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Stereochemistry of Decahydroisoquinolines and Related Compounds. VII.[1] Syntheses of *trans*-2-Methyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-7-isoquinolinols[2]

Shoshichiro Kimoto, Masao Okamoto, Takaaki Mizumoto, and Yasuhiro Fujiwara

Kyoto College of Pharmacy[3]

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The hitherto unknown stereoisomer of *trans*-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-7-isoquinolinol (XIIIc) and the known isomer of *cis*-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-7-isoquinolinol (XIIIa) were stereoselectively synthesized from 4-hydroxy-1,2,3,4,5,6-hexahydrohomophthalic acid 2,4-lactone (IX). The latter compound (IX) was separated from the reduction product of diethyl 4-hydroxyhomophthalate (II) whose configuration was already decided. Furthermore, another known isomer (XIIId) having *trans* ring juncture was prepared by different method from the known procedure.

In 1963, Okamoto, *et al.* reported that high pressure–hydrogenation of 7-isoquinolinol and 2-methyl-1,2,3,4-tetrahydro-7-isoquinolinol gave two of the corresponding alcoholic bases (XIIIa, XIIIb) possessing *cis* steric configuration at the ring juncture.[4] In the same year, Durand, *et al.* reported briefly in communication the synthesis of only one (XIIId) of the *trans* isomers possessing an *equatorial* hydroxyl group by Birch reduction of 2,3,4,4a,-5,6-hexahydro-7(1*H*)-isoquinolinone with lithium in liquid ammonia.[5] However, as detailed experimental data were not yet available at that time, the authors reinvestigated the Birch reduction in the same condition as in the case of Durand, *et al.*,[5] and a similar result was obtained. Thus, the third alcoholic base (XIIId), mp 70—71°, was synthesized.

On the other hand, stereoselective synthetic trials of the titled compounds by ring closure–reaction of 4-hydroxyhexahydrohomophthalic acid derivatives possessing definite steric configuration at C–1 and C–2 positions have been undertaken in our laboratory several years ago. This paper deals mainly with syntheses of the titled compounds and the synthetical routes are shown in the following schemes (Chart 1, 2, and 3).

High pressure–hydrogenation of diethyl 4-hydroxyhomophthalate (II) (mp 70°) which was prepared according to the method of Ungnade[6] over Raney nickel afforded a neutral reduction product (III) as a viscous liquid, which has been suggested to be a mixture of some compounds having γ-lactone and ester groups from the fact that two distinct absorption bands were observed at 1778 cm^{-1} and 1725 cm^{-1} in the IR spectrum. In order to separate the mixture into pure compounds, the following reaction was attempted. Thus, a reaction of III with hydrazine hydrate in ethanol at room temperature gave a dihydrazide (VIIIa), mp 198—200°, and an unreacted diester (XIX) which showed no lactone band at all in the IR spectrum and on treatment with hydrazine hydrate again in ethanol at 110° in a sealed tube, however, the diester (XIX) afforded only a small amount of another isomeric dihydrazide (VIIIb), mp 250—252°, and an appreciable amount of XIX was recovered unchanged. Hydrolysis of

1) Part VI: S. Kimoto and M. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1045 (1967).
2) A part of this work was presented at the 24th Annual Meeting of Pharmaceutical Society of Japan, Kyoto on 8th, April 1967 and communicated on *Chem. Pharm. Bull.* (Tokyo), **15**, 370 (1967).
3) Location: *5, Nakauchi-cho, Yamashina-Misasagi, Higashiyama-ku. Kyoto.*
4) M. Okamoto and M. Yamada, *Chem. Pharm. Bull.* (Tokyo), **11**, 554 (1963).
5) S. Durand and R.C. Moreau, *Compt. Rend.*, **257**, 2673 (1963); *idem, Bull. Soc. Chim. France*, **1966**, 3428.
6) H.E. Ungnade, D.V. Nightingale, and H.E. French, *J. Org. Chem.*, **10**, 533 (1945).

