Lösungen wurden zusammen einmal mit Äther ausgeschüttelt. Aus der $CHCl_3$- und Äther-Lösung wurden ca. 1.7 g rohe Benzoesäure erhalten. Die wässerige Schicht wurde unter vermindertem Druck verdampft, der Rückstand mit einer gesättigten $NaHCO_3$-Lösung alkalisch gemacht und mit $CHCl_3$ extrahiert. Die $CHCl_3$-Lösung gab nach dem Trocknen mit Na_2SO_4 und Abdampfen des Lösungsmittels 380 mg öligen Rückstand, welcher bei der chromatographischen Reinigung durch eine Aluminasäule in 350 mg Pyridin-N-oxyd(weniger adsorbierbar) und ca. 10 mg Substanz getrennt wurde. Die letztere gab beim Umkristallisieren aus Aceton schwachgelbe Nadeln vom Schmp. 165~169°, welche bei einer Mischprobe mit 3-Nitropyridin-N-oxyd bei 165~169° schmolzen.

Zusammensetzung

Durch Nitrierung von Chinolin-N-oxyd mit Benzoylnitrat in Chloroform- bzw. Dioxan-Lösung wurde das 3-Nitrochinolin-N-oxyd mit befriedigender Ausbeute erhalten. Pyridin-N-oxyd gibt bei ganz analoger Reaktion das 3-Nitropyridin-N-oxyd trotz sehr schlechter Ausbeute. UV-Absorptionsspektren der isomeren Mononitroderivate des Chinolin-N-oxydes wurden verglichen.

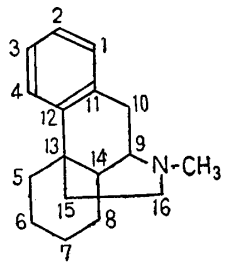
(Eingegangen am 24. November, 1956)

U. D. C. 547.833.9.07

15. Norio Sugimoto, Susumu Ohshiro, Hiroshi Kugita, and Seiichi Saito: Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. XI.[1] Synthesis of N-Methyl-6-aza-des-N-morphinan (2-Methyl-5,10b-trimethylene-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*]isoquinoline).

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

N-Methylmorphinan, synthesized by Grewe in 1946, should come in nine kinds of position isomers (5, 6, 7, 8, 9, 10, 14, 15, 16) with the transposition of ring nitrogen. It would be very interesting to compare the physicochemical and pharmacological properties between these isomers and morphinan. Of these isomers, des-N-morphinans with the ring nitrogen transposed to 9- and 16-position were synthesized by Sugimoto and others,[2,3] and 15-aza-des-N-morphinan (allomorphinan) was prepared by Ochiai and others.[4] It had been found that the des-N-morphinan with nitrogen in 9-position possesses analgesic action comparable to that of morphine series.



N-Methylmorphinan

Some time ago, Sugimoto and others[1] reported on the preparation of 5-oxo- (II) and 8-oxo-5,6,7,8-tetrahydroisoquinoline (II′) by the chromium trioxide oxidation of 5,6,7,8-tetrahydroisoquinoline (I). This 5-oxo-5,6,7,8-tetrahydroisoquinoline (II) was used as the starting material, reacted with benzylmagnesium chloride to form 5-benzyl-5-hydroxy-5,6,7,8-tetrahydroisoquinoline (III), which was heated with hydrochloric acid to effect intramolecular dehydration, and 5-benzylidene compound (IV)** was prepared. Hydrogenation of (IV)

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** Assumed from the structural determination of 8-benzylidene-5, 6, 7, 8-tetrahydroisoquinoline (cf. the following paper).

