UDC 547.837.07

163. Mitsuo Sasamoto: Synthesis in the Morphinan Group. V.*1 Grewe Cyclization of *d*- and *l*-1-(3,4-Ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline.*2

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In a previous paper,[1] synthesis of *rac*-2,3- and *rac*-3,4-ethylenedioxy-N-methylmorphinan (II and III) was reported. For pharmacological evaluation, their optical resolution was attempted and the result also was described; i.e. though the latter (III) could be resolved by means of dibenzoyl-*d*-tartaric acid, all attempts with the former (II) ended fruitless.

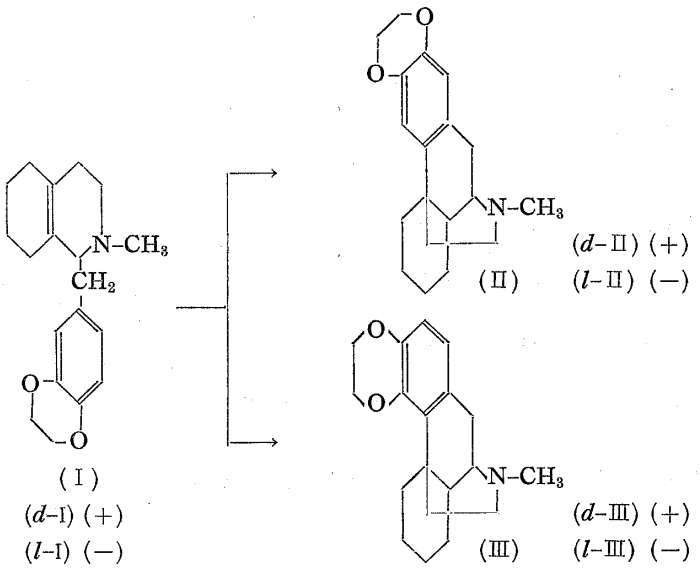

Chart 1. (I), (II), (III) Racemate

In view of the fact that Schnider, *et al.*[2] succeeded in preparation of *l*- and *d*-3-hydroxy-N-methylmorphinan by the Grewe cyclization of *d*- and *l*-1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline, *rac*-1-(3,4-ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (I) was resolved and the *dextro* (*d*-I) and *levo* (*l*-I) isomers were obtained. When these compounds were cyclized according to the method of Grewe there were produced two pairs of optically active position-isomers; (*d*-I) gave *d*-2,3- and *d*-3,4-ethylenedioxy-N-methylmorphinan (*d*-II and *d*-III), and (*l*-I) yielded *l*-2,3 and *l*-3,4 derivatives (*l*-II and *l*-III). (*d*-III) and (*l*-III) thus obtained were identical with the ones obtained by resolution of racemic (III).[1]

The crude (I) of $b.p_2$ 200~205° was purified through crystalline hydrogenoxalate. The liberated faint yellow oily (I) and equimolar amount of *d*-tartaric acid were dissolved in ethanol and the resultant solution was allowed to stand in an ice chest for 8 days. Crystalline solid that separated was repeatedly purified from ethanol to furnish colorless plates of m.p. 148~149°, $[\alpha]_D^{18}$ +34.0° (c=0.5, MeOH), which gave correct analyses for (I) hydro-

*1 Part IV. M. Sasamoto: This Bulletin, **8**, 329(1960).
*2 Presented before the Kanto Local Monthly Meeting of the Pharmaceutical Society of Japan, January, 1960.
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1) Part III. M. Sasamoto: This Bulletin, **8**, 324(1960).
2) O. Schnider, A. Brossi, K. Vogler: Helv. Chim. Acta, **37**, 710(1954).

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gentartrate with one-half mole of crystal water. The free base was a light yellow oil, $[\alpha]_D^{19}$ +30.0° (c=0.5, MeOH), whose hydrogenoxalate separated from ethanol as colorless prisms of m.p. 134~135°, $[\alpha]_D^{20}$ +30.0° (c=0.5, MeOH).

Since hydrogen-*d*-tartrate of the antipodal base could not be obtained in crystalline state from the mother liquor of (*d*-I) hydrogen-*d*-tartrate, the free base was recovered, which was dissolved in ethanol with dibenzoyl-*d*-tartaric acid. After 2 days' standing of this solution in an ice chest there separated a crystalline solid, which was repeatedly purified from ethanol to give colorless plates of m.p. 161~162° (decomp.), $[\alpha]_D^{20}$ −97.0° (c=0.5, MeOH), whose analyses tallied well with the expected values. The free base was a faint yellow oil of $[\alpha]_D^{22}$ −31.0° (c=0.5, MeOH) and its hydrogenoxalate separated from ethanol in colorless prisms of m.p. 134~135°, $[\alpha]_D^{20}$ −29.5° (c=0.5, MeOH).

The above-described resolution process may be reversed using dibenzoyl-*d*-tartaric acid to separate (*l*-I) first, followed by recovery of (*d*-I) by the agency of *d*-tartaric acid as shown by (B) in Chart 2.

