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.

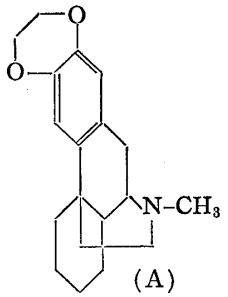
(Received September 5, 1959)

UDC 547.837.07

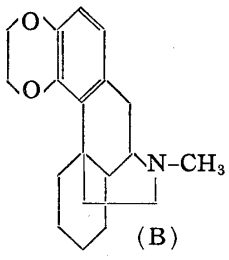
60. Mitsuo Sasamoto : Synthesis in the Morphinan Group. IV.[1] Structural Proof of 2,3- and 3,4-Ethylenedioxy-N-methylmorphinan.*[1]

(*Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd.*[*2])

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)



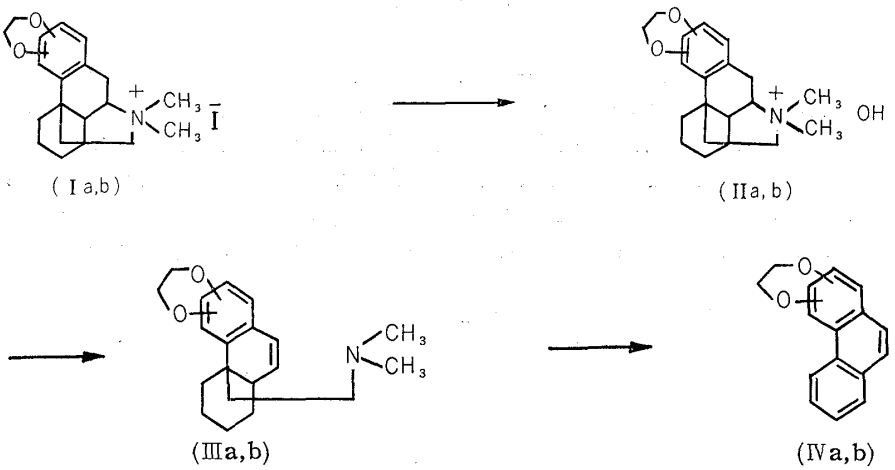
(B)

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).
3) A. Grüssner, J. Hellerbach, A. Brossi, O. Schnider : *Ibid.*, **39**, 1371(1956).

degradation, because 2,3- and 3,4-ethylenedioxyphenantherene were obtained respectively as shown in Chart 1, and were identified with authentic specimens prepared by the standard method, thus providing at the same time the structural proof for (A) and (B).



(Ⅰa,b) (Ⅱa,b) (Ⅲa,b) (Ⅳa,b)

a-Series : 2,3-ethylenedioxy- b-Series : 3,4-ethylenedioxy-

Chart 1.

The intermediary methine bases (Ⅲa and Ⅲb) have their ultraviolet absorption maxima at 278 and 273 mμ, respectively, as compared with that of 3-methoxy-13-(2-dimethylaminoethyl)-5,6,7,8,13,14-hexahydrophenanthrene at 270 mμ (ε 13400) according to Schnider, *et al.*[3]

Aromatization of the foregoing methine bases was carried out by heating them with 10% palladium-carbon at 320° for 6 hours in N_2 atmosphere. The products were neutral and melted at 113~114° and 77.5~79°, whose ultraviolet absorption spectra are acceptable as those of phenanthrene derivatives. From their infrared spectra it was presumed that they both are phenanthrenes disubstituted in the A-ring. Thus, chemical support for this view was rendered desirable.

2-Nitrobenzaldehyde was condensed with sodium 3,4-ethylenedioxyphenylacetate[1] according to the Perkin condensation, when a single 2-nitro-α-(3,4-ethylenedioxyphenyl)-cinnamic acid (Ⅴ) was obtained, which was reduced to the corresponding aminocinnamic acid*[3] (Ⅵ).

Pschorr condensation of (Ⅵ) gave two kinds of phenanthrenecarboxylic acid, which were decarboxylated to yield two phenanthrenes, the one of m.p. 113~114° and the other of m.p. 77.5~79°. Through mixed melting point test they were found to be identical with the ones derived from the compounds (A) and (B), respectively, and their ultraviolet and infrared curves were also super-imposable. The identity was also proved through direct comparison of each pair of the picrates.

