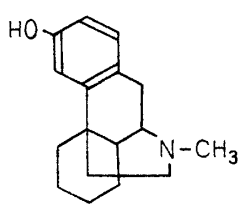
U.D.C. 547.831.3 : 547.833.3 : 615.783

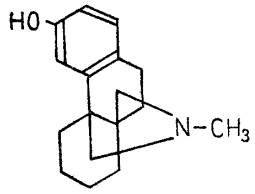
36. Hiroshi Kugita : Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. VII.[1] Synthesis of 3-Hydroxy-N-methyl-4b, 8a-methanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenanthrene.

(Osaka Research Laboratory, Gohei Tanabe & Co., Ltd.)*

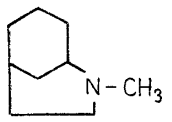
In the preceding paper of this series[1] were described the synthesis and pharmacological effect of 3-hydroxy-N-methyl-4b,8a-ethanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenanthrene, a compound in which the morphan skeleton (B) in 3-hydroxy-N-methylmorphinan (A) had been substituted with a decahydroisoquinoline ring. In the present paper will be described the synthesis and pharmacological tests of 3-



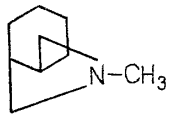
(A)



(C)



Morphan
(B)



Hexahydroisoindoline
(D)

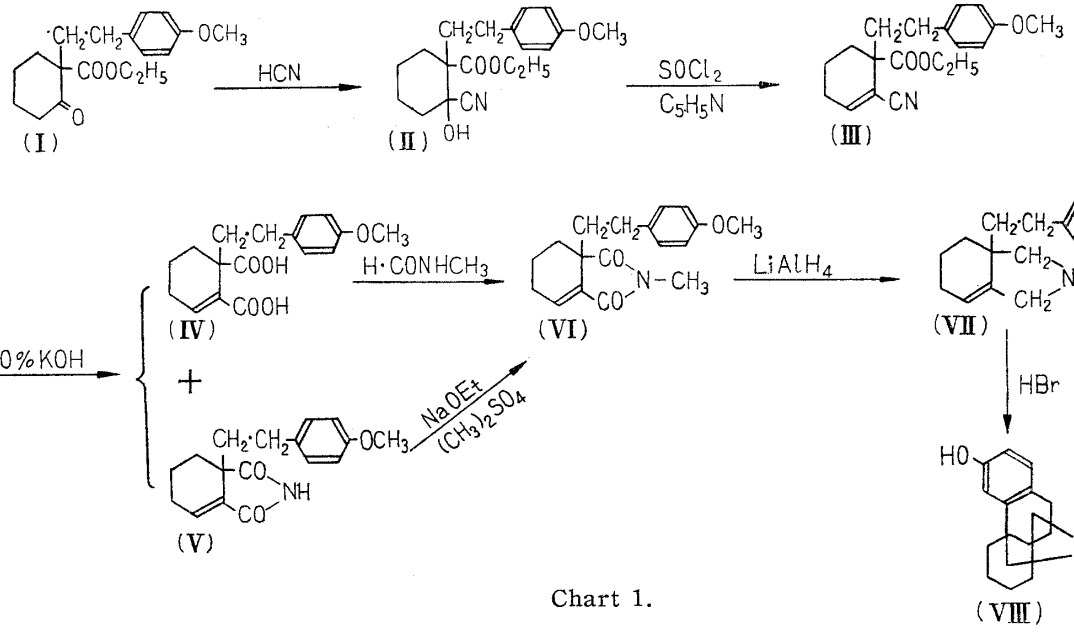


Chart 1.

* Honjo-Kawasaki-cho, Ohyodo-ku, Osaka (釘田博至).

1) This constitutes a part of a series entitled "Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics" by Norio Sugimoto. Part VI : This Bulletin, **4**, 29(1956).

hydroxy-N-methyl-4b, 8a-methanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenanthrene (C), a compound obtained by the replacement of the morphan skeleton in (A) with a hexahydroisoindoline ring (D). The route of this synthesis is shown in Chart 1.