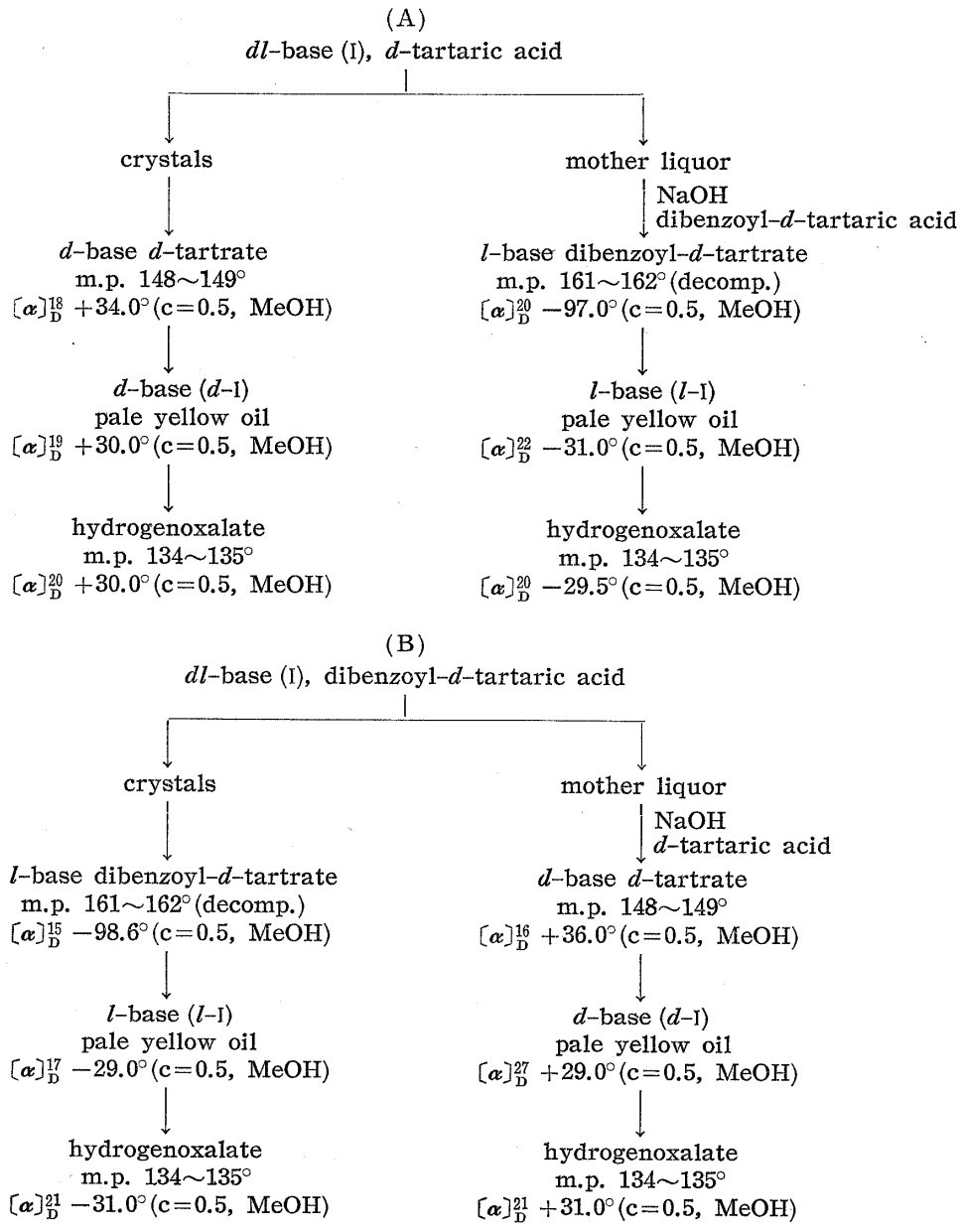

Chart 2. Optical Resolution of (I)

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When (*d*-I) and (*l*-I) thus prepared were heated with phosphoric acid at 135° for 60 hours, there were obtained the cyclized oily bases in a yield of 92.6% and 94.8%, respectively, no phenolic bases being traced in the cyclized products.

For the separation of 2,3- and 3,4-isomers in the cyclization products, benzoic acid was found to be a reagent of choice. Thus, for instance, the crude cyclized base from (*d*-I) was mixed with an equimolar amount of benzoic acid and the mixture was dissolved in acetone. After keeping the acetone solution in an ice chest for about 1 week, there separated a crystalline solid, which was repeatedly purified from acetone–ethanol to furnish colorless prisms of m.p. 153~155°, $[\alpha]_D^{16}$ +27.0° (c=1.0, MeOH). The perchlorate formed colorless plates (from ethanol), m.p. 239~240°, $[\alpha]_D^{16}$ +27.0° (c=1.0, MeOH), and the methiodide (*d*-IV) separated from acetone–ethanol in colorless grains of m.p. 259~260°, $[\alpha]_D^{26}$ +8.0° (c=1.0, MeOH). The band at 866 cm^{-1} (m) in the infrared spectrum of (*d*-IV), similar to that of the methiodide (IV) of (II), suggested the presence of 1,2,4,5-tetrasubstituted benzene ring in (*d*-IV), which represented 2,3-ethylenedioxymorphinan derivative. This view was further supported chemically when 2,3-ethylenedioxyphenanthrene was obtained from (*d*-IV) via the route detailed in the experimental section.