The absorption at 873 cm^{-1} in the infrared absorption curve of (XVI) shows the presence of 1,2,4,5-tetrasubstituted benzene ring, hence 2,3-ethylenedioxy structure was attributed to this compound. Besides a similar deduction of (XVII) as 3,4-ethylenedioxyphenanthrene from the presence of 828 cm^{-1} (1,2,3,4-tetrasubstituted benzene), this compound (XVII) was also synthesized independently.

3,4-Ethylenedioxy-6-bromobenzaldehyde (Ⅸ) was prepared either by bromination of

*[3] Through the Perkin condensation of 2-nitrobenzaldehyde with sodium 3,4-methylenedioxyphenylacetate, H. Shirai and N. Oda (Yakugaku Zasshi, **79**, 241(1959)) obtained two kinds of cinnamic acid, presumably *cis* and *trans*, because one of them furnished a carbostyril derivative on being reduced.

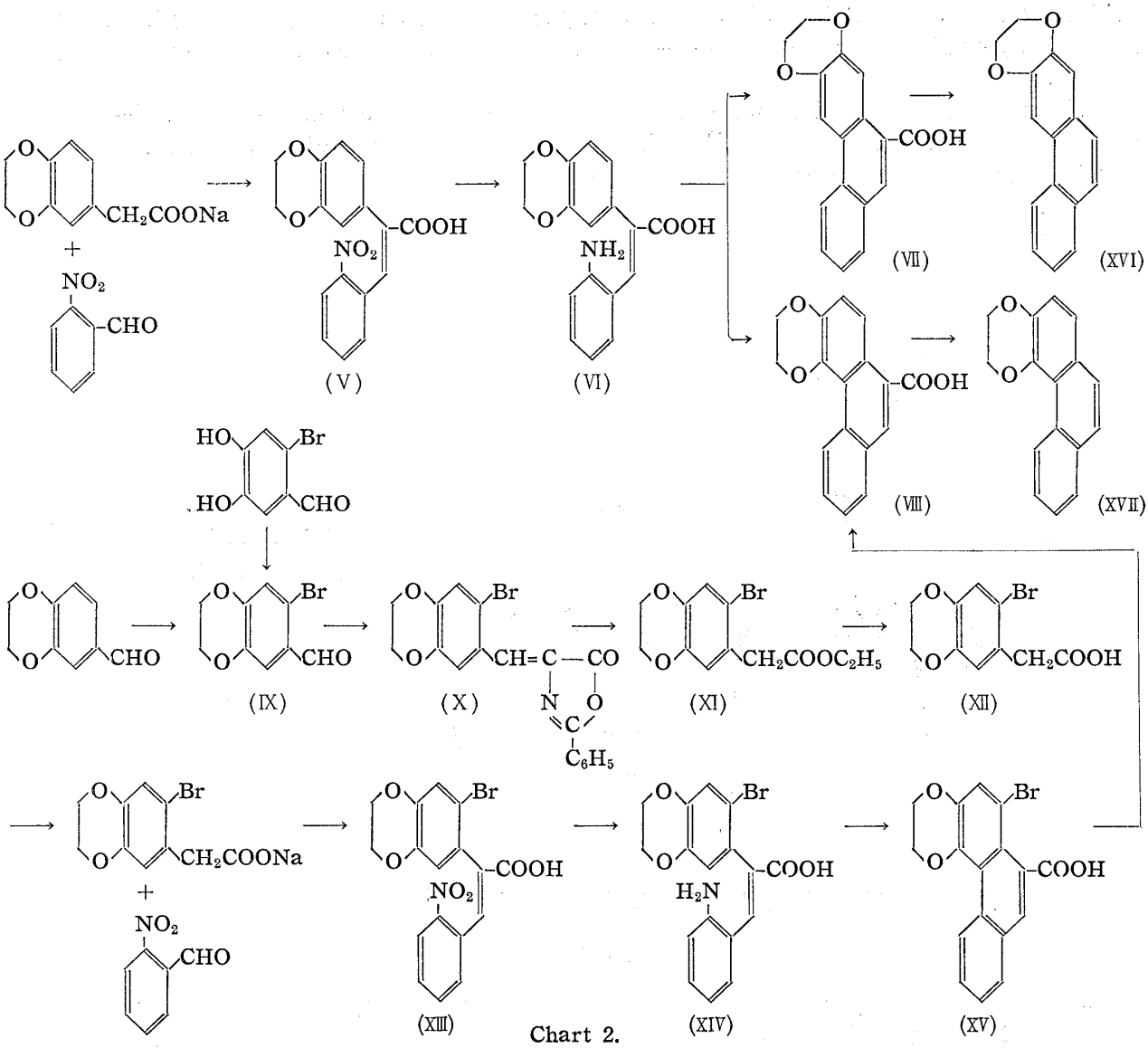


Chart 2.

6-formylbenzodioxane[4] or by ethylenation of 6-bromoprotocatechualdehyde[5]; the former was the preferred method, but the latter served to prove the structure. The bromoaldehyde was condensed with hippuric acid according to the Erlenmeyer method and the azlactone (X) was converted to 3,4-ethylenedioxy-6-bromophenylacetic acid (XII) by the standard method, whose sodium salt was condensed with 2-nitrobenzaldehyde to yield