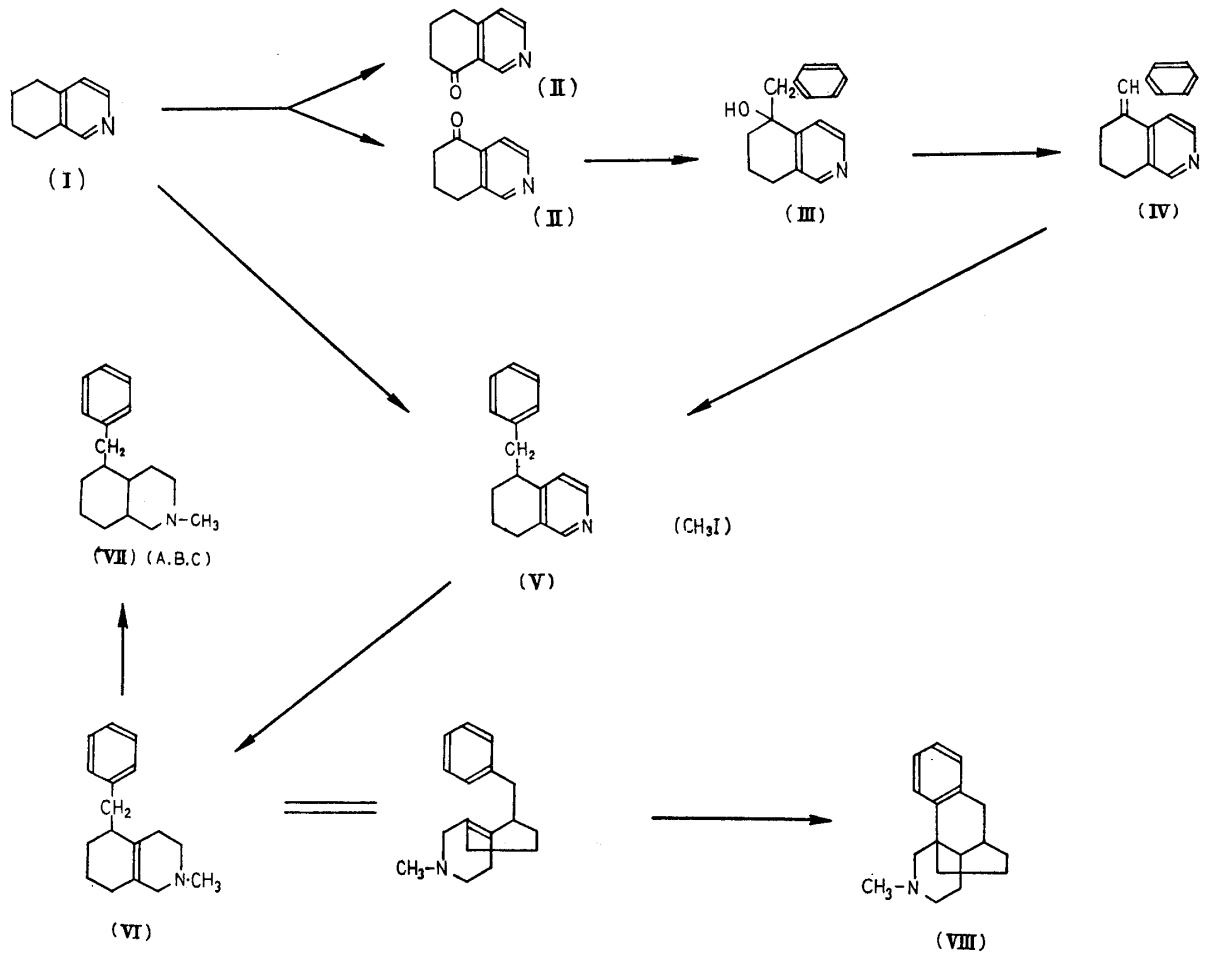
1) Part X: J. Pharm. Soc. Japan, **76**, 1308(1956).
2) N. Sugimoto, H. Kugita: This Bulletin, **3**, 11(1955).
3) N. Sugimoto, S. Oshiro: *Ibid.*, **4**, 352, 356(1956).
4) E. Ochiai, K. Harasawa: *Ibid.*, **3**, 369(1955).

with 5% palladium-carbon resulted in the absorption of 1 mole of hydrogen to form 5-benzyl-5,6,7,8-tetrahydroisoquinoline (V)(picrate, m.p. 165°).

On the other hand, (I) was derived to its potassium salt by the application of potassium amide in liquid ammonia, according to the methed of Bergstrom and others,[5,6] and applied with benzyl chloride, from which 5-benzyl-5,6,7,8-tetrahydroisoquinoline (V) (picrate, m.p. 166°) was obtainod in a good yield. Since (V) showed no depression of the melting point on admixture with the compound obtained from 5-oxo-5,6,7,8-tetrahydroisoquinoline, the structure of one of the oxidation products of (I) by chromium trioxide was indirectly proved to be the 5-oxo compound.

