Picrate : Orange needles (from EtOH), m.p. 148~149°. The picrate was not depressed on admixture with 9-methylphenanthrene picrate,[8] m.p. 151°.

Summary

1. N-Methyl-16-aza-des-N-morphinan is an isomer of N-methylmorphinan in which the nitrogen has shifted from 17- to 16-position in its structure.

2. N-Methyl-16-aza-des-N-morphinan was synthesized by the rearrangement of N-methyl-4-benzyl-1, 2, 3, 4, 5, 6, 7, 8-octahydroisoquinoline.

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69. Norio Sugimoto and Susumu Ohshiro : Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines. IX.[1] Synthesis of 3-Hydroxy-N-methyl-16-aza-des-N-morphinan (3-Hydroxy--N-methyl-4b, 9-methanoiminomethano-4b, 5, 6, 7, 8, 8a, 9, 10-octahydrophenanthrene).

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

As is well known with synthetic analgesics in general, compounds possessing a hydroxyl group substituted in the position *meta* to the quaternary carbon directly bonded to a benzene ring are far more powerful in analgesic activity than those not possessing a hydroxyl group. In accordance with such general rules, 3-hydroxy-N-methyl-16-aza-des-N-morphinan was synthesized.

The route of the synthesis was exactly the same as that reported in the preceding paper.[1] 1-Ethoxycarbonylmethyl-2-ethoxycarbonylcyclohex-1-ene (I) is derived to its potassium salt in benzene, chilled to 0°, and *p*-methoxybenzyl chloride is added gradually. The mixture is allowed to stand at room temperature for 1 hour, then warmed gradually, and maintained at 80° for 2 hours. The diester (II) introduced with a *p*-methoxybenzyl group is saponified by warming with conc. alkali to form (III), which is purified, heated with methylformamide at 200° to form 4-(*p*-methoxy)-benzyl-1, 3-dioxo-octahydroisoquinoline (IV), and reduced with lithium aluminum hydride in ether, by the usual method, to 4-(*p*-methoxy)benzyl-octahydroisoquinoline (V), which comes as a slightly yellow liquid, possessing an unsaturated bond and markedly colors in air. (V) is boiled for 20 hours with an excess of 48% hydrobromic acid, during which a part undergoes resinification, decolorized, and filtered. On cooling the filtrate, the hydrobromide of the expected N-methyl-3-hydroxy-16-aza-des-N-morphinan (VI) separates out. Concentration of the mother liquor affords second and third crop of crystals.

The free base, recrystallized from hydrated ethanol, possesses one mole of the water of crystallization, which is lost on drying with application of heat, and such crystals melt at 163~165°, turning red at the same time. The infrared spectrum of this compound exhibits specific absorption due to out-of-plane vibrations of 1, 3, 4-substituted benzene ring[2] at 11.75 and 12.4 μ, indicating that the unsaturated bond

* Honjo-Kawasaki-cho, Ohyodo-ku, Osaka (杉本典夫, 大城 進).

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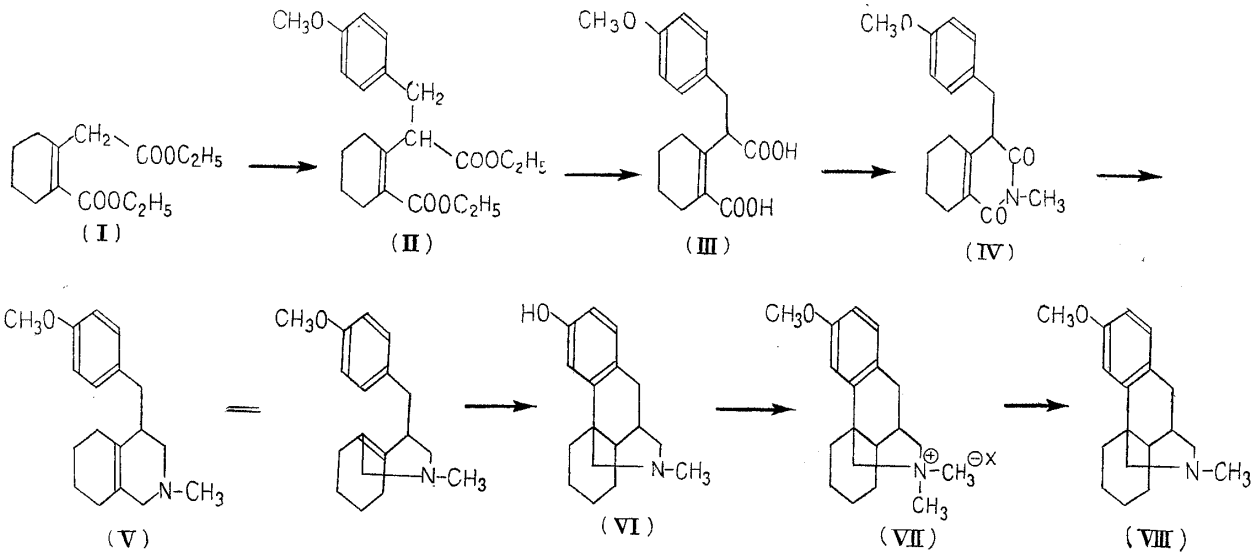
2) This Bulletin, **4**, 29(1956).