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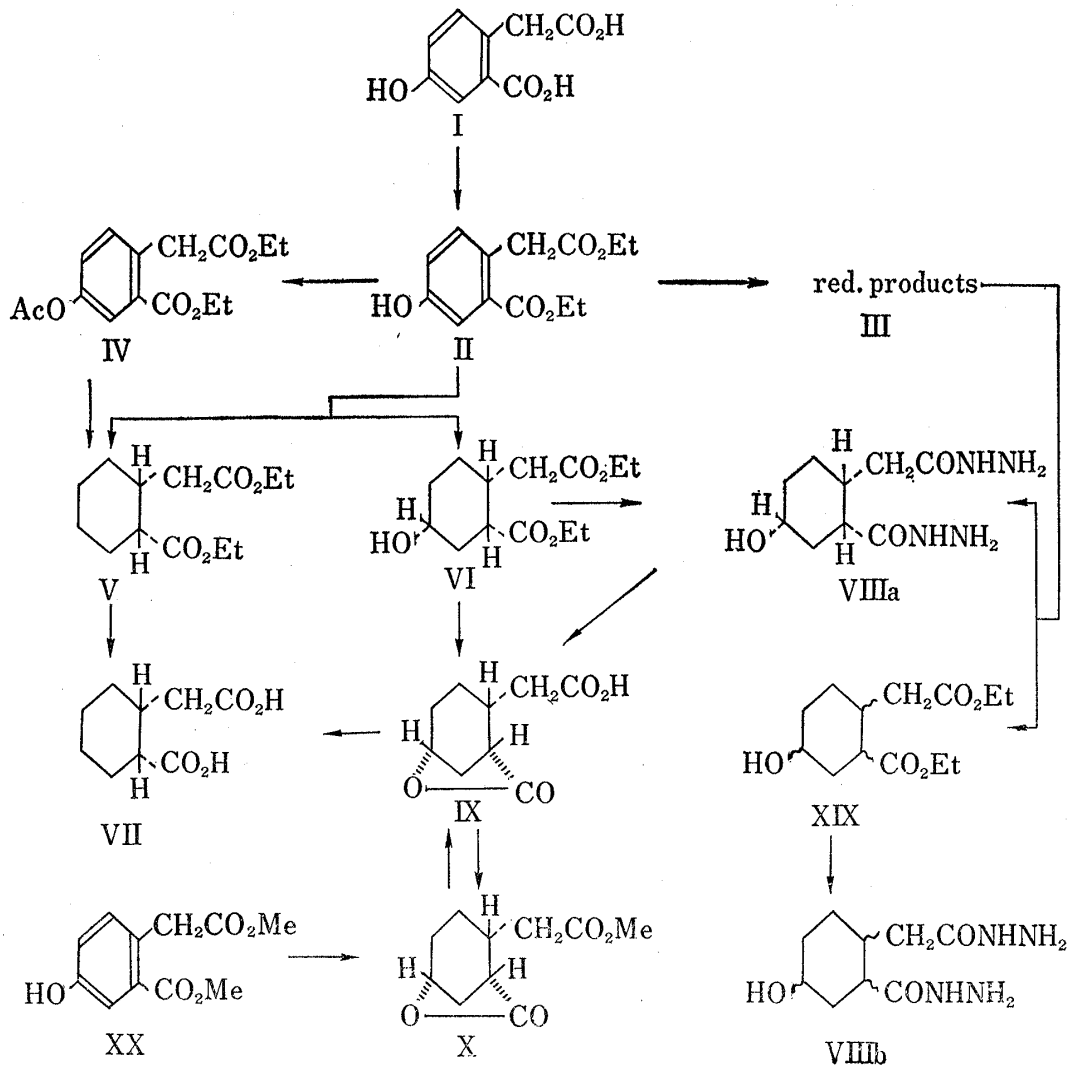

Chart 1

the former dihydrazide (VIIIa) with boiling dilute hydrochloric acid gave a lactone carboxylic acid (IX) (mp 117—120°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1778), which was converted to the methyl ester (X), mp 87—88°, with diazomethane in usual manner, which was alternatively prepared by high pressure–hydrogenation of dimethyl 4-hydroxyhomophthalate (XX) over Raney nickel in 54% yield. Unfortunately, hydrolysis of the latter dihydrazide (VIIIb) afforded an oily acid which was not crystallized by treatment with any usual solvent and this was described later.

For the lactone carboxylic acid (IX) it was clarified that the hydroxyl group at C-4 and the carboxyl group at C-2 exist in relation of *cis* configuration from the above evidence of lactone-forming. Moreover, for the purpose of confirmation of the steric configuration at C-1 and C-2 positions of IX, the following experiments were tried. At first, catalytic hydrogenation of IX over platinum oxide in acetic acid solution containing a few drops of perchloric acid for a long time afforded *cis*–hexahydrohomophthalic acid (VII) on opening of the lactone ring and hydrogenolysis. Next, hydrogenation of the ester (II) over platinum oxide in acetic acid solution afforded the corresponding hydroxyhexahydro–ester (VI) and diethyl *cis*–hexahydrohomophthalate (V). The former ester (VI) was converted to the above–mentioned dihydrazide (VIIIa). Hydrolysis of the esters (VI and V) gave the lactone carboxylic acid (IX) and the known *cis* acid (VII), respectively. Moreover, in the case of catalytic hydrogenation of the O-acetate (IV), the aromatic ring was hydrogenated and the acetoxyl group was removed simultaneously to give diethyl *cis*–hexahydrohomophthalate (V) exclusi-

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vely, which was identified by conversion to the corresponding *cis* acid (VII). Thus, it was clarified that the ester (VI), the dihydrazide (VIIIa) and the carboxylic acid (IX) possessed all *cis* configuration at C–1, C–2 and C–4 positions.

