U. D. C. 547.837.6.07 : 615.783.19

68. Norio Sugimoto and Susumu Ohshiro : Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. VIII.[1] Synthesis of N-Methyl-16-aza-des-N-morphinan* (N-Methyl-4b,9-methanoiminomethano-4b, 5, 6, 7, 8, 8a, 9, 10-octahydrophenanthrene).

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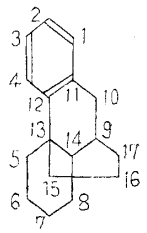
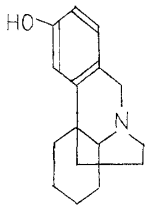
Sugimoto had earlier made a proposal for the naming of the compounds in which the nitrogen in morphinan skeleton had been displaced to other positions[2] but it is now announced that the structure 4b,9-trimethylen-4b, 5, 6, 7, 8, 8a, 9, 10-octahydrophenanthrene (A) would henceforth be designated as des-N-mophinan. Itfollows, therefore, that 3-hydroxy-9-azamorphinan mentioned in Part IV of this series[3] would become 6-hydroxy-4a,10-trimethylene-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthridine (B).



(A)



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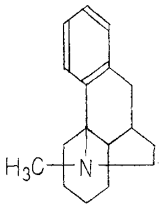

(C)

Des-N-Morphinan

Sugimoto and his co-workers have published[3,4] results on the syntheses and pharmacological tests of comopounds related to morphinan by the cyclization-condensation or rearrangement of hydrogenated quinolines and isoquinolines.

The position of the nitrogen in morphinan skeleton is at 17 but isomers having the nitrogen in 5, 6, 7, 8, 9, 10, 14, 15, or 16 may be possible and it seems interesting to compare the physical, chemical, and pharmacological properties of these isomers with those of morphinan.

In 1955, Sugimoto and his associates first prepared 6-hydroxy-4a,10-trimethylene-1, 2, 3, 4,4a,9,10,10a-octahydrophenanthridine[3] (B) and this was followedb y that of N-methyl-15-aza-des-N-morphinan[5] (C) by Ochiai and his school.

As the third of such series, synthesis of a compound in which the nitrogen had shifted to 16-position of morphinan, i.e. N-methyl-16-aza-des-N-morphinan, will be described in the present paper. This compound contrasts with the earlier (B) compound which showed a powerful activity comparable with morphine, in possessing the nitrogen adjacent to 17-position but on the other side of the earlier compound, and presents an interesting pharmacological problem.