a single nitrocinnamic acid (XIII). Reduction of (XIII) by means of ferrosulfate in the presence of ammonia furnished the corresponding aminocinnamic acid (XIV). Pschorr condensation of (XIV) under the standard working conditions, in the presence of the usual amount of Gattermann copper, yielded chiefly the bromine-free (VIII), probably together with a minute amount of (XV), as shown by the presence of a trace of bromine in analysis (cf. Experimental section). In the presence of a minute amount of Gattermann copper, however, the Pschorr condensation proceeded without any side reaction and (XV) was produced as the single product.

When debrominated with zinc-copper couple,[6] (XV) yielded a phenanthrene-carboxylic

4) S. Sugasawa, Y. Arata : This Bulletin, **4**, 406(1956).
5) A. H. Parijs : Rec. trav. chim., **49**, 33(1930).
6) D. R. P. 84,891.

acid which was proved to be identical with (Ⅷ) obtained as above, showing the latter to be 3,4-ethylenedioxyphenanthrene-10-carboxylic acid, while (Ⅶ) is the 2,3-ethylenedioxy isomer.

Thus, it was proved beyond doubt that the crystalline base of m.p. 123~124°, described in Part Ⅲ of this series,[1] is 3,4-ethylenedioxy-N-methylmorphinan and the oily one therefore is the 2,3-ethylenedioxy isomer.