Reaction of 2-ethoxycabonyl-2-(*p*-methoxyphenethyl)cyclohexanone[1] (I) and liquid hydrogen cyanide at 0° afforded the cyanohydrin (II), which was dehydrated, without further purification, with thionyl chloride and pyridine to 1-cyano-2-ethoxycarbonyl-2-(*p*-methoxyphenethyl)cyclohex-6-ene (III). This compound (III) resisted hydrolysis and heating it with 30% potassium hydroxide for 40 hours resulted in a small formation of the dicarboxylic acid (IV). Due to insufficient saponification, a portion was obtained as the phthalimide (V). The dicarboxylic acid (IV) yielded N-methylphthalimide (VI) on heating with methylformamide and was identified by admixture with the compound obtained by heating sodium phthalimide (V) with dimethyl sulfate. Methylphthalimide (V) was reduced with lithium aluminum hydride in the usual manner to the tetrahydroisoindoline (VII) and by heating the oxalate of (VII) with 48% hydrobromic acid to effect concurrent demethylation and rearrangement, the objective 3-hydroxy-N-methyl-4b, 8a-methanoiminomethano-4b,5,6,7,8,-8a,9,10-octahydrophenanthrene (VIII) was finally obtained.

The infrared absorption spectrum of (VIII) exhibits the absorption of a 1,3,4-trisubstituted benzene,[2] with sharp absorptions at 11.45, 12.12, and 12.45 μ. It may be assumed from this fact that in this case, as in the case of the ethanoiminomethano-octahydrophenanthrene[1] described earlier, the cyclization occurred in the position *meta* to the methoxyl group. As for the question of which of the carbon atoms, at C_{4b} or C_5, had bonded with the benzene ring, it is thought that a stable six-membered ring had been formed by cyclization between C_{4b}-carbon and the benzene ring, rather than the formation of a seven-membered ring, from the consideration of the tension of the carbon ring, as in the preceding case.

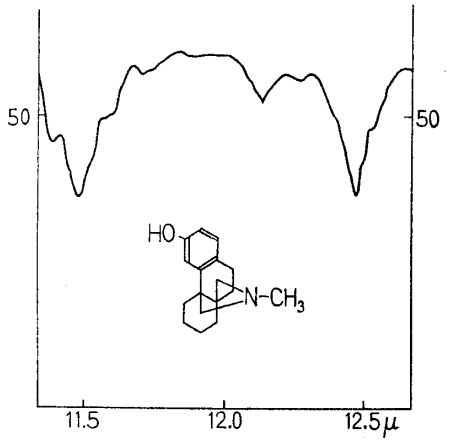


Fig. 1.

Infrared Spectrum of (VIII) (in Nujol)

As for the pharmacological action of this compound (VIII), its analgesic action determined by Dr. H. Fujimura of the Pharmacological Laboratory, Medical Faculty, University of Kyoto, by the Haffner method using mice was 0.2 mg./10 g., showing it has no analgesic action. Its toxicity, LD_{50}, was 0.5~0.6 mg./10 g., about five times stronger than morphine.

The author expresses his gratitude to Prof. S. Sugasawa of the University of Tokyo, and to Dr. Masao Fujisawa, Director of this Laboratory, for their kind encouragement. The author is

2) R. C. Gore, N. B. Colthup : J. Opt. Soc. Am., **40**, 397(1950); D. H. Whiffen, H. W. Thompson: J. Chem. Soc., **1945**, 268; R. A. Friedel : J. Am. Chem. Soc., **73**, 2881(1951).

indebted to Mr. Keishi Kodera of this Laboratory for the infrared spectral data, and to Miss F. Hisamichi and Mr. T. Yoda of the Tokyo Research Laboratory for microanalytical data.

Experimental

1-Cyano-2-ethoxycarbonyl-2-(*p*-methoxyphenethyl)cyclohex-6-ene (III)—Liquid HCN (from 130 g. KCN), chilled in a freezing mixture, was treated with a few drops of saturated KCN solution and 50 g. of the keto ester (I) was added in drops. The mixture was kept in ice water over night, then neutralized with 3 drops of conc. H_2SO_4, and the excess HCN was removed by suction. The pale yellow residue was dehydrated with pyridine (40 cc.) and $SOCl_2$ (28.5 g.) in the usual manner. Yield, 33.0 g. of b.p_3 204~209°.

1,2-Dicarboxy-2-(*p*-methoxyphenethyl)cyclohex-6-ene (IV) and 2-(*p*-Methoxyphenethyl)-2,3,4,5-tetrahydrophthalimide (V)—A mixture of the cyano ester (III) (6.0 g.) and 30% KOH (10g. KOH in 23 cc. H_2O) was boiled for 60 hrs. and the cooled reaction mixture was shaken with ether. The separated aqueous layer was acidified with conc. HCl and extracted with ether. After washing the ether extract with $NaHCO_3$ solution to remove acid substances, the ether was evaporated and the residue was recrystallized from EtOH to yield 0.65 g. of the phthalimide (V) as white needles, m.p. 157~159°. *Anal.* Calcd. for $C_{17}H_{19}O_3N$: N, 4.9. Found: N, 4.55.