For the preparation of this compound, 1-hydroxycarbonylmethyl-2-hydroxycar-

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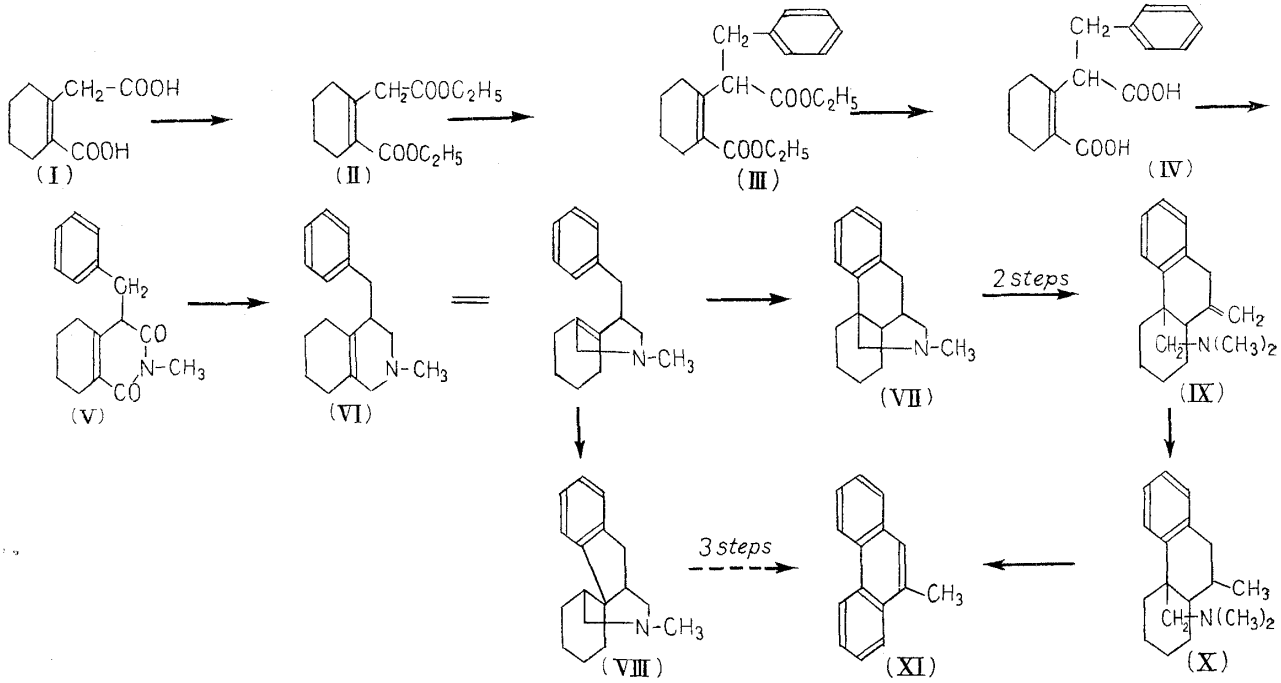
1) Part VII : This Bulletin, **4**, 189(1956).
2) J. Pharm. Soc. Japan, **75**, 183(1955).
3) This Bulletin, **3**, 11(1955) (C. A., **50**, 1815(1956)).
4) *Ibid.*, **4**, 29(1956).
5) *Ibrid.* **3**, 369(1955).

bonylcyclohex-1-ene[6] (I) is esterified as an azeotropic mixture, the diester (II) thereby obtained is derived to its potassium salt in dehydrated benzene, and reacted with benzyl chloride to form ethyl α-(2-ethoxycarbonylcyclohex-1-enyl)hydrocinnamate (III). (III) is saponified by heating with conc. alkali hydroxide to the diacid (IV) and heated with methylformamide to 200° to form 4-benzyl-N-methyl-1,3-dioxo-octahydroisoquinoline (V), which is reduced with lithium aluminum hydride by the usual method in ether to 4-benzyl-N-methyl-octahydroisoquinoline (VI), an oily substance which easily colors brown in the air. (VI) undergoes rearrangement on being heated with 85% phosphoric acid for 65~70 hours at 160~170° and forms 16-aza-des-N-morphinan (VII), m.p. 80~82°, not possessing any unsaturated bond. Its infrared absorption spectrum exhibits specific absorption at 13.08 and 13.62 μ[7] for out-of-plane vibration of *ortho*-disubstitution in the benzene ring, while that of the starting material (VI) exhibits specific absorption of a mono-substituted benzene ring at 13.4 and 14.32 μ. It is assumed, therefore, that the double bond in (VI) had shifted to the *ortho* position of the benzene ring.



For the proof of the bonding by this rearrangement, whether the bonding occurred between the *ortho* position of the benzene ring and 9-position of the isoquinoline ring, forming a six-membered ring (VII), or with 10-position, forming a five-membered ring (VIII), the following experiments were carried out.

The methiodide of (VII) was converted to methohydroxide, submitted to the Hofmann degradation, and afforded a product (IX) as a liquid, which possessed an unsaturated bond and absorbed one mole of hydrogen on hydrogenation with Adams' platinum catalyst. The compound thereby obtained, 10-methyl-4b-dimethylaminomethyloctahydrophenanthrene (X), a colorless liquid, showed different properties from those of the starting compound (VII), as shown in Table I.

