UDC 547.837.07

59. Mitsuo Sasamoto: Synthesis in the Morphinan Group. III.[1] A Synthesis of 2,3- and 3,4-Ethylenedioxy-N-methylmorphinan and their Optical Resolution.[2]

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In view of the fact that methyl ether of 3-hydroxy-N-methylmorphinan, which was prepared first by Schnider and Grüssner[3] after the morphinan synthesis of Grewe and Mondon,[4] is a potent antitussive, it appeared worthwhile to synthesize 2,3- and 3,4-ethylenedioxy-N-methylmorphinan for physiological evaluation.

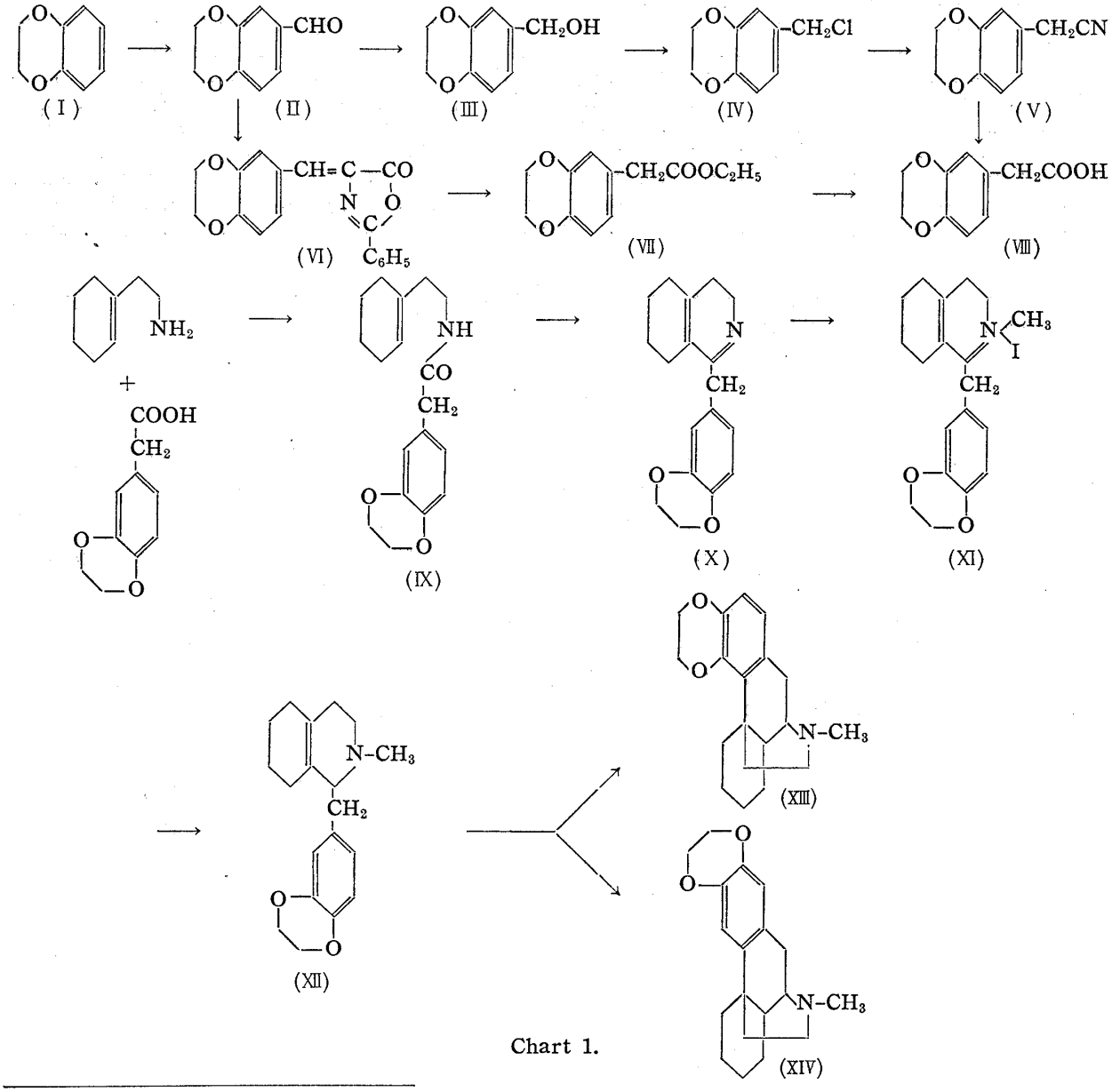

Chart 1.