in (V) had shifted to the *ortho* position of the benzene ring, as was anticipated.

On methylation of the hydroxyl group in (VI) by the application of dimethyl sulfate to a solution of its hydrobromide dissolved in potassium hydroxide, N-methyl-3-methoxy-16-aza-des-N-morphinan (VIII) was obtained.



As for the position of the bonding by rearrangement, whether the 9- or 10-position of the isoquinoline ring had bonded with the *ortho* position of the benzene ring, it is impossible to imagine that there has been any effect of the methoxyl group and, in accordance with the case reported in the preceding paper, it seems probable that the bonding occurred at 9-position, forming a six-menbered ring (VI).

The ultraviolet absorption spectra of the hydrobromide of N-methyl-3-hydroxymorphinan and that of N-methyl-3-hydroxy-16-aza-des-N-morphinan are shown in Fig. 1.

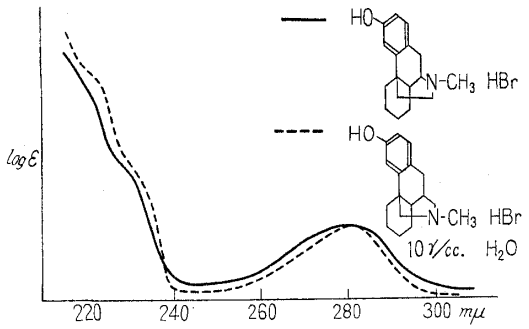


Fig. 1.

Ultraviolet Spectra
(in H_2O)

Pharmacological activity of this compound was tested by Dr. Hajime Fujimura of the Pharmaceutical Department, University of Kyoto. Its toxicity, LD_{50}, is about 1.2 mg./10 g. by intraperitoneal injection in mouse. Its analgesic action, tested by the Haffner method in mice, is 0.5 mg./10 g., which is almost nil. The compound gives only a weak tail-raising reaction and almost no hyperglecemia.

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Experimental

Ethyl α-(2-Ethoxycarbonylcyclohex-1-enyl)-*p*-methoxyhydrocinnamate (II)—A solution of 1-ethoxycarbonylmethyl-2-ethoxycarbonylcyclohex-1-ene (I) (17.0 g) in dehyd. benzene (30 cc.) was added in drops with stirring to the solution of EtOK prepared from powdered K (2.8 g.), dehyd. EtOH (3.8cc.), and dehyd. benzene (100 cc.) at 30~40° during 1 hr. The freed EtOH was quickly distilled off with a portion of benzene in an oil bath at 110~120°. To this K salt of the diester, a soultion of *p*-methoxybenzyl chloride (14 g.) in dehyd. benzene (20 cc.) was added in drops at below 0°. After keeping at room temp. for 1 hr., the temperature was gradually raised to 40~50°, kept there for 2 hrs., and finally heated at 80° for 2 hrs. The reaction mixture was decomposed with ice water, ethereal layer was washed with water, dried, and evaporated. Pale yellow oil, $b.p_1$ 205~209°. Yield, 15 g.(59%) Analytical sample, $b.p_{1.5}$ 218°. *Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.95; H, 7.85. Found: C, 69.95; H, 7.55.

α-(2-Hydroxycarbonylcyclohex-1-enyl)-*p*-methoxyhydrocinnamic Acid (III)—Above diester (45 g.) was heated to boiling with 40% KOH solution (KOH 80 g. in H_2O 120 cc.) and a homogeneous solution was obtained after 3 hrs. Then water (100 cc.) was added and additional heating was continued for further 5 hrs. After cooling, the reaction mixture was diluted with water and extracted with ether. The aq. layer was acidified with conc. HCl and organic layer was extracted with ether, which was dried and evaporated. The residual semisolid was recrystallized from AcOEt to give 29 g.(75%) of (III) as white pillars, m.p. 147°(decomp.). *Anal.* Calcd. for $C_{17}H_{20}O_5$: C, 67.1; H, 6.6. Found: C, 66.7; H, 6.7.