Dehydrogenation of the octahydrophenanthrene (X) by heating with Diels-Gadke's 30% palladium-carbon for 6 hours at 310~320° affords an oily product which solidifies immediately. Recrystallization from ethanol gives 9-methylphenanthrene (XI), m.p.

6) A. R. Kan, *et al.*: J. Chem. Soc., **1932**, 2426; R. Grewe, *et al.*: Ber., **81**, 279(1948).
7) Orr,. Thompson: J. Chem. Soc., **1950**, 218; Cannon, Sutherland: Spectrochim. Acta, **4**, 373(1951).

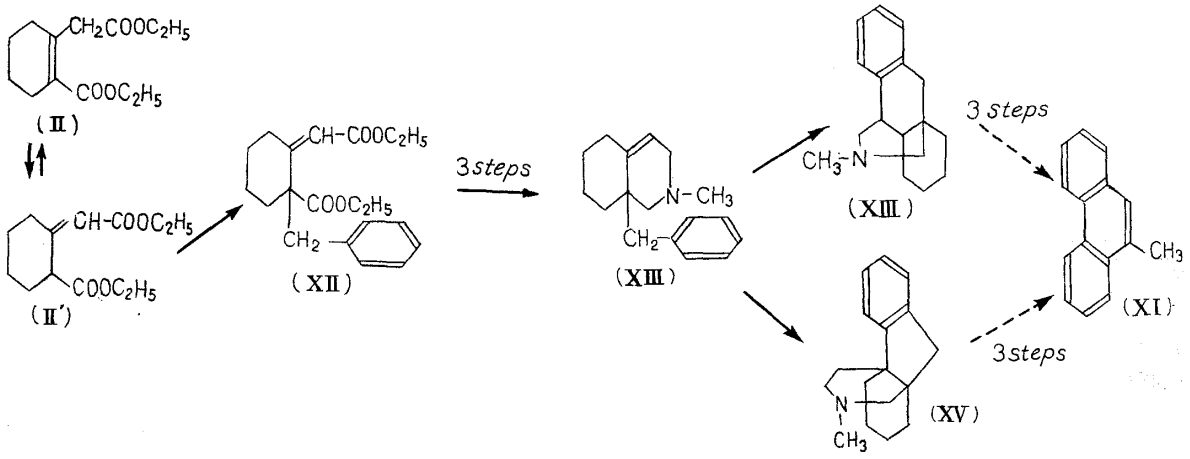
Tabll I.

	Compound (Ⅶ)	Compounn (Ⅹ)
m.p.	80~82°	Oil
b.p.	172~177°/1, 5 mm.	155~160°/2. 5 mm.
U. V. λ_{max}	268, 275 mμ	268, 273 mμ
Paper Chromatography (BuOH : AcOH : H_2O = 5 : 1 : 4) (Dragendorff reagent)	Rf 0.79	Rf 0.72

85~88°(picrate, m.p. 148~149°), undepressed on admixture with 9-methylphenanthrene,[8] m.p. 89~90°(picrate, m.p. 151°), obtained by another route.

The foregoing experimental results show that the bonding of the rearrangement had occurred at the *ortho*-position of the benzene ring and 9-position of the isoquinoline ring, forming the expected six-membered B-ring and confirm the synthesis of (Ⅶ). The formation of 9-methylphenanthrene from (Ⅷ) through the Hofmann degradation, hydrogenation, and dehydrogenation is a very complicated process and leaves no room for any doubt.

