C, 59.25; H, 6.22; N, 11.52. Found : C, 59.1; H, 6.06; N, 11.82. A mixed melting point with the sample from crystalline methiodide was depressed.

Summary

Synthesis of a morphinan analog in which the ring nitrogen was transposed to 6-position has been described. A benzyl group was introduced into 5-position of 5,6,7,8-tetrahydroisoquinoline, whose methohalide was reduced to the octahydroisoquinoline, and the objective compound was obtained by heating the latter in hydrobromic acid to effect rearrangement-cyclization.

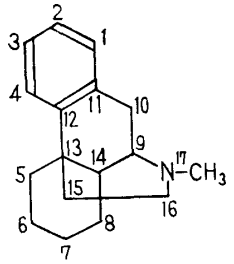
(Received December 4, 1956)

U. D. C. 547.833.9

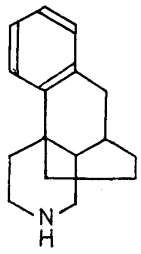
16. Norio Sugimoto and Hiroshi Kugita : Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. XII.[1] Synthesis of N-Methyl-7-aza-des-N-morphinan (3-Methyl-5,10b-trimethylene-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline).

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

Of the isomers of N-methylmorphinan formed by the transposition of its ring nitrogen, Sugimoto and others synthesized des-N-morphinans possessing ring nitrogen in 6-,[1] 9-,[2] and 16-position,[3] and Ochiai and others[4] reported the synthesis of 15-aza-des-N-morphinan (allomorphinan). The present paper describes the synthesis of another isomeric N-methyl-des-N-morphinan with the ring nitrogen in 7-position.



N-Methylmorphinan



7-Aza-des-N-morphinan

Analgesics in general are known to possess a tertiary amine bonded to the carbon, third from the quaternary carbon bonded directly to the phenyl group. In the morphinan skeleton, the nitrogen (17) is present inside the D-ring, with the quaternary carbon (13) in the center. Considering the C-ring of 7-aza-des-N-morphinan with the quaternary carbon (13) in the center, it can easily be seen that the position (17) of the nitrogen in D-ring of morphinan correponds to 7-position of the C-ring. It may therefore be said that the synthetic and pharmacological studies on such a structurally interesting N-methyl-7-aza-des-N-morphinan and a subsequently developed 3-hydroxy compound would be highly interesting.

---

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

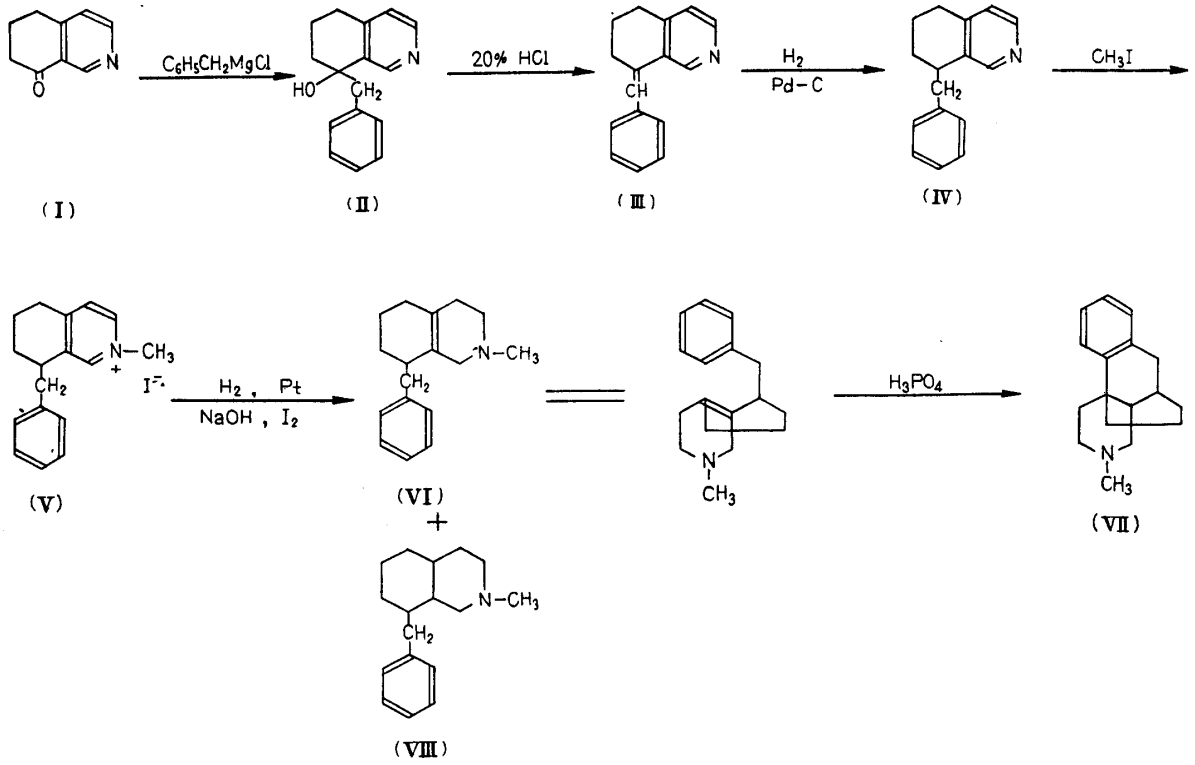
1) Part XI : This Bulletin, **5**, 62(1957).
2) N. Sugimoto, H. Kugita : This Bulletin, **3**, 11(1955).
3) N. Sugimoto, S. Ohshiro : *Ibid.*, **4**, 352, 356(1956).
4) E. Ochiai, K. Harasawa : *Ibid.*, **3**, 369(1955).