*1 Toda-machi, Kita-adachi-gun, Saitama-ken (笹本光雄).

1) Part II. S. Saito: This Bulletin, **4**, 438(1956).
2) Presented before the March meeting of the Pharmaceutical Society of Japan (1957) and the 1st Kanto Local Meeting of the Pharmaceutical Society of Japan, November, 1957.
3) O. Schnider, A. Grüssner: Helv. Chim. Acta, **32**, 821(1949).
4) R. Grewe, A. Mondon: Chem. Ber., **81**, 279(1948).

The synthesis was carried out according to the method of Schnider as shown in Chart 1.

3,4-Ethylenedioxybenzyl alcohol, one of the starting materials, was prepared from 6-formylbenzodioxane[5] through crossed Cannizzaro reaction and converted into the corresponding chloride by means of thionyl chloride in the presence of pyridine. The crude chloride, when treated with potassium cyanide solution, gave the nitrile which, on being hydrolyzed by alkali, furnished 3,4-ethylenedioxyphenylacetic acid. The same acid was also prepared with equal success from benzodioxane via the azlactone as usual, as will be described in the Experimental section.

The amide was advantageously prepared by dehydrating the crystalline salt of the foregoing acid with 2-(1-cyclohexenyl)ethylamine,[6] obtained quantitatively by mixing equimolar amounts of the two materials in ether.

Preparation of the amide by the Schotten-Baumann method met with little success, due to marked resinification in converting the acid into the corresponding chloride.

The amide thus obtained was treated with phosphoryl chloride in boiling benzene to give 90% yield of the hexahydroisoquinoline as a faint yellow oil. For the best result reaction time was limited from 1.5 to 2 hours; longer heating resulted in the decrease of yield.

Since the base (X) was fairly unstable, this was directly converted to the methiodide, which was reduced either catalytically or with sodium borohydride, yielding the base (XII), which gave one and the same hydrogenoxalate of m.p. 142~144°, giving the correct analysis for the expected structure.

For Grewe cyclization the foregoing octahydroisoquinoline was heated with syrupy phosphoric acid at 140~145° for 45 hours. The resultant crude morphinan, produced in 80~85% yield, was a mixture of the theoretically possible 2,3- and 3,4-ethylenedioxy derivatives, the separation of which was possible through their hydrochlorides. As was expected, the presence of phenolic base was not traced in the cyclization products.

A mixture of isomeric hydrochlorides, prepared by introducing dry hydrogen chloride through the ether solution of the crude base, was a fairly hygroscopic solid, which was dissolved in pure acetone and the solution was allowed to stand for ca. one week, when a hydrochloride of m.p. 254~255° separated out, which gave a free base of m.p. 123~124°. The hydrogenoxalate also came as crystals of m.p. 237~238°(decomp.).

The free base recovered from the acetone filtrate was oily, whose hydrogenoxalate, however, was obtained crystalline and melted at 209~210°(decomp.) when pure. The free base recovered from the pure oxalate remained oily again and the hydrochloride was hygroscopic and could not be induced to crystallize. The hydriodide, however, was obtained crystalline and melted at 245~247°.

The preliminary structural assignment of these two isomeric bases was made by examining their infrared spectra, which are given in Fig. 1.

Thus, 3,4-ethylenedioxy structure (XIII) was assigned to the base of m.p. 123~124° and 2,3-ethylenedioxy structure (XIV) to the oily base.

Chemical evidence in support of the above view will be presented in the forthcoming paper.

According to Benson, *et al.*,[7] *l*-3-hydroxy-N-methylmorphinan is a potent analgesic, while *d*-3-methoxy-N-methylmorphinan is an effective antitussive.

For optical resolution of (XIII) *d*-tartaric acid in ethanol or methanol was proved to be ineffective and *d*-camphorsulfonic acid was also of no use. However, when a mixture

5) S. Sugasawa, Y. Arata : This Bulletin, **4**, 406(1956).
6) O. Schnider, J. Hellerbach : Helv. Chim. Acta, **33**, 1437(1950).
7) W. M. Benson, P. L. Stefko, L. O. Randall : J. Pharmacol. Exptl. Therap., **109**, 189(1953).