The methiodide of (V) was then submitted to catalytic reduction with the Adams' platinum catalyst, in alkaline medium in the presence of a small amount of iodine, and although some resinous matter formed, two moles of hydrogen was absorbed to form 5-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (VI). Purification of (VI) through the perchlorate separated it into crystalline and noncrystalline perchlorates. The noncrystalline perchlorate was proved to have been mixed with (VI) and 5-benzyldecahydroisoquinoline (VII), formed by further hydrogenation, by the formation of their picrolonates or methiodide.

The crystalline perchlorate of (VI) was heated with 85% phosphoric acid at 100° to effect rearrangement but the reaction did not materialize. This was effected by heating in 48% hydrobromic acid at 150° for 25 hours. About one-half of the base thereby



5) F. W. Bergstrom : J. Org. Chem., **10**, 452(1945).
6) F. W. Bergstrom : J. Am. Chem. Soc., **53**, 3027, 4065(1931).

obtained distilled out at around 160°/2 mm. Hg, and the remainder was a pale brown, translucent polymer which failed to distil out even at b.p_1 250°. The distillate easily solidified to the objective N-methyl-6-aza-des-N-morphinan (Ⅷ), m.p. 116~117°. Recrystallization of (Ⅷ) gave colorless prisms and its recrystallization mother liquor did not yield any recovered starting material.

This substance does not possess an unsaturated bond and its infrared absorption spectrum (Fig. 1) exhibited an absorption at 13.35 μ, attributable to the out-of-plane vibration of the benzene ring by *ortho*-substitution, that it may be assumed that the rearrangement-cyclization had taken place as anticipated.

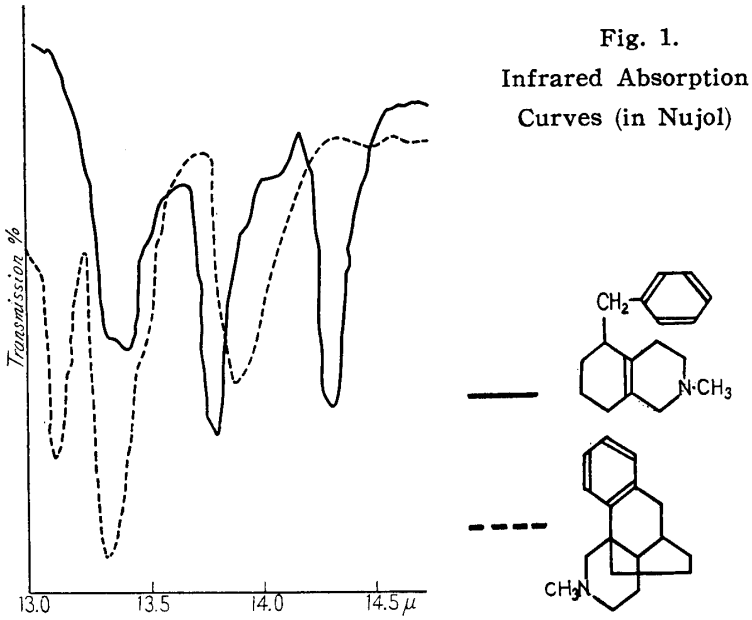
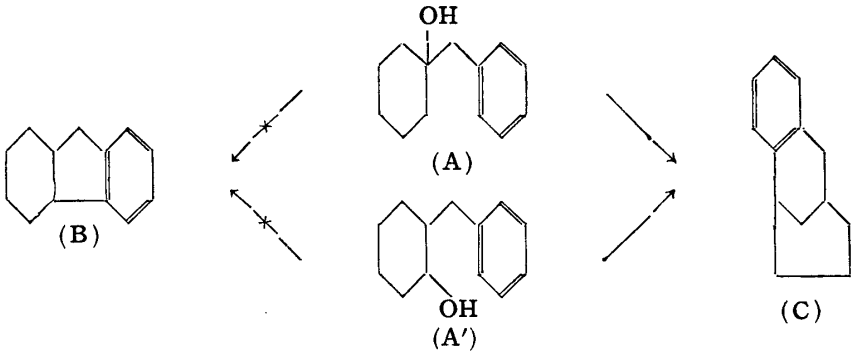


Fig. 1.
Infrared Absorption
Curves (in Nujol)