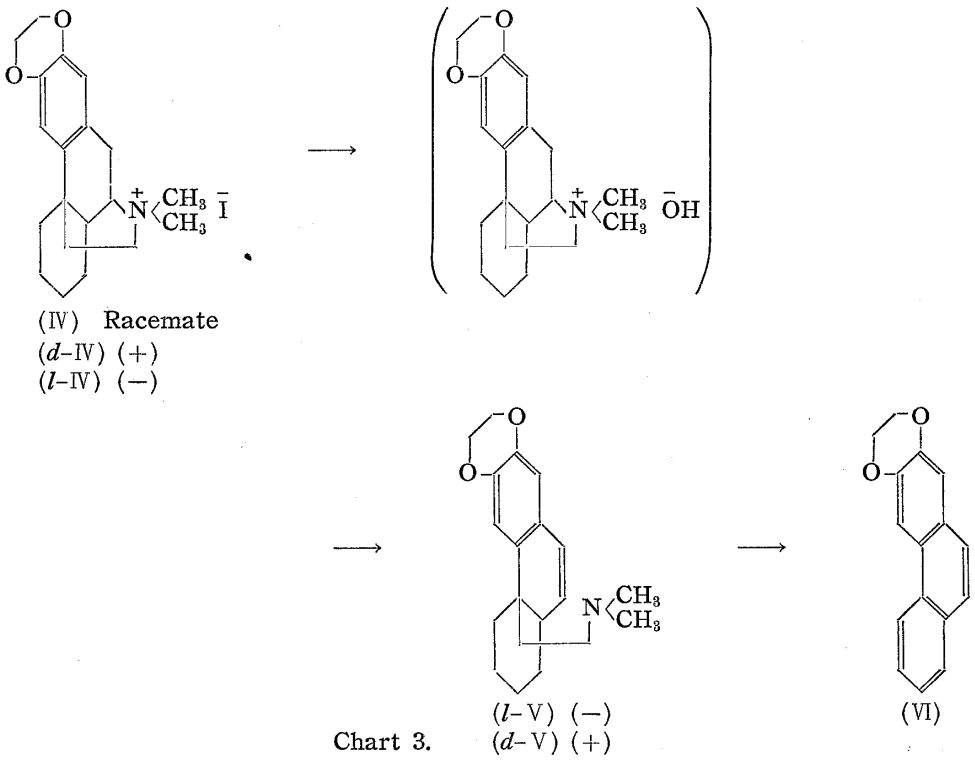

Chart 3.

From the acetone mother liquor of (*d*-II) benzoate, an oily base was recovered. When dry hydrogen chloride was introduced into an anhydrous ether solution of the latter, there separated a hygroscopic hydrochloride, which was dissolved in acetone and the solution was allowed to stand in an ice chest. After about 10 days, a small amount of solid separated, which formed colorless prisms (C) of m.p. 333~337°, $[\alpha]_D^{14}$ +27.0° (c=1.0, MeOH). Reference to this compound (C) will be made later.

The base left dissolved as hydrochloride in the acetone mother liquor of (C) was found advantageously recoverable through a crystalline perchlorate, which separated from ethanol in colorless needles of m.p. 252° (decomp.), $[\alpha]_D^{16}$ +16.0° (c=0.5, MeOH). The free base was also obtained crystalline, forming colorless pillars of m.p. 141~142°, $[\alpha]_D^{15}$ +36.0° (c=0.5, MeOH), from petroleum ether, and was found to be identical by mixed melting point test and through comparison of their infrared spectra with *d*-3,4-ethylenedioxy-

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N-methylmorphinan reported previously.[1] Their identity was further established by comparing their dibenzoyl-*d*-tartrates of colorless plates, m.p. 167~169° (decomp.), $[\alpha]_D^{14}$ −44.44° (c=0.45, MeOH). The hydrochloride of (*d*-III) formed colorless grains of m.p. 249~251°, $[\alpha]_D^{14}$ +24.0° (c=0.5, MeOH), distinctly different from (C).

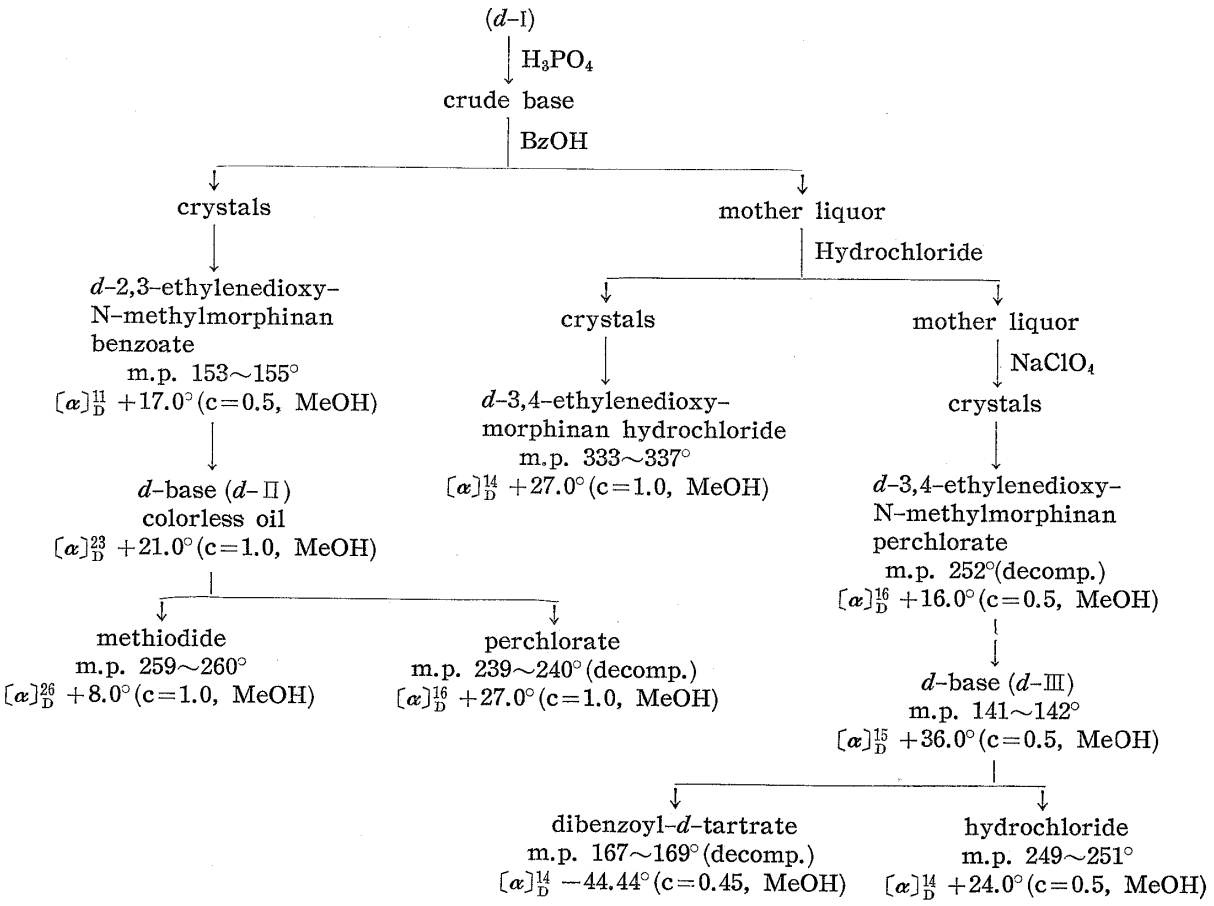

Chart 4. Grewe Cyclization of (*d*-I)

The Grewe cyclization of (*l*-I) and after-treatment of the product was made exactly as above. Thus, through a crystalline benzoate of the crude cyclized base, there was isolated first *l*-2,3-ethylenedioxy-N-methylmorphinan (*l*-II), whose structure was inferred from its infrared spectral data and then proved chemically beyond doubt. Preparation of (*l*-III) was again effected through its crystalline perchlorate and the base isolated melted at 141~142°, alone or admixed with a specimen of *l*-3,4-ethylenedioxy-N-methylmorphinan obtained previously.[1] The experimental process is shown in Chart 5.