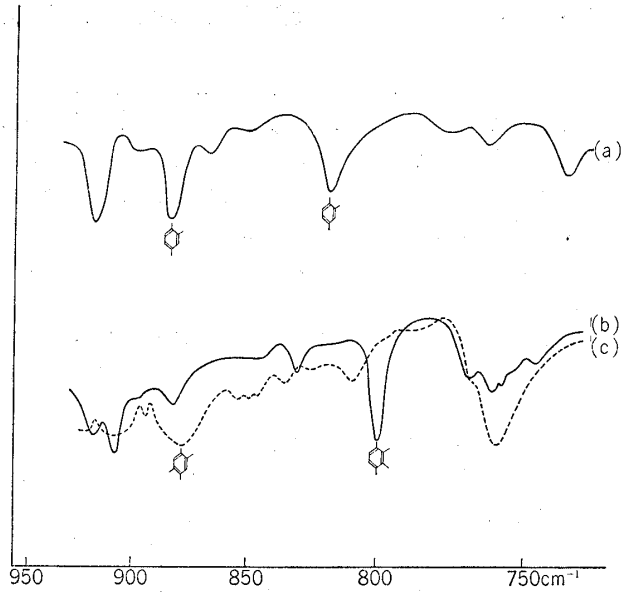

Fig. 1. Infrared Absorption Spectra of Hydrogenoxalate (Nujol, Perkin-Elmer Model 21)
(a) : (XII), (b) : (XIII), (c) : (XIV)

of equimolar portions of dibenzoyl-*d*-tartaric acid and (XIII) of m.p. 123~124°, dissolved in methanol, was allowed to stand in an ice-chest for 10 days, a crystalline solid separated and formed colorless prisms, m.p. 168~170°(decomp.), $[\alpha]_D^{21}$ −66.0° (c=1, MeOH), when purified from the same solvent. From the original methanolic mother liquor another solid was obtained, which was purified from methanol to give colorless plates, m.p. 167~169°(decomp.), $[\alpha]_D^{21}$ −44.0° (c=1, MeOH). Both of these salts gave correct analyses for $C_{37}H_{39}O_{10}N$, which corresponds to hydrogendibenzoyl-*d*-tartrate of (XIII).

The free base recovered from the former was purified from petroleum ether to form colorless pillars, m.p. 141~142°, $[\alpha]_D^{20}$ −37.2° (c=1, MeOH), and the latter furnished the antipodal base as colorless pillars, m.p. 141~142°, $[\alpha]_D^{22}$ +37.0° (c=1, MeOH), from petroleum ether.

The effort for the resolution of (XIV) by similar means using a variety of solvents was so far abortive, but optically active forms of (XIV) were prepared by another method which will be reported at a later date.

Experimental

6-Formylbenzodioxane (II)[5]—To a solution of benzodioxane (I) (116.5 g.) in dry benzene (1165 cc.), finely powdered $Zn(CN)_2$ (303 g.) was added. After dry HCl gas was introduced into the cold reaction mixture for 1.5 hr., powdered dry $AlCl_3$ (340 g.) was added in small portions and then dry HCl gas was introduced into the mixture for further 4 hr. at 40~45°. After standing overnight at room temp., 10% HCl was added to decompose the excess reagents and the reaction mixture was heated to reflux gently for 30 min. After cool, the separated oil was taken up in benzene and worked up as usual. (II) was obtained as a colorless liquid of $b.p_1$ 115~120°, m.p. 46~50° (125 g. or 89.0%).

3,4-Ethylenedioxybenzyl Alcohol (III)—To a cold solution of the aldehyde (II) (227 g.) in MeOH (295 cc.), 37% formalin (180 cc.) and KOH (250 g.) in H_2O (180 cc.) were added, the whole mixture was heated at 65° for 2 hr., finally refluxed for 15 min., and MeOH was evaporated. After cool, the reaction mixture was extracted with benzene and worked up as usual. (III) was obtained as a colorless liquid of $b.p_3$ 145~149° (225 g. or 98.0%).

