Depression.

Einwirkung von Benzoylnitrat auf Chinaldin—Eine Lösung von 1.02 g Chinaldin in 20 ccm $CHCl_3$ wurde mit 1.3 ccm Benzoylnitrat ganz analog wie beim Chinaldin-N-oxyd behandelt und 910 mg Chinaldin regeneriert.

Zusammenfassung

Chinaldin-N-oxyd gibt beim Behandeln mit Benzoylnitrat in Chloroform-Lösung das 3-Nitrochinaldin-N-oxyd und das 2-Benzoyloxymethylchinolin mit einer Ausbeute von 20.6% bzw. 30.3%. Vermehrt man die Menge des Benzoylnitrates bei dieser Reaktion ist die Ausbeute beider Verbindungen geringer und ausserdem wird ein gelbbraunes Kristall vom Schmp. 249~250°(Zers.) und von der Zusammensetzung $C_{20}H_{10}O_6N_6$ erhalten. Das letztere entsteht auch, wenn man das 3-Nitrochinaldin-N-oxyd mit Benzoylnitrat analogerweise behandelt. Für die Konstitution des letzteren haben die Verfasser eine Glyoximsuperoxyd-Formel (E) vorgeschlagen.

(Eingegangen am 25. März, 1957)

UDC 547.833.9

57. Norio Sugimoto and Susumu Ohshiro: Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. XIII.[1] Synthesis of 3-Hydroxy-N-methyl-6-aza-des-N-morphinan (N-Methyl-9-hydroxy-5,10b-trimethylene-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]isoquinoline).

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Synthesis of N-methyl-6-aza-des-N-morphinan and its physicochemical properties were described in earlier paper of this series.[2] In accordance with the general rule with synthesized analgesics that compounds with a hydroxyl in 3-position are the most potent drugs, the 3-hydroxy compound of the said morphinan derivative was synthesized by a method similar to that reported earlier[2] and its pharmacological effect was tested.

According to the method of Bergstrom, *et al.*,[3,4] 5,6,7,8-tetrahydroisoquinoline (I) was derived to its potassium salt by reaction with potassium amide in liquid ammonia, the salt was reacted with *p*-methoxybenzyl chloride, and 5-(*p*-methoxybenzyl)-5,6,7,8-tetrahydroisoquinoline (II) was obtained in a good yield. (II) was derived to its methiodide (III) by the usual method and submitted to catalytic reduction in alkaline medium, with Raney nickel as a catalyst. Absorption of two moles of hydrogen afforded N-methyl-5-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (IV). This base, when purified as its oxalate, is separated into crystalline oxalate (IV-oxalate) and non-crystalline oxalate (VI-oxalate).

The base liberated from the crystalline oxalate (IV) possesses one unsaturated bond (*q. v.*) and is the objective octahydro compound. The base liberated from the non-crystalline oxalate does not contain an unsaturated bond and since its picrolonate was identical with one of the decahydroisoquinoline derivative (VI) synthesized by another route, this base was assumed to be a further hydrogenated product.

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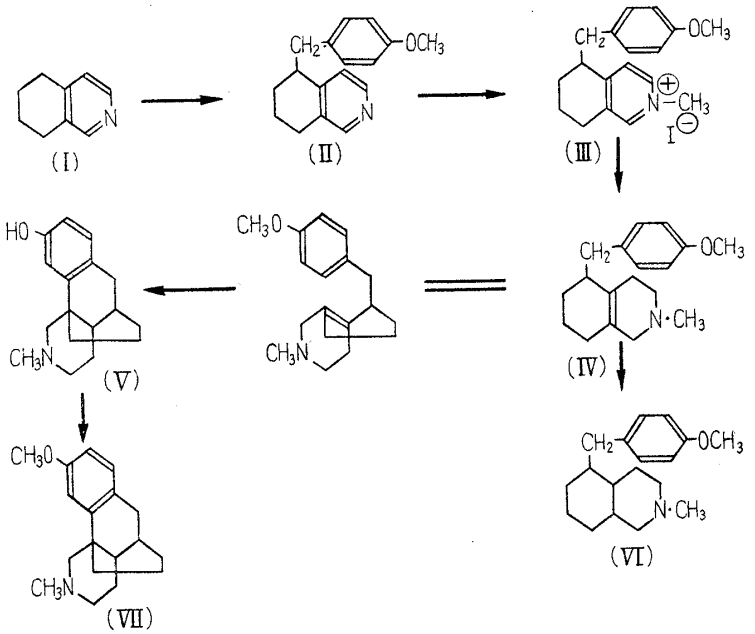
1) Part XII. N. Sugimoto, H. Kugita: This Bulletin, **5**, 67(1957).
2) Part XI. N. Sugimoto, *et al.*: *Ibid.*, **5**, 62(1957).
3) F. W. Bergstrom: J. Org. Chem., **10**, 452(1945); *idem.*: J. Am. Chem. Soc., **53**, 3027, 4065(1931).
4) B. Witkop: J. Am. Chem. Soc., **70**, 2617(1948).