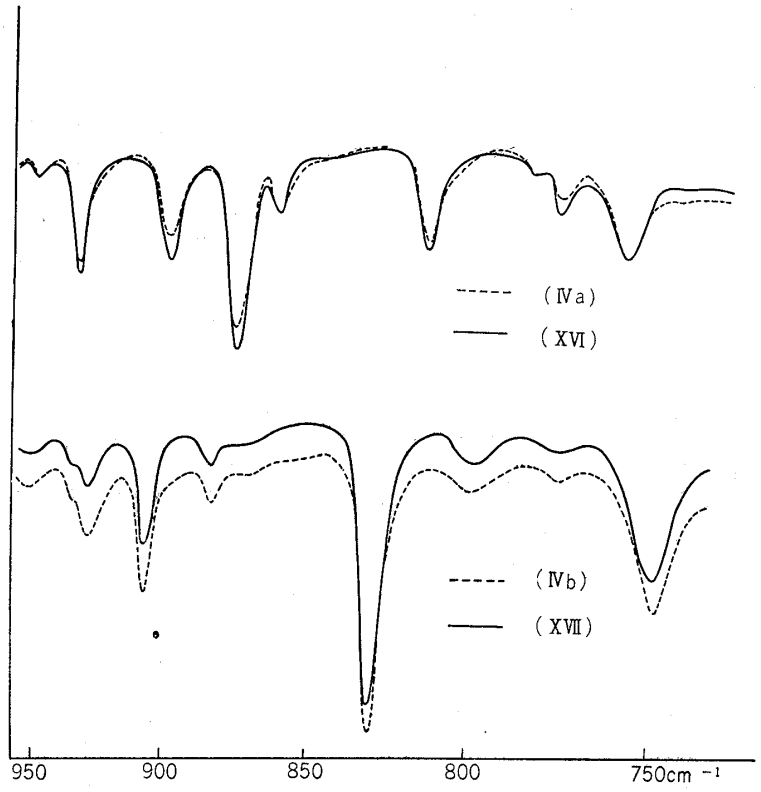


Fig. 1. Infrared Absorption Spectra (Nujol, Perkin-Elmer Model 21)

Experimental

Hofmann Degradation of 2,3-Ethylenedioxy-N-methylmorphinan (A).

2,3-Ethylenedioxy-13-(2-dimethylaminoethyl)-5,6,7,8,13,14-hexahydrophenanthrene (IIIa)—An intimate mixture of the methiodide (Ia) (246 mg.) and Ag_2O, freshly prepared from $AgNO_3$ (124 mg.), in H_2O (5 cc.) was warmed at 50° for 12 hr. with stirring. After cool, the filtrate was evaporated under a reduced pressure (below 50°). It afforded the methohydroxide (Ⅱa) which gave negative Beilstein's test. (Ⅱa) was heated at 120° (bath temp.) for 1.5 hr. The benzene extract of the reaction mixture afforded a pale yellow liquid (163.4 mg. or 93.5%); UV λ_{max}^{EtOH} mμ (log ε): 227~228 (4.32), 278 (3.96). Hydrogenoxalate: Colorless small cubes (from EtOH-Et_2O), m.p. 197~198° (decomp.). *Anal.* Calcd. for $C_{22}H_{29}O_6N$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.44; H, 7.08; N, 3.93.

2,3-Ethylenedioxyphenanthrene (IVa)—(Ⅲa) (140 mg.) was heated with Pd-C (10%, 16 mg.) at 320° (bath temp.) for 6 hr. in N_2 atmosphere. After cool, the reaction mixture was extracted with Et_2O and the extract was washed successively with dil. HCl, H_2O, dil. NaOH, and H_2O. The dried Et_2O solution was evaporated, leaving (Ⅳa) (50.7 mg. or 48%) as colorless plates, m.p. 92~102°. By recrystallization from EtOH the m.p. was raised to 113~114°. UV λ_{max}^{EtOH} mμ (log ε): 255 (4.77), 279 (4.41). *Anal.* Calcd. for $C_{16}H_{12}O_2$: C, 81,34; H, 5.12. Found: C, 81.35; H, 5.18.
Picrate: Yellow prisms (from $CHCl_3$), m.p. 175~176°.

Hofmann Degradation of 3,4-Ethylenedioxy-N-methylmorphinan (B).

3,4-Ethylenedioxy-13-(2-dimethylaminoethyl)-5,6,7,8,13,14-hexahydrophenanthrene (IIIb)—A mixture of the methiodide (Ib) (522 mg.) and Ag_2O, freshly prepared from $AgNO_3$ (262 mg.), in H_2O (5 cc.) was treated as above. On heating the methohydroxide (Ⅱb), (Ⅲb) was obtained as a pale yellow liquid (323 mg. or 87.1%). UV λ_{max}^{EtOH} mμ (log ε): 222 (4.33), 273 (4.01).
Hydrogenoxalate: Colorless plates (from EtOH), m.p. 171~173° (decomp.). *Anal.* Calcd. for $C_{22}H_{29}O_6N$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.42; H, 7.04; N, 3.59.

3,4-Ethylenedioxyphenanthrene (IVb)—(Ⅲb) (187 mg.) was heated with Pd-C (10%, 20 mg.) at 320°

(bath temp.) for 6 hr. in N_2 atmosphere. On working up as above, (IVb) was obtained as colorless prisms, m.p. 75~77° (24 mg. or 17.0%). By recrystallization from EtOH the m.p. was raised to 77.5~79°. UV λ_{max}^{EtOH} mμ (log ε) : 251 (4.68), 280 (4.08), 299~300 (3.94), 309 (3.96). *Anal.* Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found : C, 81.17; H, 5.36.
Picrate : Yellow needles (from $CHCl_3$), m.p. 150~151°.