3,4-Ethylenedioxybenzyl Chloride (IV)—To an ice-cold solution of the alcohol (III) (225 g.) in dry benzene (685 cc.), pyridine (4 cc.) and $SOCl_2$ (325 g.) were added dropwise. After stirring at 25° for 2 hr., the reaction mixture was allowed to stand overnight at room temp. and then poured into ice water. The organic layer was washed with $NaHCO_3$ solution and worked up as usual. (IV) was obtained as a pale yellow liquid (250 g. or quantitative), which was used for the next reaction without purification.

3,4-Ethylenedioxyphenylacetonitrile (V)—To a boiling solution of the crude chloride (IV) (8.9 g.) in benzene (12 cc.) an aq. solution of KCN (16.6 g. in 35 cc. of H_2O) was added dropwise. After stirring for 4 hr. under reflux, the separated benzene layer was worked up as ususl. (V) was obtained as a

colorless liquid of b.p_5 152~155° (6.4 g. or 75.7%).

2-Phenyl-4-(3,4-ethylenedioxybenzylidene)-5-oxazolone (VI)—An intimate mixture of the aldehyde (II) (15.2 g.), hippuric acid (19.1 g.), anhyd. AcONa (8 g.), and Ac_2O (29.4 g.) was heated gently over a free flame to give a clear reddish brown solution, from which crystals soon began to separate. The whole mixture was heated on a water bath for 1.5 hr., then EtOH (41 cc.) was added to the hot reaction mixture, and the whole was allowed to stand at room temp. overnight. The crystals were collected on a filter, washed with a small amount of cold EtOH and a large amount of hot water, and dried. (VI) was obtained as yellow crystals, m.p. 180~185° (18.9 g. or 66.5%).

Ethyl 3,4-Ethylenedioxyphenylacetate (VII)—A mixture of the azlactone (VI) (18.9 g.) and 10% NaOH (95 cc.) was heated at 130~150° (bath temp.) for 7 hr. until the odor of NH_3 disappeared. After cool, 40% NaOH (8 cc.) was added followed by H_2O_2 solution (18.4 cc.; 30% H_2O_2 and H_2O 1:1) dropwise with stirring below 15°. The whole mixture was allowed to stand overnight at room temp. The reaction mixture was acidified with dil. HCl and extracted with benzene. After evaporation of the dried benzene solution, a mixture of EtOH (95 cc.) and conc. H_2SO_4 (1.6 cc.) was added to the residue and the mixture was heated to reflux on a water bath for 4 hr. After removing EtOH *in vacuo*, the reaction mixture was basified with Na_2CO_3 solution and extracted with Et_2O. The ether solution was worked up as usual, giving (VII) as a colorless liquid of b.p_7 168~171° (8.3 g. or 60.7%).

3,4-Ethylenedioxyphenylacetic Acid (VIII)—i) A mixture of the nitrile (V) (6.4 g.) and MeOH-KOH solution (KOH 3.3 g., MeOH 15 cc., H_2O 15 cc.) was refluxed for 10 hr. with stirring. After removing MeOH, the reaction mixture was washed with Et_2O, the aq. solution was acidified with dil. HCl, and chilled. Colorless crystals that separated were collected, washed with H_2O, and dried. (VIII) was obtained as colorless leaflets, m.p. 63~70° (5.6 g. or 79%). By recrystallization from benzene-petr. ether the m.p. was raised to 73~74°. *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 62.10; H, 5.46.

ii) A mixture of the ester (VII) (128.4 g.) and 10% NaOH (580 cc.) was heated on a water bath for 2 hr. with stirring. After treating with charcoal, the alkaline solution was worked up as described above to yield (VIII) as colorless leaflets, m.p. 61~67° (111.7 g. or quantitatively). Recrystallization from benzene-petr. ether gave pure (VIII), m.p. 73~74°, which showed no depression on admixture with the sample obtained as above.

N-[2-(1-Cyclohexenyl)ethyl]-3,4-ethylenedioxyphenylacetamide (IX)—To an ice-cooled solution of the acid (VIII) (6.2 g.) in anhyd. Et_2O an ethereal solution of 2-(1-cyclohexenyl)ethylamine[6] (4 g.) was added, the separated salt was collected, washed with anhyd. Et_2O, and dried. The salt was obtained as colorless needles, m.p. 132~142° (10.1 g. or 99.0%). By recrystallization from EtOH-Et_2O the m.p. was raised to 149~151°. *Anal.* Calcd. for $C_{18}H_{25}O_4N$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.47; H, 7.91; N, 4.39.