The nature of the compound (C) will now be discussed. As mentioned above, this high-melting compound is not identical with the hydrochloride of either (*d*-III) or (*d*-II), since the latter hydrochloride is not obtained as a solid. In the Grewe cyclization experiments, formation of aporphine and isomorphinan derivatives as by-products has often been reported. A band at 813 cm^{-1} in the infrared spectral curve of (C) suggests the presence of 1,2,3,4-tetrasubstituted benzene ring and moreover a broad band at 2700~2250 cm^{-1} implies this compound as a secondary base. In conformity with this view, Herzig-Meyer determination of (C) revealed the absence of $N-CH_3$ group, while the compound (III) taken as standard responded to this test. Therefore, (*d*-III) was demethylated by the cyanogen bromide method[3,4] and the product was characterized as a crystalline hydrochloride (VIII),

3) R. Grewe, A. Mondon: Ber., **81**, 279(1948).
4) O. Schnider, A. Grüssner: Helv. Chim. Acta, **34**, 2211 (1951).

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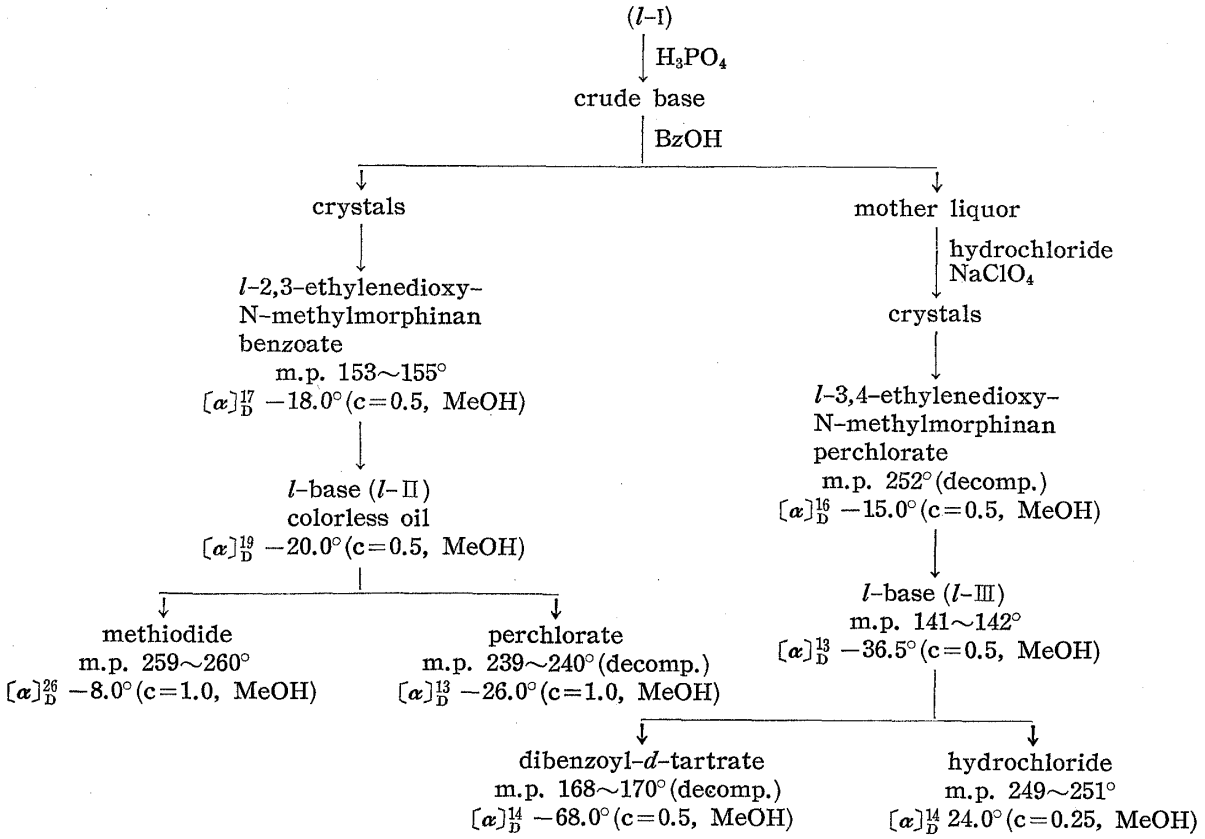

Chart 5. Grewe Cyclization of (*l*-I)

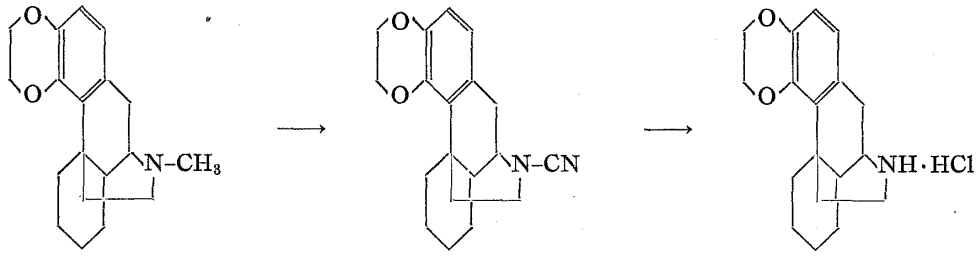

Chart 6.

which formed colorless prisms of m.p. 333~337°, $[\alpha]_D^{11}$ +28.0°(c=0.5, MeOH), and was proved to be identical with (C) by direct comparison.