Sugimoto and others[5] earlier reported on the oxidation of 5,6,7,8-tetrahydroisoquinoline with chromium trioxide and showed that the 8-oxo compound, rather than the 5-oxo compound, is obtained in a good yield. The present synthesis of the subject compound used this 8-oxo-5,6,7,8-tetrahydroisoquinoline (I) as the starting material. Grignard reaction of (I) and benzylmagnesium chloride afforded 8-benzyl-8-hydroxy-5,6,7,8-tetrahydroisoquinoline (II) which was heated with 20% hydrochloric acid to effect dehydration, forming 8-benzylidene-5,6,7,8-tetrahydroisoquinoline (III). The structure of this compound was determined by its ultraviolet absorption spectrum.

Catalytic reduction of the benzylidene compound (III) with 5% palladium-carbon catalyst resulted in the absorption of one mole of hydrogen to form 8-benzyl-5,6,7,8-tetrahydroisoquinoline (IV). The methiodide (V) of (IV) was then submitted to catalytic reduction in methanol in the presence of sodium hydroxide and a small amount of iodine, with platinum catalyst and the product formed on absorption of two moles of hydrogen was purified as the hydrochloride, affording 2-methyl-8-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (VI) hydrochloride. In this reduction, further hydrogenated decahydroisoquinoline (VIII) also formed as a by-product.

The cyclization reaction of 8-benzyloctahydroisoquinoline (VI) proceeded very poorly compared to similar reactions of 1-benzyl-,[6] 4-benzyl-,[3] and 5-benzyl-octahydroisoquinoline[1] witnessed in the past. Heating of (VI) with 85% phosphoric acid at 170~180° for 80 hours finally afforded the objective N-methyl-7-aza-des-N-morphinan (VII), but the yield was poor and the majority turned into a pale yellow, resinous polymer.

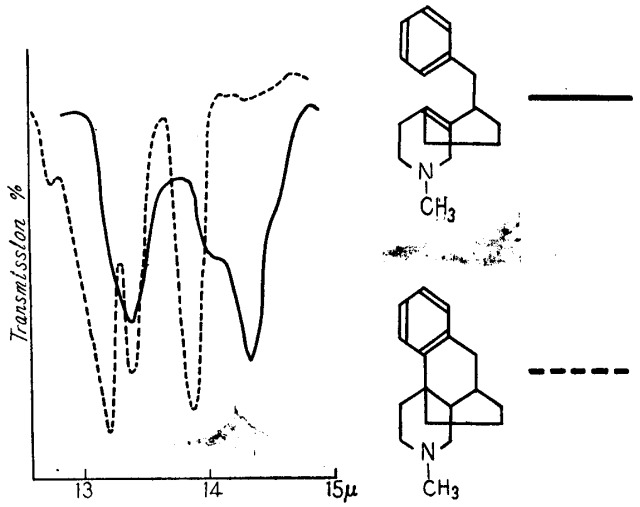
The infrared absorption spectrum of the product exhibited the absorption of C-H out-of-plane vibration at 13.2 μ, indicating that the ring closure had taken place in the