As for this rearrangement-cyclization, two positions can be assumed; one is the bonding of the *ortho*-position of the benzene ring and 9-position of the isoquinoline ring (formation of a six-membered ring) and the other with 10-position of the isoquinoline ring (formation of a five-membered ring). It is assumed, from the reports of Grewe,[7] Ochiai,[4] Sugimoto,[3] and Saito,[8] that the six-membered ring formation had also taken place in this case. According to Cook, *et al.*[9] and Bardhan, *et. al.*,[10] dehydrative cyclization of 1-benzyl-1-cyclohexanol (A) and 2-benzyl-1-cyclohexanol (A′) by phosphorus pentoxide failed to yield the objective hydrogenated fluorene (B) and only 3,4-benzobicyclo-[3.3.1]nonane (C) alone had been obtained. In the present case, therefore, similar rearrangement-cyclization may be assumed to have occurred between the *ortho*-position of the benzene ring and 9-position of the octahydroisoquinoline ring, forming a six-membered ring.

The crude octahydro compound (Ⅵ), prior to purification, was submitted to catalytic reduction in glacial acetic acid, containing a few drops of conc. sulfuric acid, over Adams' platinum catalyst, and afforded three kinds of product; a picrolonate of m.p. 204~206°, a methiodide of m.p. 214~216°, and a methopicrate of m.p. 159~161°. For these three kinds of decahydroisoquinoline (Ⅶ), there are the two compounds in which the hydrogen in 5-position takes the anti and syn types, with 9 and 10 positions in *cis* configuration, and two compounds in which the benzyl group in 5-position takes the equatorial and

7) R. Grewe : Ber., **81**, 279(1948).
8) S. Saito : This Bulletin, **4**, 438(1956).
9) J. W. Cook, C. L. Hewett : J. Chem. Soc., **1936**, 62.
10) J. C. Bardhan, R. C. Banerjee : *Ibid.*, **1956**, 1809.



axial conformation, with 9 and 10 positions in *trans* configuration, making a total of four that can naturally be anticipated. Since it is known through the work of Witkop[11] that the catalytic reduction in the presence of conc. sulfuric acid results in the formation of a *cis* compound in the majority and only a part of the product possesses the *trans* configuration, it may be imagined that, in the present case, three compounds (VIIIA,B,C) with 9 and 10 positions in *trans* configuration but the benzyl group not in axial configuration had been obtained. However, mutual steric configurations of these isomers still remain obscure.

The writers express their gratitude to Professor S. Sugasawa of the University of Tokyo and to Dr. Fujisawa, Director of this Laboratory, for their unfailing guidance and encouragement. They are indebted to Mr. Keiji Kodera for infrared spectral analysis and to Mrs. F. Hisamichi and Mr. T. Yoda for elemental analyses.

Experimental

5-Benzyl-5-hydroxy-5,6,7,8-tetrahydroisoquinoline (III)—An ethereal solution of (II) (2.7 g.) was added slowly to the Grignard reagent prepared from Mg (0.57 g.), benzyl chloride (2.7 g.), and dehyd. ether (30 cc.), and the mixture was refluxed for 3 hrs. The reaction mixture was decomposed with saturated aq. NH_4Cl solution. The ethereal layer was separated, dried, and evaporated. Residue solidified and was recrystallized from a mixture of ligroine and AcOEt. Yield, 1.45 g. of colorless pillars (III), m.p. 140°. *Anal.* Calcd. for $C_{16}H_{17}ON$: C, 80.3; H, 7.16; N, 5.85. Found: C, 80.45; H, 7.1; N, 6.0.

5-Benzylidene-5,6,7,8-tetrahydroisoquinoline (IV)—The hydroxy compound (III) (1.35 g.) was heated with 20% HCl (15 cc.) for 4 hrs. Most of the HCl solution was removed under reduced pressure, the residue was neutralized with K_2CO_3, extracted with ether, and dried. On evaporating the solvent, unreacted starting material crystallized and it was removed by filtration, and washed with a small amount of ether, 0.5 g. of (III) being recovered. The product run over at 167~174°/2 mm. by distillation of combined mother liquor. Yield, 0.6 g. of a pale yellow liquid (IV).

Picrate: Yellow needles (from AcOH), m.p. 183~184°. *Anal.* Calcd. for $C_{22}H_{18}O_7N_4$; C, 58.66; H, 4.03; N, 12.44. Found: C, 58.5; H, 4.25; N, 12.75.