Formation of the compound (C) was not to be ascribed to the drastic working conditions prevailing in the Grewe reaction, because nothing of this kind was traced in the cyclization product of (*l*-I). Therefore, this compound (C) must have been formed from *nor*-(*d*-I) contaminated in (*d*-I). As shown in Chart 7 the octahydroisoquinoline derivative (I) was prepared by reduction of the methiodide (X) of the hexahydroisoquinoline (IX). Since the methiodide (X) was obtained amorphous and not induced to crystallize, this was reduced directly after being washed with ether. The octahydro base (I) thus obtained distilled at 200~205°/2 mm. Hg, in which the presence of (XI : *nor*-(I)) as contamination was proved by isolation of a small amount of its hydrogenoxalate from the acetone-ethanolic mother liquor of (I) hydrogenoxalate. Hydrogenoxalate (XI), a solid of m.p. 182° (decomp.), was identified with an authentic specimen prepared by reduction of (IX).

Optical resolution of (I) was then carried out according to the method B in Chart 2 using dibenzoyl-*d*-tartaric acid with the free base recovered from the hydrogenoxalate of

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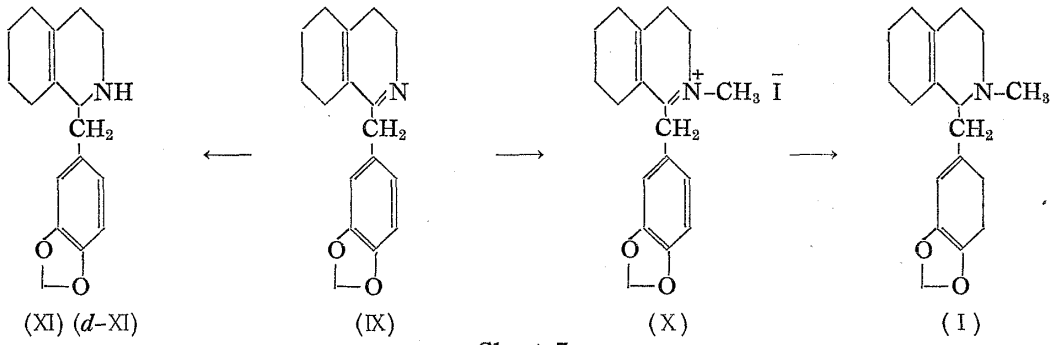

(XI) (*d*-XI) (IX) (X) (I)

Chart 7.

m.p. 142~144°, which still must have contained some amount of (XI). *d*-Acid salt of (*l*-I) separated first was obtained in a pure state, leaving (*d*-I) and (XI) combined with the acid in the mother liquor, hence the recovered (*d*-I) was contaminated with (XI). On further purification of (*d*-I) as hydrogen-*d*-tartrate, the base (XI) also underwent optical resolution and a minute amount of (*d*-XI) hydrogen-*d*-tartrate separated out with (*d*-I) hydrogen-*d*-tartrate, giving rise to (C) on the Grewe cyclization of the free (*d*-I) recovered.

Experimental*4

***d*- and *l*-1-(3,4-Ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (*d*-I and *l*-I)** —i) Optical resolution with *d*-tartaric acid : A mixture of *dl*-1-(3,4-ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (1.656 g.), *d*-tartaric acid (828 mg.), and EtOH (5 cc.) was warmed to make a clear solution. After standing in an ice chest for 8 days, colorless crystals that separated were collected and recrystallized from Me_2CO-EtOH to the *d*-base *d*-tartrate (451 mg.) as colorless plates, m.p. 148~149°.

The mother liquor of the above crystallization was evaporated under a reduced pressure. The residue was basified with NaOH and extracted with Et_2O. The Et_2O solution was worked up as usual to afford a pale yellow oil (952 mg.), which was dissolved in EtOH (8.1 cc.) with dibenzoyl-*d*-tartaric acid (1.2 g.). After standing in an ice chest for 2 days, colorless crystals that separated were collected and recrystallized from EtOH to *l*-base dibenzoyl-*d*-tartrate (804 mg.) as colorless plates, m.p. 161~162° (decomp.).

d-1-(3,4-Ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline *d*-tartrate : Colorless plates, m.p. 148~149°. *Anal.* Calcd. for $C_{23}H_{31}O_8N \cdot \frac{1}{2}H_2O$: C, 60.25; H, 7.03; N, 3.06. Found : C, 60.84; H, 6.62; N, 3.21. $[\alpha]_D^{18}$ +34.0° (c=0.5, MeOH).

Base : Pale yellow oil, $[\alpha]_D^{19}$ +30.0° (c=0.5, MeOH).

Hydrogenoxalate : Colorless prisms (from EtOH), m.p. 134~135°. *Anal.* Calcd. for $C_{21}H_{27}O_6N$: C, 64.76; H, 6.99; N, 3.60. Found : C, 64.70; H, 7.20; N, 3.61. $[\alpha]_D^{20}$ +30.0° (c=0.5, MeOH).

l-1-(3,4-Ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline dibenzoyl-*d*-tartrate: Colorless plates, m.p. 161~162° (decomp.). *Anal.* Calcd. for $C_{37}H_{39}O_{10}N \cdot \frac{1}{2}H_2O$: C, 66.67; H, 6.05; N, 2.10. Found : C, 66.23; H, 6.09; N, 2.34. $[\alpha]_D^{20}$ −97.0° (c=0.5, MeOH).

Base : Pale yellow oil, $[\alpha]_D^{22}$ −31.0° (c=0.5, MeOH).

