15 cc) was hydrogenated at atmospheric pressure in the presence of 15% Pd-C (0·2 g as the catalyst. Three equivalents of hydrogen were absorbed in 30 min, and further absorption was very slow. The filtrate from the catalyst was concentrated to about 3 cc, cooled and the separated crystals purified from ethanol giving VI (0·15 g 84%) as colourless needles, m.p. 210–212°. The diazo test was positive in acidic solution.

Found: C, 79·64; H, 9·44; N, 10·49. $C_{17}H_{24}N_2$ requires: C, 79·7; H, 9·3; N, 10·25%).

3-*Hydroxy*-N-*methyl*-8-*aza-des*-N-*morphinan*(VII). A solution of VI (1·3 g) in 3-N-sulphuric acid was cooled to 3° and treated dropwise with vigorous stirring for 10 min with a solution of sodium nitrite (0·43 g) in water (5 cc). The reaction mixture was maintained at this temperature for 30 min, and then added at once with stirring to 50% sulphuric acid (56 cc) at 70°. The mixture was then heated at 85° for 30 min, cooled, and basified with aqueous ammonia. The semi-solid substance was extracted with ether, and the ethereal solution extracted with 10% aqueous sodium hydroxide. The aqueous layer was washed with ether, and treated with solid sodium bicarbonate. The precipitated solid was extracted with ether, washed and dried. The residue was recrystallized from methanol (with charcoal and VII (1·1 g 84%) was obtained as a colourless columns, m.p. 204–205°.

(Found: C, 79·33; H, 9·01; N, 5·44. $C_{17}H_{23}NO$ requires: C, 79·6; H, 8·7; N, 5·25%).

Hydrochloride: Colourless plates (from methanol–ether), m.p. 279° (dec).

(Found: C, 65·6; H, 8·35; N, 4·50. $C_{17}H_{24}NO\,Cl{\cdot}H_2O$ requires: C, 65·1; H, 8·1; N, 4·54%).

Picrate: Yellow granulars (from methanol), m.p. 214–216°.

(Found: C, 56·78; H, 5·39; N, 11·52. $C_{23}H_{26}N_4O$- requires: C, 56·35; H, 5·05; N, 11·44%)

3-*Methoxy*-N-*methyl*-8-*aza-des*-N-*morphinan*-(VIII). Excess of ethereal diazomethane was added to a suspension of VII (0·35 g) in methanol (10 cc) and the mixture was allowed to stand for 3 days a room temp. After evaporation of the solvent, the residue was distilled *in vacuo*, giving VIII (0·35 g) as a viscous pale yellow oil, b.p. 175–180° (bath temp.) /0·3 mm.

Picrate: Yellow columns (from ethanol), m.p. 196·5–198·5°.

(Found: C, 57·59; H, 5·64; N, 11·29. $C_{24}H_{28}N_4O_8$ requires: C, 57·3; H, 5·25; N, 11·3%).

3-*Methoxy*-10-*oxo*-N-*methyl*-8-*aza-des*-N-*morphinan*(IX). A mixture of VIII (100 mg), chromium trioxide (45 mg) in N-sulphuric acid (18 cc) was treated dropwise with stirring at room temperature for a period of 3 hr with 10-N-sulphuric acid (2 cc). The reaction mixture, which gradually changed from orange to green was allowed to stand overnight at room temp. The mixture basified with aqueous ammonia, extracted with ether, washed with water, dried and acidified to congo red with ethanolic hydrogen chloride, was allowed to stand for 5 hr at 0°.

The separated crystalline IX-hydrochloride was collected and recrystallized from ethanol–ether, giving 50 mg of colourless needles, m.p. 250° (dec).

(Found: C, 67·18; H, 7·46; N, 4·35. $C_{18}H_{24}NO_2Cl$ requires: C, 67·25; H, 7·45; N, 4·00%).

Picrate: Yellow granules (from acetone), m.p. 251° (dec).

(Found: C, 56·03; H, 5·09; N, 10·89. $C_{24}H_{26}N_4O_9$ requires: C, 56·00; H, 5·15; N, 10·3%).

Acknowledgements—The author is indebted to Messrs. K. Kodera and K. Furusaki for infra-red and ultra-violet spectral measurements, and to Mrs. F. Hisamichi and Messrs. T. Yoda and T. Kawano for elemental analyses reported herein.