The salt (10.1 g.) was heated at 170~175° (bath temp.) for 40 min. under a reduced pressure to form the amide. After cool, the reaction mixture was taken up in Et_2O. The ether solution was washed successively with dil. HCl, H_2O, $NaHCO_3$ solution, and H_2O. Evaporation of the dried ether solution left (IX) as colorless prisms, m.p. 62~67° (8.5 g. or 89.2%). Recrystallization from benzene-petr. ether gave pure (IX), m.p. 76~78°. *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.26; H, 7.86; N, 4.97.

1-(3,4-Ethylenedioxybenzyl)-3,4,5,6,7,8-hexahydroisoquinoline (X)—A mixture of the acetamide (IX) (20 g.) in anhyd. benzene (144 cc.) and $POCl_3$ (20.4 g.) was heated to reflux for 2 hr. After cool, the reaction mixture was poured into ice water and warmed. The separated aq. solution was treated with charcoal, basified with KOH, and extracted with Et_2O. The dried ether solution was evaporated, leaving (X) as a pale yellow oil (16.8 g. or 89.5%). Attempts to obtain a crystalline picrate were unsuccessful.

1-(3,4-Ethylenedioxybenzyl)-3,4,5,6,7,8-hexahydroisoquinoline Methiodide (XI)—To a cooled solution of the hexahydroisoquinoline (X) (16.8 g.) in Me_2CO (39 cc.) a solution of MeI (23.5 g.) in Me_2CO (91 cc.) was added at 0°. After standing at room temp. overnight, the solvent was removed under reduced pressure and the residue was washed with dehyd. Et_2O. (XI) was obtained as yellow-red fine powder (25 g. or 99.2%).

1-(3,4-Ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (XII)—i) To a cooled solution of the methiodide (XI) (10.3 g.) in anhyd. MeOH (205 cc.) $NaBH_4$ (4.85 g.) was added in small portions at 0° to 5° during 30 min. After standing at room temp. overnight, the solvent was removed under a reduced pressure and 2% NaOH (375 cc.) was added to the residue. The alkaline solution was extracted with Et_2O, the Et_2O extract was washed with H_2O, and dried. The Et_2O was evaporated, and the residue was distilled, giving (XII) as a pale yellow liquid, b.p_3 207~210° (4.1 g. or 56.5%).

The hydrogenoxalate formed colorless needles (from Me_2CO-EtOH), m.p. 142~144°. *Anal.* Calcd. for $C_{21}H_{27}O_6N \cdot \frac{1}{2}H_2O$: C, 63.30; H, 7.08; N, 3.51. Found: C, 63.59; H, 6.87; N, 3.57. IR ν_{max}^{Nujol} cm^{-1}: 885, 820 (1,2,4-trisubstituted benzene).

ii) To a solution of the methiodide (XI) (11.7 g.) in MeOH (50 cc.) a solution of KOH (1.62 g.) in MeOH

(60 cc.) containing a small amount of H_2O was added. The solution was hydrogenated at atmospheric pressure in the presence of PtO_2 catalyst (1.3 g.), 1 molar equivalent of H_2 being absorbed during about 3 hr. The color of the solution changed from red-brown to yellow. The filtrate from the catalyst removal was evaporated under a reduced pressure, the residue was added with H_2O, and extracted with Et_2O. The ether solution was worked up as usual, giving (XII) as a pale yellow liquid, b.p_2 200~205° (5.6 g. or 68.0%).

The hydrogenoxalate melted at 142~144° and showed no depression on admixture with the sample obtained as above.

3,4-Ethylenedioxy-N-methylmorphinan (XIII)—The octahydroisoquinoline (XII) (10.8 g.) was heated with H_3PO_4 (d=1.7; 108 cc.) at 140~145° (bath temp.) for 45 hr. The mixture was cooled, diluted with H_2O, and treated with charcoal. The filtrate was basified with NaOH, extracted with Et_2O, and worked up as usual, whereupon a pale yellow liquid (9.3 g.) was obtained.