Hydrogenoxalate : Colorless prisms (form EtOH), m.p. 134~135°. *Anal.* Calcd. for $C_{21}H_{27}O_6N$: C, 64.76; H, 6.99; N, 3.60. Found : C, 64.69; H, 7.42; N, 3.85. $[\alpha]_D^{20}$ −29.5° (c=0.5, MeOH).

ii) Optical resolution with dibenzoyl-*d*-tartaric acid : A mixture of *dl*-1-(3,4-ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (709 mg.), dibenzoyl-*d*-tartaric acid (890 mg.), and EtOH (6 cc.) was warmed to make a clear solution. After standing for 2 days at room temperature and then for 9 days in an ice chest, colorless crystals that separated were collected and recrystallized from EtOH to *l*-base dibenzoyl-*d*-tartrate (439 mg.) as colorless plates, m.p. 161~162° (decomp.).

The mother liquor of the above crystallization was evaporated under a reduced pressure. The residue was basified with NaOH and extracted with Et_2O. The Et_2O solution was worked up as usual to afford a pale yellow oil (952 mg.), which was dissolved in Me_2CO (10 cc.) with *d*-tartaric acid (211 mg.). After standing for 1 day at room temperature and then 1 day in an ice chest, colorless crystals that separated were collected and recrystallized from Me_2CO-EtOH to *d*-base *d*-tartrate (402 mg.) as colorless plates, m.p. 148~149°.

*4 All m.p.s are uncorrected.

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l-1-(3,4-Ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline dibenzoyl *d*-tartrate: Colorless plates, m.p. 161~162° (decomp.), $[\alpha]_D^{15}$ −98.6° (c=0.5, MeOH).

Base: Pale yellow oil, $[\alpha]_D^{17}$ −29.0° (c=0.5, MeOH).

Hydrogenoxalate: Colorless prisms (from EtOH), m.p. 134~135°, $[\alpha]_D^{21}$ −31.0° (c=0.5, MeOH).

d-1-(3,4-Ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline *d*-tartrate: Colorless plates, m.p. 148~149°, $[\alpha]_D^{16}$ +36.0° (c=0.5, MeOH).

Base: Pale yellow oil, $[\alpha]_D^{27}$ +29.0° (c=0.5, MeOH).

Hydrogenoxalate: Colorless prisms (from EtOH), m.p. 134~135°, $[\alpha]_D^{21}$ +31.0° (c=0.5, MeOH).

d-2,3-Ethylenedioxy-N-methylmorphinan (*d*-II)—(*d*-I) (5.4 g.) was heated with H_3PO_4 (*d*=1.7) (18 cc.) at 135° (bath temp.) for 60 hr. The mixture was cooled, diluted with H_2O, and warmed on a water bath for 0.5 hr. After cool, the mixture was diluted with H_2O (144 cc.) and treated with charcoal. The filtrate was basified with NaOH, extracted with Et_2O, and the extract was worked up as usual, affording a pale yellow oil (5.0 g.; 92.6%). To a solution of this base in Me_2CO (34 cc.), BzOH (2.05 g.) was added and the mixture was warmed to give a clear solution. After standing in an ice chest for 1 week, separated crystals were collected and recrystallized from Me_2CO-EtOH to (*d*-II) benzoate (687 mg., 9.0%) as colorless prisms, m.p. 153~155°, $[\alpha]_D^{11}$ +17.0° (c=0.5, MeOH). *Anal.* Calcd. for $C_{26}H_{31}O_4N \cdot \frac{1}{4}H_2O$: C, 73.30; H, 7.45; N, 3.29. Found: C, 72.78; H, 7.47; N, 3.62.

Base: Colorless oil, $[\alpha]_D^{23}$ +21.0° (c=1.0, MeOH).

Perchlorate: Colorless plates (from EtOH), m.p. 239~240° (decomp.), $[\alpha]_D^{16}$ +27.0° (c=1.0, MeOH). *Anal.* Calcd. for $C_{19}H_{26}O_6NCl$: C, 57.07; H, 6.55; N, 3.50. Found: C, 57.10; H, 6.50; N, 3.13.

Methiodide: Colorless grains (from Me_2CO-EtOH), m.p. 259~260°, $[\alpha]_D^{26}$ +8.0° (c=1.0, MeOH). *Anal.* Calcd. for $C_{26}H_{28}O_2NI$: C, 54.65; H, 6.39; N, 3.17. Found: C, 54.45; H, 6.58; N, 3.09.

d-3,4-Ethylenedioxymorphinan Hydrochloride (C)—The combined mother liquor of the crystallization of (*d*-II) benzoate, described above, was evaporated under a reduced pressure. The residue was basified with NaOH and extracted with Et_2O. The extract was worked up as usual to afford a pale yellow oil (4.1 g.). This base was dissolved in dehyd. Et_2O and dry HCl gas was introduced through this solution. The hygroscopic hydrochloride separated which after being washed with anhyd. Et_2O and dried, was dissolved in Me_2CO. After standing in an ice chest for 10 days, the small amount of solid that separated was collected. On recrystallization from EtOH, it afforded colorless needles (16 mg.), m.p. 333~337°, $[\alpha]_D^{14}$ +27.0° (c=1.0, MeOH). *Anal.* Calcd. for $C_{18}H_{24}O_2NCl \cdot \frac{1}{4}H_2O$: C, 66.25; H, 7.56; N, 4.29. Found: C, 66.12; H, 7.09; N, 4.52.

This compound showed no depression on admixture with *d*-3,4-ethylenedioxymorphinan hydrochloride, obtained from *d*-3,4-ethylenedioxy-N-methylmorphinan.

d-3,4-Ethylenedioxy-N-methylmorphinan (*d*-III)—The mother liquor of the crystallization of (C), described above, was evaporated under a reduced pressure. The residue was dissolved in H_2O and $NaClO_4$ solution was added. An oily product was obtained, which crystallized from EtOH and was repeatedly recrystallized from the same solvent to pure (*d*-III) hydrochloride (602 mg., 8.6%) as colorless needles, m.p. 252° (decomp.), $[\alpha]_D^{16}$ +16.0° (c=0.5, MeOH). *Anal.* Calcd. for $C_{19}H_{26}O_6NCl$: C, 57.07; H, 6.55; N, 3.50. Found: C, 57.61; H, 6.80; N, 3.38.