2-Nitro-α-(3,4-ethylenedioxyphenyl)cinnamic Acid (V)—A mixture of sodium 3,4-ethylenedioxyphenylacetate[1] (3.00 g.), 2-nitrobenzaldehyde (2.83 g.), and Ac_2O (15 cc.) was heated at 110~120° (bath temp.) for 20 hr. with stirring. The reaction mixture became red within 10 min. The cooled reaction mixture was added with water (30 cc.) and warmed on a water bath. After evaporating to a small volume, 5% NH_4OH (170 cc.) was added to the residue and washed with Et_2O. The alkaline solution was acidified with dil. HCl and extracted with AcOEt. AcOEt was evaporated and the residue was crystallized from MeOH. (V) was obtained as yellow prisms, m.p. 195~197° (2.80 g. or 61.7%). *Anal.* Calcd. for $C_{17}H_{13}O_6N$: C, 62.39; H, 4.00; N, 4.28. Found : C, 62.08; H, 3.85; N, 4.45.

2-Amino-α-(3,4-ethylenedioxyphenyl)cinnamic Acid (VI)—To an ice-cold mixture of $FeSO_4 \cdot 7H_2O$ (24 g.) in H_2O (20 cc.) and 28% NH_4OH (35.2 cc.) the nitrocinnamic acid (V) (2.78 g.) in 5% NH_4OH (58.3 cc.) was added dropwise and the mixture was warmed on a water bath for 10 min. After filtration, the residue was washed with hot H_2O, the combined filtrate and washing was acidified to pH 5 with dil. HCl, and (VI) was obtained as pale yellow powder, m.p. ca. 183° (2.50 g. or quantitative). It was positive to carbylamine and diazo reactions.

2,3- and 3,4-Ethylenedioxyphenanthrene-10-carboxylic Acid (VII and VIII)—To an ice-cold solution of the crude aminocinnamic acid (VI) (2.46 g.) in MeOH (52 cc.) and 20% H_2SO_4 (32.5 cc.) *N* $NaNO_2$ (26 cc.) was added dropwise at 0° with stirring and the mixture was stirred for additional 30 min. The mixture was diluted with H_2O (39 cc.) and Gattermann-Cu (13 g.) was added in small portions. After evolution of N_2 ceased, the reaction mixture was warmed on a water bath for 30 min. and basified with NH_4OH. After removal of Cu, the filtrate was concentrated under a reduced pressure, acidified with dil. HCl, and taken up in Et_2O. On repeated recrystallization from MeOH, (VII) was obtained as colorless needles, m.p. 272~274° (189 mg. or 8.2%). *Anal.* Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found : C, 73.00; H, 4.34.

The residue obtained on evaporation of the mother liquor of recrystallization was repeatedly recrystallized from EtOH, affording (VIII) as colorless prisms, m.p. 241~243° (72 mg. or 3.1%). *Anal.* Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found : C, 72.53; H, 4.37.

3,4-Ethylenedioxy-6-bromobenzaldehyde (IX)—i) 6-Formylbenzodioxane[4] (25 g.) in cold glacial AcOH (50 cc.) was brominated with Br_2 (10 cc.) in glacial AcOH (25 cc.) as usual. After standing at room temp. overnight, the excess Br_2 and HBr were distilled off under a reduced pressure and the residue was poured into ice-water. On repeated recrystallization from EtOH, it afforded (IX) as colorless leaflets, m.p. 149~150° (5.8 g. or 15.7%). *Anal.* Calcd. for $C_9H_7O_3Br$: C, 44.47; H, 2.90; Br, 32.88. Found : C, 44.64; H, 3.25; Br, 33.66.
ii) A mixture of 6-bromoprotocatechualdehyde[5] (378 mg.), ethylene bromide (494 mg.), and NaOH (150 mg.) in H_2O (0.15 cc.) and EtOH (3.85 cc.) was heated under reflux on a water bath for 44 hr. After removal of the solvent, water was added and the mixture was extracted with Et_2O. On working up as usual, (IX) was obtained as colorless leaflets, m.p. 147~148° (55.5 mg. or 13.1%). Recrystallization from EtOH gave a pure compound of m.p. 149~150°, which showed no depression on admixture with the sample obtained as above.