N-Methyl-4-(*p*-methoxybenzyl)-1,3-dioxo-1,2,3,4,5,6,7,8-octahydroisoquinoline (IV)—The di-acid (III) (5.0 g.) was heated with N-methylformamide (8 g.) in an oil bath at 200~205° for 8 hrs. The mixture was poured into water and the separated oil was extracted with ether. Ethereal solution was dried, evaporated, and the residue was distilled at 221~224°/0.5 mm. Yield, 4.0 g.(85%) of pale yellow viscous oil (IV). Analytical sample, $b.p_{0.5}$ 222°. *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.2; H, 7.05; N, 4.7. Found: C, 72.0; H, 6.7; N, 4.7.

N-Methy-4-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (V)—The solution of the above imide (9.3 g.) in dehyd. ether (100 cc.) was added in drops with vigorous stirring to a suspension of $LiAlH_4$ (4.0 g.) in dehyd. ether (300 cc.) at 0° to 3° during a period of 1 hr. and refluxed for about 20 hrs. The reaction mixture was decomposed with water (13 cc.) under chilling at such a rate that the temperature never exceeded 10° and freed from inorganic material. The ethereal layer was washed with NaCl solution, dried, and evaporated. The residual oil was distilled at 186~188°/2 mm. to give a pale yellow oil. Yield, 4.4 g.(53%). This oil rapidly decolorized 0.1% $KMnO_4$ solution. Picrolonate: Yellow needles (from EtOH), m.p. 186~188°. *Anal.* Calcd. for $C_{18}H_{25}ON \cdot C_{10}H_8O_5N_4$; C, 62.8; H, 6.2; N, 13.1. Found: C, 63.1; H, 6.1; N, 13.2.

N-Methyl-3-hydroxy-16-aza-des-N-morphinan (VI)—Above octahydroisoquinoline (V) (3.0 g.) was dissolved in 48% HBr (60 cc.) and heated in an oil bath at 140~145° for 20 hrs. After cooling, the reaction mixture was filtered with charcoal and allowed to stand over night in a refrigerater. The deposited crystals were collected and recrystallized from hyd. EtOH. The mother liquor was concentrated to give a second crop of crystals. It gave orange color with $FeCl_3$ solution. Hydrobromide; Colorless needles (from hyd. EtOH), m.p. over 280°. *Anal.* Calcd. for $C_{17}H_{23}ON \cdot HBr \cdot H_2O$: C, 57.3; H, 7.3. Found: C, 56.9; H, 7.3. Base: Aqueous solution of the hydrobromide was neutralized with NH_4OH. Colorless needles (from hyd. EtOH), m.p. 163~165°(sint. 90°). *Anal.* Calcd. for $C_{17}H_{23}ON \cdot H_2O$ (room temp., 24 hrs.): C, 74.3; H, 9.15; N, 5.1. Found: C, 74.8; H, 9.3; N, 4.9. *Anal.* Calcd. for $C_{17}H_{23}ON$ (60°, 40 hrs.): C, 79.3; H, 9.0; N, 5.45. Found: C, 79.15; H, 8.9; N, 5.3.

N-Methyl-3-methoxy-16-aza-des-N-morphinan (VIII)—N-Methyl-3-hydroxy-16-aza-des-N-morphinan hydrobromide (0.2 g.) was dissolved in 10% KOH (10 cc.) and vigorously shaken with three 0.3-cc. portions of Me_2SO_4, neutralized with HCl, and KI added. The separated hard oil was collected by decantation. This oil was treated with fresh AgCl at 90° for 1 hr. and converted to methochloride of the 3-methoxy compound. AgI was filtered off and the filtrate was concentrated *in vacuo* to dryness. The residue was distilled *in vacuo* to colorless oil, $b.p_2$ 250~260° (bath temp.) with decomposition. This oil solidified on cooling to colorless needles (from hyd. EtOH), m.p. 106~108°. *Anal.* Calcd. for $C_{18}H_{25}ON$: C, 79.65; H, 9.3; N, 5.15. Found: C, 79.9; H, 9.15; N, 5.25.

Picrate: Yellow pillars (from AcOH), m.p. 210~212°. *Anal.* Calcd. for $C_{18}H_{25}ON \cdot C_6H_3O_9N_3$: N, 11.2. Found: N, 11.1

Summary

N-Methyl-3-hydroxy-16-aza-des-N-morphinan was synthesized and its pharmacological action was examined. The compound did not show any analgesic action.

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