Base: Colorless prisms (from petr. ether), m.p. 141~142°, $[\alpha]_D^{15}$ +36.0° (c=0.5, MeOH). *Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42; N, 4.67. Found: C, 76.31; H, 8.48; N, 4.18.

This compound showed no depression on admixture with the sample reported previously.[1]

Dibenzoyl-*d*-tartrate: Colorless plates (from MeOH), m.p. 167~169° (decomp.), $[\alpha]_D^{14}$ −44.44° (c=0.45, MeOH).

Hydrochloride: Colorless grains (from EtOH-Et_2O), m.p. 249~251°, $[\alpha]_D^{14}$ +24.0° (c=0.5, MeOH). *Anal.* Calcd. for $C_{19}H_{26}O_2NCl \cdot \frac{1}{2}H_2O$: C, 66.17; H, 7.89; N, 4.06. Found: C, 66.42; H, 7.43; N, 4.22.

Hofmann degradation of *d*-2,3-Ethylenedioxy-N-methylmorphinan (*d*-II); 4a-(2-Dimethylaminoethyl)-6,7-ethylenedioxy-,1,2,3,4,4a,10a-hexahydrophenanthrene (*l*-V)—An intimate mixture of the methiodide (*d*-IV) (245 mg.) and Ag_2O, freshly prepared from $AgNO_3$ (124 mg.) in H_2O (2.7 cc.), was warmed at 50° for 12 hr. with stirring. After cool, the filtrate was evaporated under a reduced pressure (below 50°). The methohydroxide was heated at 120° (bath temp.) for 1.5 hr. and the benzene extract of the reaction mixture afforded (*l*-V) (159 mg. or 91.3%) as pale yellow crystals, m.p. 108.5~110°, $[\alpha]_D^{27}$ −72.0° (c=0.5, MeOH).

Hydrogenoxalate: Colorless prisms (from EtOH), m.p. 167~168°, $[\alpha]_D^{25}$ −64.0° (c=0.25, MeOH). UV λ_{max}^{EtOH} mμ (log ε): 227 (4.42), 277 (3.87), 302~303 (3.67), 315 (3.63). *Anal.* Calcd. for $C_{22}H_{29}O_6N$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.74; H, 7.14; N, 3.54.

2,3-Ethylenedioxyphenanthrene (VI)—(*l*-V) (116 mg.) was heated with 10% Pd-C (25 mg.) at 320° (bath temp.) for 6 hr. in N_2 atmosphere. The reaction mixture was allowed to stand at room temp. and extracted with Et_2O. The Et_2O solution was washed successively with dil. HCl, H_2O, dil. NaOH, and H_2O, dried, and Et_2O was evaporated. The residual oil was chromatographed on alumina in

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benzene and afforded (VI) (38 mg. or 43.6%) as colorless plates, m.p. 100~105°. Recrystallization from EtOH raised the m.p. to 113~114°. UV λ_{max}^{EtOH} mμ (log ε): 255 (4.79), 279 (4.47), *Anal.* Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.62; H, 5.31. This compound showed no depression on admixture with 2,3-ethylenedioxyphenanthrene reported previously.*1

***d*-3,4-Ethylenedioxy-N-cyanomorphinan (VII)**—A solution of (*d*-III) (179 mg.) in $CHCl_3$ (0.9 cc.) was heated under reflux with BrCN (92 mg.) for 2 hr. After evaporation of the solvent under a reduced pressure, the residual oil was taken up in Et_2O, worked up as usual, and the residual oil was chromatographed on alumina in benzene. (VII) (139 mg. or 75.5%) was obtained as a colorless oil, $[\alpha]_D^{11}$ +95.0° (c=0.5; MeOH).

***d*-3,4-Ethylenedioxymorphinan (VIII)**—(VII) (119 mg.) was heated under reflux with 6% HCl (3.6 cc.) for 6.5 hr. to a clear solution. On allowing the solution to stand overnight at room temp., the colorless crystals separated, which were washed with a small amount of cold H_2O, dried, and washed with Et_2O to afford (VIII) (54 mg. or 49.5%) as colorless prisms, m.p. 333~337°, $[\alpha]_D^{11}$ +28.0° (c=0.5, MeOH). *Anal.* Calcd. for $C_{18}H_{24}O_2NCl \cdot \frac{1}{4}H_2O$: N, 4.29. Found: N, 4.23.

***l*-2,3-Ethylenedioxy-N-methylmorphinan (*l*-II)**—(*l*-I) (4.7 g.) was heated with H_3PO_4 (16 cc.) in the same way as described for (*d*-II). The base was obtained as a pale yellow oil (4.46 g. or 94.8%). To a solution of this base in Me_2CO (30 cc.), BzOH (1.82 g.) was added and the mixture was warmed to give a clear solution. On working up as above, (*l*-II) (534 mg. or 8.1%) was obtained as colorless prisms (from Me_2CO-EtOH), m.p. 153~155°, $[\alpha]_D^{17}$ −18.0° (c=0.5, MeOH). *Anal.* Calcd. for $C_{26}H_{31}O_4N \cdot \frac{1}{4}H_2O$: C, 73.30; H, 7.45; N, 3.29. Found: C, 73.31; H, 7.54; N, 3.64.
Base: Colorless oil. $[\alpha]_D^{19}$ −20.0° (c=0.5, MeOH).
Perchlorate: Colorless plates (from EtOH), m.p. 239~240° (decomp.), $[\alpha]_D^{13}$ −26.0° (c=1.0, MeOH). *Anal.* Calcd. for $C_{19}H_{26}O_6NCl \cdot \frac{1}{2}H_2O$: C, 55.81; H, 6.65; N, 3.43. Found: C, 55.73; H, 6.16; N, 3.43. Methiodide: Colorless grains (from Me_2CO-EtOH), m.p. 259~260°, $[\alpha]_D^{26}$ −8.0° (c=1.0, MeOH). *Anal.* Calcd. for $C_{20}H_{28}O_2NI$: C, 54.65; H, 6.39; N, 3.17. Found: C, 54.44; H, 6.41; N, 3.24.