The crude base was dissolved in dehyd. Et_2O, to which dry HCl gas was introduced. The crude hydrochloride separated, which was washed with anhyd. Et_2O, and dried. This was dissolved in Me_2CO (10 cc.) and kept in a refrigerator for 1 week. Fine crystals that separated were collected and washed with a small amount of Me_2CO, giving hydrochloride of (XIII), m.p. 217~220° (2.02 g. or 16.7%). On recrystallization from EtOH it afforded colorless needles, m.p. 254~255°. *Anal.* Calcd. for $C_{19}H_{26}O_2NCl$: C, 67.94; H, 7.80; N, 4.17. Found: C, 67.46; H, 7.81; N, 3.92.

The free base obtained from the hydrochloride formed colorless prisms from Et_2O, m.p. 123~124°. *Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.41; N, 4.68. Found: C, 75.73; H, 8.19; N, 4.95.

Hydrogenoxalate: Colorless leaflets (from EtOH), m.p. 237~238° (decomp.). *Anal.* Calcd. for $C_{21}H_{27}O_6N$: C, 64.76; H, 6.98; N, 3.59. Found: C, 64.35; H, 6.98; N, 3.74. IR ν_{max}^{Nujol} 802 cm^{-1} (1,2,3,4-tetrasubstituted benzene).

Methiodide: Colorless small cubes (from EtOH), m.p. 256~257°. *Anal.* Calcd. for $C_{20}H_{28}O_2NI$: C, 54.65; H, 6.39; N, 3.17. Found: C, 54.16; H, 6.56; N, 3.14.

2,3-Ethylenedioxy-N-methylmorphinan (XIV)—The combined mother liquor of the crystallization of (XIII) hydrochloride, described above, was evaporated under a reduced pressure. The residue was dissolved in H_2O, basified with NH_4OH, and extracted with Et_2O. The ether solution was worked up as usual to afford a pale yellow oil (7.3 g.). To EtOH (15 cc.) solution of the oil, anhyd. oxalic acid (2.2 g.) was added and the mixture was warmed to give a clear solution. After standing in a refrigerator for 1 week, hydrogenoxalate of (XIV) was obtained as colorless prisms, m.p. 182~189° (decomp.) (4.45 g. or 31.6%). Recrystallization from EtOH gave a pure compound, m.p. 209~210° (decomp.). *Anal.* Calcd. for $C_{21}H_{27}O_6N \cdot \frac{1}{2}H_2O$: C, 63.30; H, 7.08; N, 3.51. Found: C, 63.04; H, 6.88; N, 3.63. IR ν_{max}^{Nujol} 878 cm^{-1} (1,2,4,5-tetrasubstituted benzene).

The free base (XIV) recovered from the oxalate could not be induced to crystallize. The hydrochloride was very hygroscopic.

Hydriodide: Colorless small cubes (from MeOH-EtOH), m.p. 245~247°. *Anal.* Calcd. for $C_{19}H_{26}O_2NI$: C, 53.40; H, 6.13; N, 3.26. Found: C, 53.85; H, 6.38; N, 3.16.

Methiodide: Colorless small cubes (from EtOH), m.p. 248~249°. *Anal.* Calcd. for $C_{20}H_{28}O_2NI$: C, 54.65; H, 6.39; N, 3.17. Found: C, 54.41; H, 6.31; N, 3.19.

(−)- and (+)-3,4-Ethylenedioxy-N-methylmorphinan—A mixture of *dl*-3,4-ethylenedioxy-N-methylmorphinan (m.p. 123~124°, 630 mg.), dibenzoyl-*d*-tartaric acid (792 mg.), and MeOH (11.2 cc.) was warmed to form a clear solution. After standing in an ice-chest for 10 days, fine crystals that separated were collected by filtration. On recrystallization from MeOH it afforded (−)-dibenzoyl-*d*-tartrate (624 mg.) as colorless prisms of m.p. 168~170° (decomp.).