The crystalline oxalate of (IV) was heated with 48% hydrobromic acid for 15 hours to effect rearrangement-cyclization, the reaction mixture was treated in the usual manner, and the base obtained was recrystallized from acetone to 6-aza-des-N-morphinan (V) as colorless needles, m.p. 146~147°. Its hydrochloride was obtained as colorless granular crystals, m.p. 241~243°. This compound (V) was found to be free from any double bond, dissolved in alkali hydroxide, and colored dusky yellowish green with ferric chloride solution. Its infrared spectrum exhibited the characteristic out-of-plane absorption of 1,3,4-trisubstituted benzene ring at 11.85 and 12.20 μ. It was therefore concluded that the double bond in (IV) had undergone rearrangement and cyclization to the *ortho*-position in the benzene ring, as anticipated. There is still a question of whether this cyclization had occured to form a six-membered or five-membered ring, but in accordance with past results,[2] it seems safe to conclude that the cyclization had occurred in the 9-position of the isoquinoline ring and *ortho*-position of the benzene ring to form a six-membered ring.

The compound (V) was methylated by the application of ether solution of diazomethane in methanol to form 3-methoxy-N-methyl-6-aza-des-N-morphinan (VII).

The octahydro compound (IV) was further hydrogenated in glacial acetic acid, in the presence of conc. sulfuric acid, with Adams' platinum oxide catalyst, according to the method of Witkop,[4] and two kinds of decahydro compound (VI) were obtained after absorption of one mole of hydrogen. The two compounds formed a picrolonate of m.p. 191~193° and of m.p. 163~165°. As was suggested in earlier report,[2] these are the two out of the four possible stereoisomers of the decahydro compounds, in which the 9-10 position is in *trans*-configuration and the benzyl is not in axial.

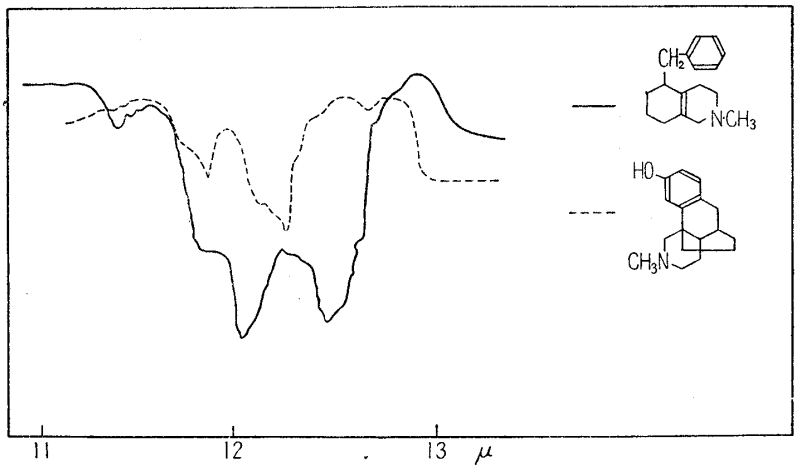
During the reduction of the methiodide of (III), a part of the base obtained from non-crystalline oxalate formed a picrolonate of m.p. 163~165° and this was found by mixed fusion to be identical with the picrolonate mentioned above.