2-Phenyl-4-(3,4-ethylenedioxy-6-bromobenzylidene)-5-oxazolone (X)—An intimate mixture of the bromobenzaldehyde (IX) (7.01 g.), hippuric acid (5.17 g.), anhyd. AcONa (2.37 g.), and Ac_2O (13 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., EtOH (17 cc.) was added while hot, and the whole was allowed to stand at room temp. overnight. The crystals were collected and washed with a small amount of cold EtOH and a large amount of hot H_2O. (X) was obtained as yellow needles, m.p. 253~257° (7.34 g. or 66.0%). Recrystallization from AcOEt gave the pure compound of m.p. 263~264°. *Anal.* Calcd. for $C_{18}H_{12}O_4NBr$: C, 55.98; H, 3.13; N, 3.63. Found : C, 56.20; H, 3.32; N, 3.94.

Ethyl 3,4-Ethylenedioxy-6-bromophenylacetate (XI)—A mixture of the azlactone (X) (7.32 g.) and 10% NaOH (40 cc.) was heated at 130~150° (bath temp.) for 10 hr. until an odor of NH_3 was no longer recognized. After cool, 40% NaOH (3.1 cc.) was added and and H_2O_2 solution (6 cc.; 30% H_2O_2 and H_2O=1:1) was added dropwise with stirring below 15°, and the whole mixture was allowed to stand overnight at room temp. The reaction mixture was acidified with dil. HCl and extracted with AcOEt After evaporation of the dried AcOEt solution, a mixture of EtOH (37 cc.) and conc. H_2SO_4 (0.3 cc.) was added to the residue and the mixture was heated to reflux on a water bath for 4 hr. Working up as usual, there was obtained (XI) as a colorless liquid, $b.p_2$ 150~152° (2.88 g. or 37%).

3,4-Ethylenedioxy-6-bromophenylacetic Acid (XII)—A mixture of the ester (XI) (2.88 g.) and 10% NaOH (20 cc.) was heated on a water bath for 2 hr. with stirring. After treating with charcoal, the filtrate was acidified with dil. HCl and (XII) was obtained as colorless leaflets (from EtOH), m.p. 219~

220° (2.11 g. or 84%). *Anal.* Calcd. for $C_{10}H_9O_4Br$: C, 43.98; H, 3.32. Found : C, 44.08; H, 3.24.

2-Nitro-α-(2-bromo-4,5-ethylenedioxyphenyl)cinnamic Acid (XIII)—A mixture of sodium 2-bromo-4,5-ethylanedioxyphenylacetate (2.20 g.), 2-nitrobenzaldehyde (1.14 g.), and Ac_2O (11 cc.) was heated at 110~120° (bath temp.) for 20 hr. with stirring. The cooled reaction mixture was added with H_2O (22 cc.) and warmed on a water bath. After evaporating to a small volume, 5% NH_4OH (100 cc.) was added to the residue and washed with Et_2O. The alkaline solution was acidified with dil. HCl, taken up in AcOEt, and worked up as usual. (XIII) was obtained as yellow prisms, m.p. 211~215° (1.97 g. or 65.1%). Recrystallization from MeOH raised the m.p. to 216~217°. *Anal.* Calcd. for $C_{17}H_{12}O_6NBr$: C, 50.27; H, 2.97; N, 3.45; Br, 19.67. Found : C, 49.87; H, 3.46; N, 3.22; Br, 19.50.

2-Amino-α-(2-bromo-4,5-ethylenedioxyphenyl)cinnamic Acid (XIV)—To an ice-cold mixture of $FeSO_4 \cdot 7H_2O$ (13.2 g.) in H_2O (16.5 cc.) and 28% NH_4OH (20 cc.) the nitrocinnamic acid (XIII) (1.945 g.) in 5% NH_4OH (38 cc.) was added dropwise and the mixture was warmed on a water bath for 10 min. After filtration, the residue was washed with hot H_2O, the combined filtrate and washing was acidified to pH 4 with dil. HCl, and (XIV) was obtained as a pale yellow powder, m.p. 125~128° (decomp.) (1.329 g. or 74.0%). It was positive to carbylamine and diazo reactions.