The mother liquor of the crystallization was evaporated and the residue was recrystallized from MeOH, affording (+)-dibenzoyl-*d*-tartrate (327 mg.) as colorless plates, m.p. 167~169° (decomp.).

l-3,4-Ethylenedioxy-N-methylmorphinan dibenzoyl-*d*-tartrate: Colorless prisms, m.p. 168~170° (decomp.). *Anal.* Calcd. for $C_{37}H_{39}O_{10}N$: C, 67.56; H, 5.97; N, 2.13. Found: C, 67.48; H, 5.96; N, 2.21. $[\alpha]_D^{21}$ −66.0° (c=1, MeOH).

Base: Colorless pillars (from petr. ether), m.p. 141~142°. *Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.41; N, 4.68. Found: C, 76.43; H, 8.26; N, 4.80. $[\alpha]_D^{20}$ −37.2° (c=1, MeOH).

d-3,4-Ethylenedioxy-N-methylmorphinan dibenzoyl-*d*-tartrate: Colorless plates, m.p. 167~169° (decomp.). *Anal.* Calcd. for $C_{37}H_{39}O_{10}N$: C, 67.56; H, 5.97; N, 2.13. Found: C, 67.45; H, 6.04; N, 2.18. $[\alpha]_D^{21}$ −44.0° (c=1, MeOH).

Base: Colorless pillars (from petr. ether), m.p. 141~142°. *Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.41; N, 4.68. Found: C, 76.20; H, 8.38; N, 4.77. $[\alpha]_D^{22}$ +37.0° (c=1, MeOH).

The author expresses his deep gratitude to Prof. Emeritus S. Sugasawa of the University of Tokyo for his kind and unfailing guidance throughout the course of this work and to Dr. M. Onda and Dr. S. Yamada, the former Director of this Laboratory, for their kind encouragement. He is also grateful to Dr. K. Harasawa for advices on the interpretation of the infrared spectra. The

specific rotation was measured by Dr. H. Watanabe of the University of Tokyo, infrared spectra and elemental analyses were carried out by Mr. K. Kodera, Mrs. F. Hisamichi, and Mr. T. Yoda of this Laboratory, to all of whom the author's thanks are expressed.

Summary

For phamacological evaluation, 2,3- and 3,4-ethylenedioxy-N-methylmorphinans were prepared. 3,4-Ethylenedioxyphenylacetic acid was prepared through two different ways; 6-formylbenzodioxane was converted to the amide, from which two N-methylmorphinan were obtained according to the method of Schnider. The structures of the two isomeric N-methylmorphinans were cofirmed by infrared spectral data. 3,4-Ethylenedioxy-N-methylmorphinan was resolved into the optical antipodes, using bibenzoyl-*d*-tartaric acid.

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60. Mitsuo Sasamoto : Synthesis in the Morphinan Group. IV.[1] Structural Proof of 2,3- and 3,4-Ethylenedioxy-N-methylmorphinan.*[1]

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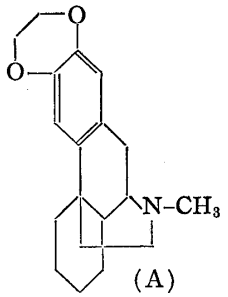
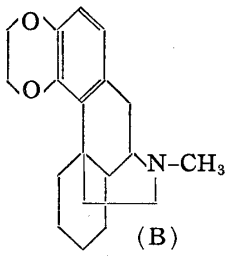
In the preceding paper[1] of this series were reported the synthesis of 2,3- and 3,4-ethylenedioxy-N-methylmorphinan (A and B) and their structural assignment based on their infrared spectral data. In the present paper will be presented chemical evidence in support of the above view.



(A)



(B)

In their study on Grewe cyclization of 1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline, Schnider, *et al.*[2] isolated a small amount of a by-product from the mother liquor of 3-hydroxy-N-methylmorphinan, the main product of the cyclization. The former was revealed to be an aporphine-type compound, because it yielded 1-ethyl-6-methoxyphenanthrene[3] by the Hofmann degradation.

Morphinan nature of both (A) and (B) was proved by the result of their Hofmann

*1 Presented before the Kanto Local Meeting of the Pharmaceutical Society of Japan, May, 1959.
*2 Toda-machi, Kita-adachi-gun, Saitama-ken (笹本光雄).
1) Part III : This Bulletin, **8**, 324(1960).
2) O. Schnider, J. Hellerbach : Helv. Chim. Acta, **33**, 1437(1950).
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