$NaHCO_3$ solution was acidified with HCl and extracted with ether. The dried ether was evaporated, a small amount of EtOH was added to the partially crystallized residue, and the collected crystals were recrystallized from dil. AcOH. Yield, 1.6 g. of the diacid (IV) as colorless pillars, m.p. 191~192°. *Anal.* Calcd. for $C_{17}H_{20}O_5$: C, 67.1; H, 6.6. Found: C, 67.05; H, 6.4.

2-(*p*-Methoxyphenethyl)-2,3,4,5-tetrahydro-N-methylphthalimide (VI)—i) A mixture of the diacid (3.0 g.) and $HCONHCH_3$ (6 g.) was heated in an oil bath (180~190°) for 5 hrs. and cooled. The separated crystals were collected by filtration, washed with $NaHCO_3$ solution, water, and then with a small amount of EtOH. Yield, 2.3 g. of N-methylphthalimide (VI) as white needles (from EtOH), m.p. 110~111°. *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.2; H, 7.05; N, 4.65. Found: C, 71.75; H, 6.85; N, 4.5.

ii) Na salt of the phthalimide (V), prepared from the imide (V) (0.8 g.) and EtONa solution (0.07 g. Na and 10 cc. EtOH), was refluxed with Me_2SO_4 (0.4 g.) for 3 hrs. in a water bath, cooled, and the crystals were collected by filtration. The crystals were washed consecutively with dil. NaOH solution, water, and EtOH and 0.5 g. of the N-methyl-imide (VI) was obtained as crystals of m.p. 110°(from EtOH), undepressed on admixture with (VI) obtained in (i).

N-Methyl-9-(*p*-methoxyphenethyl)-4,5,6,9-tetrahydroisoindoline (VII)—A solution of the N-methylphthalimide (VI) (2.5 g.) in dioxane (28 cc.) was added dropwise into a stirred solution of $LiAlH_4$ (1.0 g.) in dehyd. ether (85 cc.) and the mixture was refluxed at 41° for 3 hrs. After standing over night, the mixture was decomposed by the addition of a small amount of water, the inorganic material was filtered off, and washed with ether. The combined ether solution was extracted with dil. HCl and the acid extract was basified with K_2CO_3. The base was extracted with ether and the ether was evaporated after drying. Vacuum distillation of the residue yielded 1.8 g. of colorless oil, b.p_3 207~211°. It gave yellowish red coloration with tetranitromethane and decolorized $KMnO_4$ solution. Picrolonate: Yellow needles (from EtOH), m.p. 164~165°. *Anal.* Calcd. for $C_{28}H_{33}O_6N_5$: C, 62.8; H, 6.2; N, 13.05. Found: C, 62.6; H, 6.1; N, 12.8.

Oxalate: White granules (from EtOH), m.p. 143~145°. *Anal.* Calcd. for $C_{20}H_{27}O_5N$: N, 3.9. Found: N, 3.65.

3-Hydroxy-N-methyl-4b,8a-methanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenanthrene (VIII)—A solution of the tetrahydroisoindoline (VII) oxalate (2.3 g.) in 48% HBr (18 cc.) was heated in an oil bath (140~150°) for 6 hrs. and HBr was removed under a reduced pressure. The residue was dissolved in water, treated with activated charcoal, and filtered. The filtrate was basified with NH_3 and extracted with ether. The ether extract was dried and evaporated. The residue was warmed with a small amount of EtOH, cooled, and 0.3 g. of (VIII) was obtained as colorless granules (from EtOH), m.p. 253~255°. *Anal.* Calcd. for $C_{17}H_{23}ON$: C, 79.35; H, 9.0; N, 5.45. Found: C, 79.0; H, 8.9; N, 5.25. Hydrochloride: White granules (from EtOH), m.p. 288~290°.

Summary

3-Hydroxy-N-methyl-4b, 8a-methanoiminomethano-4b,5,6,7,8,8a,9,10-octahydrophenanthrene, a compound in which the morphan skeleton in 3-hydroxy-N-methylmorphinan had been substituted with a hexahydroisoindoline ring, was synthesized and its analgesic action was tested.

(Received February 23, 1956)