5) N. Sugimoto, H. Kugita, T. Tanaka : J. Pharm. Soc. Japan, **76**, 1308(1956).
6) R. Grewe, A. Mondon : Ber., **81**, 279(1948).
7) S. Saito : This Bulletin, **4**, 438(1956).
8) J. W. Cook, C. L. Hewett : J. Chem. Soc., **1936**, 62.
9) J. C. Bardhan, R. C. Banerjee : *Ibid.*, **1956**, 1809.

ortho position of the benzene ring. This of course leaves the question of whether the rearrangement-cyclization had occurred between the *ortho* position of the benzene ring and 10-position of the isoquinoline ring (six-membered ring formation) or with 9-position of the isoquinoline ring (five-membered ring formation), but it may be assumed from the past reports of Grewe,[6] Ochiai,[4] Sugimoto,[3] and Saito,[7] that the six-membered ring closure had also occurred in the present case. The work of Cook, *et al.*,[8] and Bardhan, *et al.*,[9] also proved the formation of 3,4-benzobicyclo[3.3.1]nonane alone on heating 1-benzyl-1-cyclohexanol and 2-benzyl-1-cyclohexanol with phosphorus pentoxide to effect dehydrative cyclization, there being no evidence of the formation of hydrogenated fluorene (cf. chart on p. 65 of this issue).

In the present case, this experimental evidence would also be applicable since the reaction corresponds to the cyclization of a benzylcyclohexene compound formed by the introduction of an N-methylmethanoiminoethano group from 2- to 3-position of 1-benzyl-2-cyclohexanone, and it may be concluded that the product is from the objective six-membered ring closure.



Infrared Absorption Spectra (in Nujol)

The writers express their gratitude to Prof. S. Sugasawa of the University of Tokyo and to Dr. Fujisawa, Director of this Laboratory, for their kind guidance and encouragnment. They are indebted to Mr. K. Kodera for infrared spectral data and to Mrs. F. Hisamichi and Mr. T. Yoda for elemental analyses.

Experimental

8-Benzyl-8-hydroxy-5,6,7,8-tetrahydroisoquinoline (II)—To a Grignard solution prepared from benzyl chloride (6.55 g.), Mg (1.35 g.), and dehyd. ether (70 cc.), a solution of 8-oxo-5,6,7,8-tetrahydroisoquinoline (I) (6.5 g.) in dehyd. ether (30 cc.) was added and refluxed for 3 hrs. Ethereal layer from the decomposed reaction mixture was dried and evaporated, giving a crystalline mass, which was triturated with a small amount of ether and filtered. 4.0 g. of m.p. 131~134°.

Ethereal filtrate was evaporated and distilled under reduced pressure. The starting oxo compound (1.6 g.) was recovered and then a viscous material run over at b.p$_4$ 205~210°. The latter was treated with ether and additional 2 g. of the product (II) was obtained. The combined base was recrystallized from ligroine—AcOEt to give colorless pillars, m.p. 133~134°.

Hydrochloride: Colorless needles (from EtOH—ether), m.p. 194°. *Anal.* Calcd. for $C_{16}H_{17}ON\cdot HCl$: C, 69.7; H, 6.55; N, 5.1. Found: C, 69.9; H, 6.55; N, 5.05.

8-Benzylidene-5,6,7,8-tetrahydroisoquinoline (III)—Dehydroxylation of (II) (4.0 g.) was effected by heating with 20% HCl for 4 hrs. HCl was removed, the residue was basified with K_2CO_3, extracted with ether, and dried. The product was obtained by distillation as a pale yellow liquid, b.p$_6$ 192~197°. Yield, 3.5 g.

Hydrochloride: Pale yellow pillars (from EtOH—ether), m.p. 202~205°. *Anal.* Calcd. for $C_{16}H_{16}NCl$: C, 74.55; H, 6.2; N, 5.45. Found: C, 74.75, H, 6.45; N, 5.5.

Picrate : Yellow needles (form AcOH), m.p. 188~190°. *Anal.* Calcd. for $C_{22}H_{18}O_7N_4$: C, 58.65; H, 4.05; N, 12.45. Found : C, 59.05; H, 4.1; N, 12.6.