***l*-3,4-Ethylenedioxy-N-methylmorphinan (*l*-III)**—The combined mother liquor of the crystallization of (*l*-II) benzoate described above was evaporated under a reduced pressure. On working up as described in (C), a pale yellow oil (3.7 g.) was obtained which was dissolved in dehyd. Et_2O and dry HCl gas was introduced into this solution. A hygroscopic hydrochloride separated and was dissolved in Me_2CO. The solution was stood in an ice chest for 1 month, but no crystals formed. The residue left after evaporation of the solution was dissolved in H_2O and $NaClO_4$ solution was added. A perchlorate (526 mg. or 8.4%) was obtained as colorless needles, m p. 252° (decomp.), $[\alpha]_D^{16}$ −15.0° (c=0.5, MeOH). *Anal.* Calcd. for $C_{19}H_{26}O_6NCl$: C, 57.07; H, 6.55; N, 3.50. Found: C, 57.38; H, 6.70; N, 3.47.
Base: Colorless prisms (from petr. ether), m.p. 141~142°, $[\alpha]_D^{13}$ −36.5° (c=0.5, MeOH). *Anal.* Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42; N, 4.67. Found: C, 76.50; H, 8.43; N, 4.33. This compound showed no depression on admixture with the authentic sample.[1]
Dibenzoyl-*d*-tartrate: Colorless prisms (from MeOH), m.p. 168~170° (decomp.), $[\alpha]_D^{14}$ −68.0° (c=0.5, MeOH).
Hydrochloride: Colorless grains (EtOH-Et_2O), m.p. 249~251°, $[\alpha]_D^{14}$ −24.0° (c=0.25, MeOH). *Anal.* Calcd. for $C_{19}H_{26}O_2NCl \cdot \frac{1}{2}H_2O$: C, 66.17; H, 7.89; N, 4.06. Found: C, 66.41; H, 7.80; N, 4.27.

Hofmann degradation of *l*-2,3-ethylenedioxy-N-methylmorphinan (*l*-II); 4a-(2-Dimethylaminoethyl)-6,7-ethylenedioxy-1,2,3,4,4a,10a-hexahydrophenanthrene (*d*-V)—An intimate mixture of the methiodide (*l*-IV) (312 mg.) and Ag_2O, freshly prepared from $AgNO_3$ (157 mg.) in H_2O (3.5 cc.), was treated as described for (*l*-V) There was obtained (*d*-V) (197 mg. or 89.1%) as colorless crystals, m.p. 108~110°. $[\alpha]_D^{27}$ +74.0° (c=0.5, MeOH).
Hydrogenoxalate: Colorless prisms (from EtOH), m.p. 167~168°, $[\alpha]_D^{25}$ +62.0° (c=0.25, MeOH). UV λ_{max}^{EtOH} mμ (log ε): 227 (4.41), 277 (3.90), 302~303 (3.70), 315 (3.65). *Anal.* Calcd. for $C_{22}H_{29}O_6N$: N, 3.47. Found: N, 3.65.

2,3-Ethylenedioxyphenanthrene (VI)—(*d*-V) (113 mg.) was heated with 10% Pd-C (25 mg.) as described above for (VI). (VI) (42 mg. or 49.4%) was obtained as colorless plates (from EtOH), m.p. 113~114°. UV λ_{max}^{EtOH} mμ (log ε): 255 (4.83), 279 (4.52). *Anal.* Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.39; H, 5.47. This compound showed no depression on admixture with the authentic sample.*1

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Summary

For pharmacological evaluation, 1-(3,4-ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline was resolved into optical antipodes, using *d*-tartaric acid or dibenzoyl-*d*-tartaric acid.

When these compounds were cyclized according to the method of Grewe, there were produced two pairs of optically active position-isomers, *d*-1-(3,4-ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline gave *d*-2,3- and *d*-3,4-ethylenedioxy-N-methylmorphinan and *l*-1-(3,4-ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline yielded *l*-2,3- and *l*-3,4-ethylenedioxybenzyl derivatives.

d-2,3- and *l*-2,3-Ethylenedioxy-N-methylmorphinans were submitted to the Hofmann degradations and their structures were confirmed from their degradation product, 2,3-ethylenedioxyphenanthrene. *d*-3,4- and *l*-3,4-Ethylenedioxy-N-methylmophinans were found to be identical with authentic samples obtained by optical resolution of 3,4-ethylenedioxy-N-methylmorphinan.

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164. Goro Chihara : Medical and Biochemical Application of Infrared Spectroscopy. V.[1] Infrared Absorption Spectra of Organic Sulfate Esters. (1).

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It has been found in recent years that many important sulfate esters of organic compounds are present in medical and biological fields. Heparin and chondroitinsulfuric acid, sulfate conjugates in detoxication, and cerebroside sulfate are all organic sulfate esters. More recently, active sulfate has been found by Lipmann and others,[2,3] and the presence of energy-rich sulfate, corresponding to energy-rich phosphate, is being discussed. In order to know directly the nature of such a bond and to obtain fundamental data for qualitative and quantitative analyses, studies based on infrared absorption spectra seemed to be required. The present series of work was instigated for such a purpose.

Systematic studies on the infrared absorption spectra of organic sulfate esters are rare. Siebert[4] made assignments of chiefly Raman spectra of potassium methylsulfate, and a few other works are found in the works of Klotz,[5] La Lau,[6] and Hadži[7] on some organic sulfates, and those of Orr[8] and Nakanishi[9] on the sulfate of polysaccharide, in

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