The problem remaining here is the position of the double bond in (Ⅱ), which could be represented as (Ⅱ) or (Ⅱ′). If the diester (Ⅱ) takes the (Ⅱ′) form, the benzyl group would be introduced into the cyclohexane ring to form 2-benzyl-2-ethoxycarbonylcyclohexylideneacetic acid ester (Ⅻ), and would form the benzyl-octahydroisoquinoline (XIII) in three steps. Its rearrangement and cyclization to a six-membered ring would afford (XIII) and to a five-membered ring would afford (XV). The compound derived from either of these through the Hofmann degradation, reduction, and dehydrogenation would have an anthracene or fluorene skeleton, but not the 9-methylphenanthrene. Therefore, there is no necessity for assuming the presence of an ester of the (Ⅱ′) type and the ester of (Ⅱ) type was benzylated as anticipated to form (Ⅲ).



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Experimental

1-Ethoxycarbonylmethyl-2-ethoxycarbonylcyclohex-1-ene (II)—1-Hydroxycarbonylmethyl-2-hydroxycarbonylcyclohex-1-ene (I) (17.0 g.) was esterified to the diester (Ⅱ) by the use of azeotropic mixture. The reaction mixture was worked up in the usual manner. Colorless oil, b.p_2 135~138°. Yield, 80%.

Ethyl-α-(2-ethoxycarbonylcyclohex-1-enyl)hydrocinnamate (III)—Dehyd. EtOH (3.6 cc.) was added

8) P. Lambert, R. H. Martin : Bull. soc. chim. Belges, **61**, 124(1952) (C. A., **47**, 3839(1953)).

to the suspenstion of powdered K (2.5 g.) in dehyd. benzene (100 cc.). To this EtOK solution was added in drops with stirring a solution of the diester (II) in dehyd. benzene (20 cc.) at 30～40° during 1 hr. The freed EtOH was distilled with a portion of benzene in an oil bath at 110～120°. The K salt of the diester was cooled to below 5° and a mixture of benzyl chloride (10 g.) in dyhyd. benzene (20 cc.) was added dropwise. After keeping for 1 hr. at room temp., the reaction was completed by heating for further 8 hrs. at 80°. The reaction mixture was decomposed with ice water, washed with water, dried, and evaporated. Pale yellow oil (III), b.p_1 175～180°. Yield, 11.5 g. (55%). *Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 72.7; H, 7.95. Found : C, 72.6; H, 7.95.

α-(2-Hydroxycarbonylcyclohex-1-enyl)hydrocinnamic acid (III)—The diester (III) (25.6 g.) was heated to boiling with 40% KOH solution (KOH 40 g. in H_2O 60 cc.) and a homogeneous solution was obtained after 3 hrs. Water (50 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 HCl and the separated oil was extracted with ether, dried, and evaporated. The residue was recrystallized from AcOEt-petr. ether to give 12.5 g.(60%) of (III) as colorless plates, m.p. 146°(decomp.). *Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.6. Found : C, 70.05, H, 6.7.

N-Methyl-4-benzyl-1, 3-dioxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroisoquinoline (V)—The above acid (III) (7.3 g.) and N-methylformamide (10 g.) were heated in an oil bath (200～205°) for 8 hrs. After cooling, the reaction mixture was poured into water and the separated oil was extracted with ether. Ethereal solution was washed with water, dried, and evaporated. The residual oil was heated over a free flame for a few minutes and then distilled *in vacuo* at 210～215°/2 mm., affording a pale yellow viscous oil, which solwly crystallized on cooling in ice water, as colorless prisms (V), m.p. 69～71° (from EtOH). Yield, 6.3 g.(90%). *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.8; H, 7.1; N, 4.7. Found : C, 75.5; H, 7.2; N, 4.7.