5-Benzyl-5,6,7,8-tetrahydroisoquinoline (V)—i) The forgoing compound (IV) (0.6 g.) was hydrogenated using 5% Pd-C (0.5 g.) and EtOH as a solvent. The absorption of theoretical volume of hydrogen was accomplished in 1 hr., after which, hydrogenation was very slow and then stopped. After filtration of the catalyst, the solvent was distilled off and residual matter was distilled *in vacuo* to yield (V) (0.55 g.) as a colorless liquid, $b.p_3$ 170~173°. Picrate: m.p. 163~165°(from acetone).

ii) To a suspension of KNH_2, prepared from K (1.17 g.) and liquid NH_3(50 cc.), was added (I) (4.0 g.) with stirring for 10 mins., giving a reddish K-salt. When benzyl chloride (3.8 g.) was added dropwise to the reaction mixture, the solution color changed to amber with vigorous evolution of NH_3. Then NH_3 was gradually evaporated during 2 hrs. at room temperature, the remaining dark 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. After evaporation of the ether, the residue was distilled *in vacuo* to give a pale yellow oil, $b.p_3$ 172~175°. It gave 4.6 g. (70%) of (V) and a small amount of the starting material (I) was recovered.

Picrate: Yellow needles (from acetone), m.p. 165~166°. *Anal.* Calcd. for $C_{22}H_{20}O_7N_4$: C, 58.4; H, 4.46; N, 12.39. Found: C, 58.3; H, 4.6; N, 12.7.

A mixed melting point of this picrate with the sample prepared by the method of (i) was not depressed.

Methiodide: Colorless prisms (from MeOH), m.p. 180~182°. *Anal.* Calcd. for $C_{17}H_{20}NI$: C, 55.89;

H, 5.48; N, 3.83. Found : C, 55.9; H, 5.6; N, 4.2.

Hydrochloride : Colorless plates (from EtOH), m.p. 237~239°.

2-Methyl-5-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (VI)—To a solution of methiodide (28.0 g.) of (V) in MeOH (200 cc.) and water (150 cc.), iodine (0.4 g.) and *N* NaOH solution (180 cc.) were added. Hydrogenation of this solution in the presence of Adams' PtO_2 (0.5 g.) resulted in the absorption of 2 moles (3910 cc.) of hydrogen in 7 hrs. After filtration of the catalyst, filtrate was acidified with dil. HCl and solvents were evaporated below 50°(bath temp.). The residue was neutralized with K_2CO_3, extracted with ether, dried, and evaporated. (VI) (14.5 g. : 76.5%) was obtained as a pale yellow oil, $b.p_{1.5}$ 153~155°

To this distillate (13.5 g.) dissolved in MeOH (15 cc.) was added aq. solution of $HClO_4$ (10 cc.) and the mixture was allowed to stand over night in an ice chamber. The separated crystalline perchlorate was filtered by suction from the non-crystalline perchlorate and washed with 50% MeOH.

(i) Free base from the above crystalline perchlorate was distilled *in vacuo* to give 7.7 g. of (VI) as a pale yellow oil, $b.p_3$ 157~159°. This base decolorized the solution of 0.2% $KMnO_4$ in acetone.

Perchlorate : Colorless needles(from hyd. MeOH), m.p. 147~149°. *Anal.* Calcd. for $C_{17}H_{23}N \cdot HClO_4$: C, 59.74; H, 7.05; N, 4.10. Found : C, 59.55; H, 7.0; N, 4.4.

Picrolonate : Yellow needles (from EtOH), m.p. 107~109°(decomp.). *Anal.* Calcd. for $C_{27}H_{31}O_5N_5$: C, 64.14; H, 6.18; N, 13.85. Found : C, 63.9; H, 6.25; N, 13.8.

Methiodide : Colorless plates (from MeOH), m.p. 219~220°. *Anal.* Calcd. for $C_{18}H_{26}NI$: C, 56.4; H, 6.79; N, 3.65. Found : C, 56.0; H, 6.9; N, 3.65.

Picrate : Yellow needles (from EtOH), m.p. 137~139°.

Hydrochloride : Colorless needles (from acetone-ether), m.p. 184~186°. *Anal.* Calcd. for $C_{17}H_{23}N \cdot HCl$: N, 5.04. Found : N, 5.15.

(ii) The free base from the above combined non-crystalline perchlorate solution was distilled *in vacuo* to give a base (5.3 g) as a pale yellow oil, $b.p_3$ 154~156°.

Picrolonate : Yellow granules (from EtOH), m.p. 204~206°. *Anal.* Calcd. for $C_{27}H_{31}O_5N_5$: C, 64.14; H, 6.18; N, 13.85. Found : C, 64.05; H, 6.6; N, 14.15.