1-Bromo-3,4-ethylenedioxyphenanthrene-10-carboxylic Acid (XV)—i) To an ice-cold solution of the crude aminocinnamic acid (XIV) (1.30 g.) in MeOH (30 cc.) and 20% H_2SO_4 (13.5 cc.), *N* $NaNO_2$ (11 cc.) was added dropwise at 0° with stirring and the mixture was stirred for additional 30 min. The mixture was diluted with H_2O (16.5 cc.) and Gattermann-Cu (5.5 g.) was added in small portions. After evolution of N_2 ceased, the reaction mixture was warmed on a water bath for 30 min. and basified with NH_4OH. After removal of Cu, the filtrate was concentrated under a reduced pressure, acidified with dil. HCl, and taken up in Et_2O. On working up as usual, there were obtained colorless crystals, m.p. 236~238° (252 mg.). *Anal.* Found : C, 72.06; H, 4.35; Br; 0.75.

ii) When a catalytic amount of the Gattermann-Cu was used in the above reaction, (XV) was obtained as colorless pillars, m.p. 254~258° (decomp.) (10.5%). By recrystallization from MeOH-Me_2CO, the m.p. was raised to 256~258° (decomp.). *Anal.* Calcd. for $C_{17}H_{11}O_4Br$: C, 56.84; H, 3.09; Br, 22.25. Found: C, 56.58; H, 3.47; Br, 22.21.

3,4-Ethylenedioxyphenanthrene-10-carboxylic Acid (VIII)—i) The foregoing compound of m.p. 236~238° (100 mg.), obtained as in (i), was heated with Zn-Cu[6] (400 mg.), *N* NaOH (3 cc.), and EtOH (1 cc.) at 95~105° (bath temp.) for 6 hr. with stirring. After removal of the catalyst, the filtrate was acidified and extracted with Et_2O. On working up as usual, colorless prisms (VIII) were obtained from Et_2O, m.p. 241~243° (76 mg.).

ii) The bromophenanthrenecarboxylic acid (XV) (9 mg.) was treated as described above. (VIII) was obtained as colorless prisms, m.p. 241~243°, which showed no depression of m.p. on admixture with both the samples obtained as above and from (VI).

2,3-Ethylenedioxyphenanthrene (XVI)—A solution of the carboxylic acid (VII) (100 mg.) in quinoline (5 cc.) was heated with Gattermann-Cu (250 mg.) at 180~200° (bath temp.) for 10 min. in N_2 atmosphere and then at 250~260° (bath temp.) for 20 min. under reflux. After working up as usual, the residue was dissolved in benzene and chromatographed on alumina. (XVI) was obtained as colorless plates, m.p. 112~114° (50 mg. or 59.3%). Recrystallization from EtOH raised the m.p. to 113~114°. UV λ_{max}^{EtOH} mμ (log ε) : 255 (4.74), 279 (4.38). *Anal.* Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found : C, 81.23; H, 5.29.

Picrate : Yellow prisms (from $CHCl_3$), m.p. 175~176°. *Anal.* Calcd. for $C_{22}H_{15}O_9N_3$: C, 56.78; H, 3.25. Found : C, 56.83; H, 2.94.

The phenanthrene (XVI) showed no depression of m.p. on admixture with (IVa) which was obtained by the Hofmann degradation of 2,3-ethylenedioxy-N-methylmorphinan. Both picrates also behaved similarly.

3,4-Ethylenedioxyphenanthrene (XVII)—The carboxylic acid (VIII) (74 mg.) was treated with Gattermann-Cu (250 mg.) in quinoline (5 cc.) as described above. (XVII) was obtained as colorless prisms, m.p. 77.5~79° (33 mg. or 53%). UV λ_{max}^{EtOH} mμ (log ε) : 251 (4.68), 280 (4.08), 299~301 (3.93), 309 (3.94). *Anal.* Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found : C, 81.43; H, 5.23.