N-Methyl-4-benzyl-1, 2, 3, 4, 5, 6, 7, 8-octahydroisoquinoline (VI)—A solution of N-methylimide (V) (6, 0 g.) in dehyd. ether (100 cc.) was added in drops with vigorous stirring to a suspension of $LiAlH_4$ (2.8 g.) in dehyd. ether (200 cc.) at 0° to 3° during a period of 1 hr. and then refluxed for 20 hrs. After cool, the mixture was decomposed with water (8.5 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 147～149°/0.5 mm., affording a pale yellow oil. (VI) rapidly decolorized 0.1% $KMnO_4$ solution and is unstable in the air. Picrolonate : Yellow rhombs (from acetone), m.p. 181～183°. *Anal.* Calcd. for $C_{17}H_{23}N \cdot C_{18}H_8O_5N_4$: C, 64.15; H, 6.2; N, 13.85. Found : C, 64.1; H, 6.4; N, 13.75. Picrate : Oil

N-Methyl-16-aza-des-N-morphinan (VII)—Octahydrosioquinoline (VI) (2.6 g.) in 85% H_3PO_4 (20 cc.) was heated in an oil bath at 160～170° for about 70 hrs. After cooling, the mixture was poured into water and basified with 20% NaOH solution. The mixture was extracted with ether, washed with water, dried, and evaporated. The residual oil was distilled at 172～177°/1.5 mm. and the distillate crystallized on cooling. The base came as colorless prisms (from MeOH), m.p. 80～82°. *Anal.* Calcd. for $C_{17}H_{23}N$: C, 84.6; H, 9.6; N, 5.8. Found : C, 84.35; H, 9.25; N, 5.9. Picrate: Yellow needles (from AcOH), m.p. 215.8°(decomp.). *Anal.* Calcd. for $C_{17}H_{23}N \cdot C_6H_3O_7N_3$; C, 58.7; H, 5.55; N, 11.9. Found : C, 58.4; H, 5.5; N, 11.65.

Methiodide : White columnars (from acetone+EtOH), m.p. 190～193°. *Anal.* Calcd. for $C_{18}H_{26}NI$: C, 56.2; H, 6.8; N, 3.65. Found : C, 56.15; N, 6.6; N, 3.5.

Methopicrate : Yellow needles (from AcOH), m.p. 187～188°. Picrolonate : Oil.

9-Methyl-4b-dimethylaminomethyl-4b, 5, 6, 7, 8, 8b, 9, 10-octahydrophenanthrene (X)—N-Methyl-16-aza-des-N-morphinan (VII) methiodide (0.7 g.) was converted to (VII) methohydroxide by heating with fresh Ag_2O at 95° for 2 hrs. AgI was filtered off and the filtrate was concentrated *in vacuo* to dryness. The residue was distilled *in vacuo* with decomposition giving colorless oil, b.$p_{2.5}$ 155～159°. Yield, 0.4 g. of the base (IX) which decolorized 0.1% $KMnO_4$ solution.

Hydrogenation of the base (IX) (0.4 g.) in the presence of Adams' PtO_2 catalyst (0.2 g.) at atmospheric pressure resulted in the absorption of about 30 cc. of H_2 (Calcd., 35 cc.) during 2 hrs. After evaporation of the solvent, the residue was distilled to give colorless oil, b.$p_{2.5}$ 155～160°. Yield, 0.3 g. of (X). (X) gave a negative test with 0.1% $KMnO_4$ solution and failed to give any crystalline derivatives.

9-Methylphenanthrene (XI)—The base (X) (200 mg.) was mixed with 30% Pd-C catalyst (130 mg.) and heated in a metal bath at 270～280°. The mixture was decomposed with vigorous evolution of amine. After 1 hr., heating was continued at 310～320° for 5 hrs. After cooling, the residue was extracted with ether, evaporated, and the residual oil was distilled at 320～345° (bath temp.). The distillate solidified on cooling and one crystallisation from EtOH gave 9-methylphenanthrene as colorless needles, m.p. 85～88°, showing blue fluorescene in EtOH solution. Yield, about 30 mg. of (XI). Admixture with 9-methylphenanthrene, m.p. 89～90°, prepared by the method of Lambert and Matin,[8] gave no m.p. depression.

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).

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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

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1) Part Ⅷ : This Bulletin, **4**, 352(1956).

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