8-Benzyl-5,6,7,8-tetrahydroisoquinoline (IV)—The benzylidene compound (III) (3.5 g.) was dissolved in EtOH (30 cc.) and hydrogenated in the presence of 5% Pd-C (1.0 g.). One mole (340 cc.) of H_2 was absorbed in 1 hr., after which hydrogenation became very slow. After filtration of the catalyst, the solvent was distilled off and the residue was distilled in vacuum, giving 3.1 g. of the product (IV) as a colorless liquid, $b.p_4$ 179~183°.

Picrate : Yellow plates (EtOH), m.p. 178~179.5°. *Anal.* Calcd. for $C_{22}H_{20}O_7N_4$: C, 58.4; H, 4.45; N, 12.4. Found : C, 58.1; H, 4.6; N, 12.45.

Methiodide : White pillars (EtOH), m.p. 213~216°. *Anal.* Calcd. for $C_{17}H_{20}NI$: C, 55.9; H, 5.5; N, 3.85. Found : C, 55.7; H, 5.55; N, 4.2.

2-Methyl-8-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (VI)—Methiodide (4.5 g.), prepared from 3 g. of 8-benzyl-tetrahydroisoquinoline (IV) was dissolved in MeOH (80 cc.), *N* NaOH (30 cc.) and I_2 (5 mg.) were added, and hydrogenated in the presence of Adams' catalyst (0.3 g.), absorbing just 2 moles of H_2 (680 cc. at 30°). Then the hydrogenation was stopped, as otherwise the absorption would continue. After filtration of the catalyst, the solution was acidified with 10 cc. of 10% HCl, MeOH was removed under reduced pressure, and the residue was basified with K_2CO_3. The separateded free base was extracted with ether, dried, evaporated, and distilled in vacuum to give 2.1 g. of colorless oil, $b.p_2$ 143~145°. This was treated with EtOH-HCl in acetone and 1.6 g. of the hydrochloride, was collected. White needles (AcOEt+EtOH), m.p. 206~209°. *Anal.* Calcd. for $C_{17}H_{23}N \cdot HCl$: N, 5.05. Found : N, 5.22.

Picrolonate : Yellow granules (EtOH), m.p. 159.5~162.5°. *Anal.* Calcd. for $C_{27}H_{31}O_5N_5$: C, 64.15; H, 6.2; N, 13.85. Found : C, 63.85; H, 6.25; N, 13.85.

Picrate : Yellow oily substance.

The free base turned brown on standing in the air and decolorized 2% $KMnO_4$ solution in acetone.

2-Methyl-8-benzyl-decahydroisoquinoline (VIII)—Acetone was removed from the mother liquor of the hydrochloride of octahydroisoquinoline (VI) and the residue was basified with K_2CO_3. Ether-extracted free base was distilled *in vacuo*. The base did not decolorize 2% $KMnO_4$ solution in acetone. It was converted to the oxalate and recrystallized from AcOEt—EtOH solutin as white needles, m.p. 185~186°.

Methiodide : White needles (AcOEt+EtOH), m.p. 227~229°. *Anal.* Calcd. for $C_{18}H_{26}NI \cdot \frac{1}{2} H_2O$: C, 54.8; H, 7.3; N, 3.55. Found : C, 54.75; H, 7.0; N, 3.95.

N-Methyl-7-aza-des-N-morphinan (VII)—A mixture of octahydroisoquinoline hydrochloride (0.8 g.) and 85% H_3PO_4 (8 cc.) was heated in an oil bath and gently refluxed for 80 hrs. at 180°. The reaction mixture was diluted with water and neutralized with NaOH solution. The separated free base was extracted with ether, dried, and evaporated. Vacuum distillation gave only a few drops of cyclized product at about 160°(2 mm. Hg) and the remainder was a non-distilling, light yellow polymer. The distillate was converted to the picrate and recrysallized from EtOH. The picrate of (VII) was obtained as yellow needles, m.p. 213~214°. *Anal.* Calcd. for $C_{23}H_{26}O_7N_4$: C, 58.7; H, 5.55; N, 11.9. Found : C, 58.65; H, 5.95; N, 12.2.

The free base gave negative test with a solution of 2% $KMnO_4$ in acetone.

Summary

The position of nitrogen in the morphinan skeleton corresponds to the 17-position of D-ring, or 7-position of the C-ring. A synthesis of the morphinan with the nitrogen in this 7-position has been described.

(Received December 4, 1956)