It is hoped that a conclusive evidence could be provided separately for the formation of a six-membered ring by the cyclization reaction described in this and earlier paper.[2]

Pharmacological tests were made by Dr. H. Fujimura in the Pharmacological Department, University of Kyoto, for analgesic activity in mice. Acute toxicity, LD_{50}, was 0.75~0.86 mg./10 g. by intraperitoneal injection, giving clonus already with 0.5 mg. of 3-hydroxy-N-methyl-6-aza-des-N-morphinan. Analgesic action measured by the Haffner

method was 0.5 mg./10 g. by intraperitoneal injection, proving this compound to have no such action. The test by the Damour-Smith method(100 v., 250 w., infrared lamp)revealed that none extended the reaction time more than 10 seconds.

Antitussive action tested by the Kasé method, using a dog, by Dr. Y. Kasé and Mr. R. Yuisono of the Pharmacological Department, University of Kumamoto, gave a value of At.D_{50} (antitussive dose) of 3.35~5.26 mg./kg., while that of the control codeine was 3.11~4.33 mg./kg., showing its action to be somewhat weaker than that of codeine.



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Experimental

5-(*p*-Methoxybenzyl)-5,6,7,8-tetrahydroisoquinoline (II)—5,6,7,8-Tetrahydroisoquinoline (I)(15.0 g.) was added to a suspension of KNH_2, prepared from K (5.0 g.) and liq. NH_3 (200 cc.), with stirring, during 10 mins., forming a reddish K salt. After 10 mins., *p*-methoxybenzyl chloride (16.2 g.) was added dropwise to the above mixture, when the solution color changed to light amber with vigorous evolution of NH_3. NH_3 was slowly evaporated during a period of 2 hrs., the remaining black gray residue was decomposed with ice water, and extracted with ether. The ethereal solution was extracted with dil. HCl, the aqueous solution was basified with K_2CO_3, extracted with ether, and dried. The residue from ether was distilled *in vacuo* to give a pale yellow oil, $b.p_{0.3}$ 182~185°. This was (II) (21.0 g. 73.5%) and a small amount of starting material (I) was recovered.

Picrate : Yellow granules (from acetone), m.p. 161~162°. *Anal.* Calcd. for $C_{17}H_{19}ON \cdot C_6H_3O_7N_3$: C, 57.26; H, 4.6; N, 11.61. Found. C, 57.2; H, 4.5; N, 11.45.

Methiodide(III) : Colorless plates (from MeOH+EtOAc), m.p. 166~168°. *Anal.* Calcd. for $C_{17}H_{19}ON \cdot CH_3I$: C, 54.68; H, 5.57; N, 3.54. Found : C, 54.7; H, 5.15; N, 4.05.

2-Methyl-5-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (IV)—5-(*p*-Methoxybenzyl)-5,6,7,8-tetrahydroisoquinoline methiodide (III) (9.7 g.) was dissolved in MeOH (100 cc.) and *N* NaOH solution (68 cc.) was added to this solution. Hydrogenation of this mixture in the pressence of Raney Ni catalyst (5 g.) resulted in the absorption of H_2 (1030 cc., 2 moles) in 1.5 hrs. The filtrate from removal of catalyst was acidified with AcOH and the solvent was evaporated under a diminished pressure. The residue was basified with K_2CO_3, extracted with ether, dried, and evaporated. (IV)(5.5 g., 83%) was obtained as a pale yellow oil, $b.p_2$ 165~170°. Oxalate prepared from this distillate and anhyd. oxalic acid (1.9 g.) in dehyd. ether was recrystallized from EtOH to (IV) oxalate (3.5 g.).

(i) The free base from the separated crystalline oxalate decolorized a solution of 0.2% $KMnO_4$ in acetone. Oxalate : Colorless plates (from EtOH), m.p. 182~183°. *Anal.* Calcd. for $C_{20}H_{27}O_5N$: C, 66.46; H, 7.53; N, 3.88. Found : C, 66.5; H, 7.8; N, 3.95.

Picrolonate : Yellow plates (from EtOH), m.p. 170~172°. *Anal.* Calcd. for $C_{18}H_{25}ON \cdot C_{10}H_8O_5N_4$: C, 62.79; H, 6.21; N, 13.08. Found : C, 62.65; H, 6.25; N, 13.45.

(ii) The free base from above mother liquor was distilled *in vacuo* to yield a pale yellow oil (1.6 g.), $b.p_2$ 166~168°.