Picrate : Yellow needles (from $CHCl_3$), m.p. 150~151°. *Anal.* Calcd. for $C_{22}H_{15}O_9N_3$: C, 56.78; H, 3.25. Found : C, 56.78; H,3.36.

The phenanthrene (XVII) showed no depression of m.p. on admixture with (IVb) which was obtained by the Hofmann degradation of 3,4-ethylenedioxy-N-methylmorphinan. Both picrates also behaved similarly.

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. S. Yamada, the former Director, and Dr. M. Onda of this Laboratory for their kind encouragement. The author is also indebted to Mr. K. Kodera of this Laboratory for infrared spectral analysis and to Mrs. F. Hisamichi and Mr. T. Yoda for microanalytical data.

Summary

2,3-Ethylenedioxy-N-methylmorphinan and 3,4-ethylenedioxy-N-methylmorphinan, synthesized earlier, were submitted to the Hofmann degradations and by syntheses of their degradation products their structures were confirmed as 2,3- and 3,4-ethylenedioxyphenanthrene.

(Received September 5, 1959)

UDC 615.779.931-011

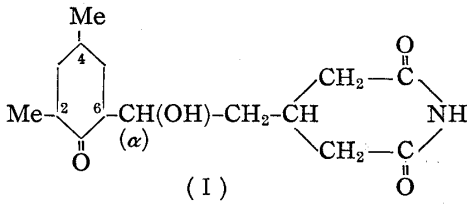
61. Tomoharu Okuda, Makoto Suzuki, and Yoshiyuki Egawa : Studies on Streptomyces Antibiotic, Cycloheximide. VII. On the Configuration of Naramycin-B and Isocycloheximide.

(*Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd.**1)

In the previous papers the authors reported the isolation, physicochemical characteristics, and absolute configuration of antifungal antibiotic Naramycin-B which is isomeric to cycloheximide and produced as a by-product of cycloheximide in the fermentation broth of *Streptomyces naraensis* nov. sp.[1~3] As referred in Part II of this series, several isomers of cycloheximide are known, among which isocycloheximide was reported by Hamilton, *et al.*[4] and Lemin, *et al.*[5] on its agricultural use and thought to be derived as described in the British and U.S. Patents[6] from cycloheximide by aging the latter in the solution or by isomerization in the presence of acid-deactivated alumina.

Recently, the authors had an opportunity to compare Naramycin-B directly with isocycloheximide in compliance with the request made by Dr. Alan J. Lemin, The Upjohn Co., U.S.A., who kindly offered the samples of isocycloheximide and its acetate.*2

In the present paper will be described the differences observed in comparing the two antibiotics and their absolute configurations deduced therefrom. Plane structure of these antibiotics is illustrated as (I).



(I)

Comparison of the two antibiotics was made mainly by physicochemical methods, viz. 1) determination of mixed melting point, 2) infrared spectra, 3) ultraviolet spectra,

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*1 Toda-machi, Kita-adachi-gun, Saitama-ken (奥田朝晴, 鈴木真言, 頴川吉之).

*2 Melting point and optical rotation of isocycloheximide and its acetate were given as m.p. 98~100°, $[\alpha]_D^{24}$ +26°(MeOH), and m.p. 162~165°, $[\alpha]_D^{24}$ +51°(MeOH), respectively.

1) T. Okuka, M. Suzuki, Y. Egawa, K. Ashino : This Bulletin, **7**, 27(1959).
2) T. Okuda : *Ibid.*, **7**, 137(1959). 3) *Idem* : *Ibid.*, **7**, 259(1959).
4) J.M. Hamilon, M. Szkolnik, E. Sondheimer : Science, **123**, 1175(1956).
5) A.J. Lemin, G.A. Boyack, W.C. Haskett, A. Steinhards, G. Swank : Abstract of Papers, 132nd Meeting of the American Chemical Society, 24A(1957).
6) Brit. Pat. 799,731 (Aug. 13, 1958); U.S. Pat. 2,903,457 and 2,903,458 (Sept. 8, 1959) (The Upjohn Company).