The mother liquor obtained by the removal of the picrolonate was neutralized, the base extracted with ether, and the residue reacted with MeI.

Methiodide : Colorless needles (from MeOH-AcOEt), m.p. 214~216°. *Anal.* Calcd. for $C_{18}H_{26}NI$: C, 56.4; N, 6.79; N, 3.65. Found : C, 56.15; H, 6.9; N, 4.05.

These compouds were identified as decahydroisoquinoline derivatives by the methods described later.

N-Methyl-6-aza-des-N-morphinan (VIII)—The octahydro base (VI) (5.0 g.) was heated with 48% HBr (100 cc.) in an oil bath at 145~150° for 25 hrs. Excess of HBr was removed under diminished pressure, the residue was dissolved in water, and basified with NH_4OH. The organic layer was extracted with ether, dried, and evaporated. The residue boiled out at 159~164°/2 mm. to yield 2.8 g. (53%) of a colorless viscous oil. The distillate gradually solidified on cooling. The crystals were collected on a sintered glass filter, washed with a small amount of petr. ether, and recrystallized from ligroine to afford 1.6 g. of (VIII) as colorless rhombs. m.p. 116~117°. *Anal.* Calcd. for $C_{17}H_{23}N$: C, 84.59; H, 9.61; N, 5.8. Found : C, 84.5; H, 9.85; N, 6.05.

Starting material was not recovered from the mother liquor.

Picrate : Yellow rhombs (from AcOH), m.p. 251°(decomp.). *Anal.* Calcd. for $C_{23}H_{26}O_7N_4$: C, 58.71; H, 5.57; N, 11.91. Found : C, 58.75; H, 5.55; N, 11.7.

2-Methyl-5-benzyldecarhydroisoquinoline(VII)-A solution of the octahydro base(VI)(2.8 g.)in AcOH (30 cc.), containing a few drops of conc. H_2SO_4, was reduced at atmospheric pressure in the presence of the Adams' PtO_2 catalyst. After 3.5 hrs., about 1 mole of H_2 was absorbed. The filtrate from the catalyst was evaporated *in vacuo*, the residue was treated in the usual manner, and the oil obtained distilled at 153~154°/3 mm. to give 2.6 g. of (VII) as a colorless oil, which gave a negative reaction with a solution of 0.2% $KMnO_4$ in acetone.

Picrolonate : Yellow plates (from AcOH), m.p. 204~206°. *Anal.* Calcd. for $C_{27}H_{33}O_5N_5$: C, 63.89; H, 6.55; N, 13.8. Found : C, 63.45; H, 6.8; N, 13.8.

Hydrochloride : Colorless plates (from MeOH+Ether), m.p. 256~258°.

The mother liquid from above-described picrolonate was neutralized, extracted with ether, and evaporated. The residual oil was boiled with MeI in MeOH, cooled, separated crystals were collected, and recrystallized.

Methiodide : Pale yellow pillars (from EtOH), m.p. 214~216°. *Anal.* Calcd. for $C_{18}H_{28}NI$: N, 3.61. Found : N, 3.85.

Methopicrate : Yellow plates (from EtOH), m.p. 118~120°. *Anal.* Calcd. for $C_{24}H_{30}O_7N_4$: C, 59.25; H, 6.22; N, 11.52. Found : C, 59.0; H, 6.15; N, 11.8.

Non-crystalline methiodide was treated with picric acid and converted to methopicrate.

Methopicrate : Yellow needles (from AcOH-ether), m.p. 159~161°. *Anal.* Calcd. for $C_{24}H_{30}O_7N_4$:

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.

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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).

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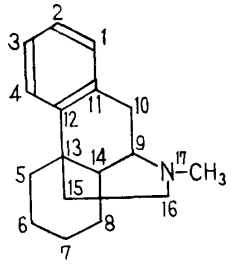
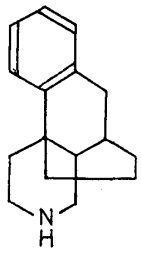
Of the isomers of N-methylmorphinan formed by the transposition of its ring nitrogen, Sugimoto and others synthesized des-N-morphinans possessing ring nitrogen in 6-,[1] 9-,[2] and 16-position,[3] and Ochiai and others[4] reported the synthesis of 15-aza-des-N-morphinan (allomorphinan). The present paper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

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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).