Picrolonate : Yellow pillars (from EtOH+acetone), m.p. 163~165°. This picrolonate was iden-

tified as one of decahydroisoquinoline derivatives prepared by a later-described methode.

3-Hydroxy-N-methyl-6-aza-des-N-mophinan (V)—(IV)-Oxalate (2.0 g.) was heated with 48% HBr (40 cc.) at 130~135° for 15 hrs. After cool, excess HBr was removed under diminishd pressure, the residue dissolved in water, and basified with aq. ammonia. The oil that separated was extracted with ether, dried, and ether was evaporated. The reddish residue was allowed to stand over night in ice chamber and the crystalline solid (V) that gradully separated was washed with acetone. Yield, 0.8 g.(56%) of colorless needles (V), m.p. 146~147°(from acetone). *Anal.* Calcd. for $C_{17}H_{23}ON$: C, 79.32; H, 9.01; N, 5.44. Found : C, 79.30; H, 9.35; N, 5.65. This base did not decolorize 0.2% $KMnO_4$ solution in acetone.

Hydrochloride : Colorless granules (from MeOH+ether), m.p. 241~243°(reddish). *Anal.* Calcd. for $C_{17}H_{24}ONCl$: C, 69.3; H, 8.18; N, 4.76; Found : C, 68.9; H, 8.6; N, 4.9.

3-Methoxy-N-methyl-6-aza-des-N-morphinan (VII)—(V)(0.35 g.) was dissolved in MeOH (10 cc.) and excess of ethereal CH_2N_2 solution was added. When the mixture was allowed to stand for 3 days at room temperature, the evolution of nitrogen gas ceased. After removing the solvent, the residue was distilled *in vacuo* to obtain a colorless viscous oil, b.p_2 175~185° (bath temp.). (VII) (0.39 g) solidified on cooling and melted at 45~47°(from petr. ether).

Picrolonate : Yellow pillars (from EtOH+acetone), m.p. 158~159°. *Anal.* Calcd. for $C_{18}H_{25}ON \cdot C_{10}H_8O_5N_4$: C, 62.79; H, 6.21; N, 13.08. Found : C, 62.55; H, 6.55; N, 12.7.

Hydrochloride : Colorless plates (from MeOH+ether), m.p. 225~226°. *Anal.* Calcd. for $C_{18}H_{26}ONCl$: C, 67.02; H, 8.46; N, 4.55. Found : C, 67.15; H, 8.6; N, 4.35.

N-Methyl-5-(*p*-methoxybenzyl)-decahydroisoquinoline (VI)—A mixture of the octahydro base (IV)(2.0 g.) in AcOH(20 cc.) containing a few drops of conc. H_2SO_4 was reduced at atomospheric pressure in the presence of Adams' PtO_2 catalyst(0.1 g.). After 5 hrs., about 1 mole of H_2 was absorbed. The filtrate from catalyst was evaporated *in vacuo*, the residue was basified with K_2CO_3, the separated oil was extracted with ether, dried, and ether was evaporated. The residual base was distilled at 191~193/0.4 mm. to give (VII) as a colorless oil, which gave a negative test with a solution of 0.2% $KMnO_4$ in acetone.

Picrolonate : Yellow plates (from acetone), m.p. 191~193°. *Anal.* Calcd. for $C_{18}H_{27}ON \cdot C_{10}H_8O_5N_4$: C, 62.55; H, 6.56; N, 13.03. Found : C, 62.2; H, 6.2; N, 13.0.

When the above mother liquor was allowed to stand, a second crop of picrolonate separated and was recrystallized from EtOH+acetone, forming yellow pillars, m.p. 163~165°. A mixed melting point with the picrolonate prepared from non-crystalline oxalate of (IV) was not depressed. *Anal.* Calcd. for $C_{18}H_{27}ON \cdot C_{10}H_8O_5N_4$: C, 62.55; H, 6.56; N, 13.03. Fonud : C, 62.45; H, 6.35; N, 13.4.

Summary

3-Hydroxy-N-methyl-6-aza-des-N-morphinan was synthesized in accordance with the methods described earlier but the compound failed to show any analgesic activity. However, it had antitussive action somewhat weaker than that of codeine.

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