Then, using the lactone carboxylic acid (IX) as a starting material, ring closure–reaction was carried out by the following manner. That is, the acid (IX) was treated with a methanolic solution of methylamine, the product was distilled *in vacuo* and the distillate was fractionally recrystallized from ether to give isomeric cyclic imides (XIa and XIb, mp 115° and mp 129°, respectively). On reduction of the former imide (XIa) with $LiAlH_4$ was prepared one of *cis*-2-methyldecahydro-7-isoquinolinol (XIIIa) (methiodide, mp 266°; picrate, mp 154—156°) which was already reported,[4] and on the contrary, on the similar reduction of the latter imide (XIb) was obtained one of *trans*-2-methyldecahydro-7-isoquinolinol (XIIIc) (methiodide, mp 251—252°; picrate, mp 189—191°), which was not identical at all with any of the three isomeric alcoholic bases already known. The base (XIIIc) was converted to the corresponding *trans* ketone (XVII) (picrate, mp 215°) on oxidation wtih chromic acid, which was reduced by Wolff–Kishner–Huang–Minlon method to give *trans*-2-methyldecahydroisoquinoline (XVIII). Therefore, it has been clarified that the ring juncture of the alcoholic base (XIIIc) is *trans*. We should like to emphasize the importance of these results from the points of stereochemical consideration. Thus, at first it has been clarified that in the alcoholic base (XIIIa) steric configuration of hydrogen atoms attached to C–7, C–9 and C–10 positions is all *cis* and that in the *trans* alcoholic base (XIIIc) configuration of hydrogen atoms attached to C–10 and C–7 positions is *cis*, namely that the configuration of the hydroxyl group in XIIIa may be an α-type and that of the hydroxyl group in XIIIc may be an α-axial–type as depicted in Chart 2. This assumption is well consistent with the data obtained in another experiments.[7] Next, in view of the synthetical facts that the *cis* alcoholic base (XIIIa) and the *trans* alcoholic base (XIIIc) are obtained from the lactone

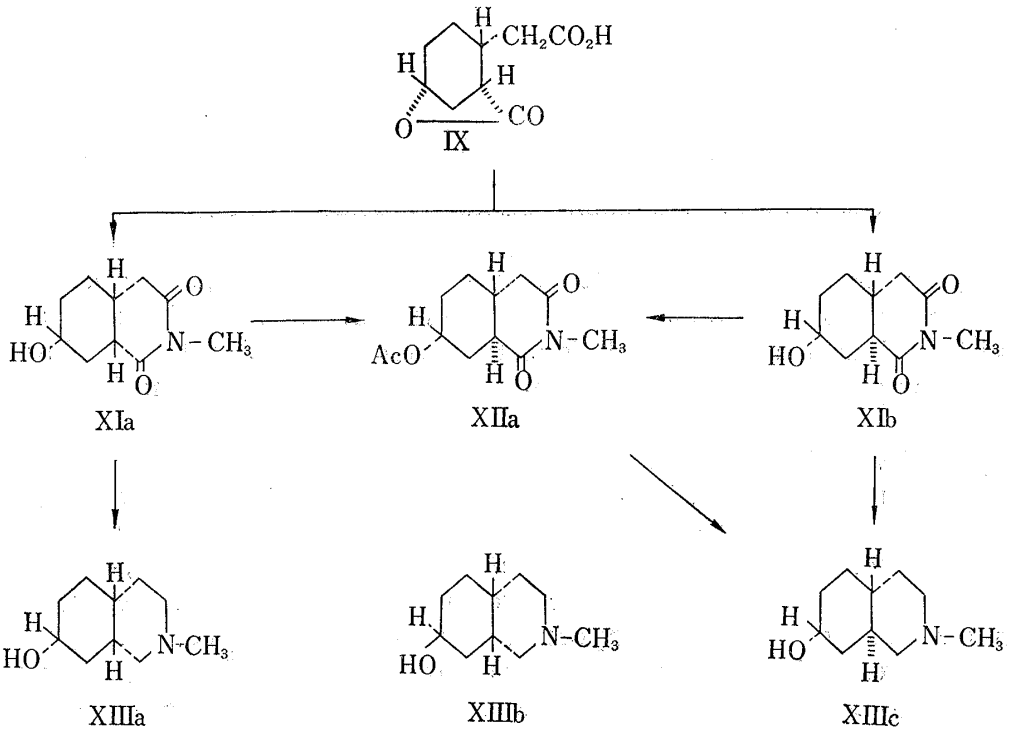

Chart 2

7) In the preceeding paper, conformational and configurational studies were discussed in details by means of a great deal of evidences such as NMR–, IR–spectrometry, consideration of rate constants of chromic acid oxidation, pK_a values and so on.[1]

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carboxylic acid (IX), the reasonable presumption to be drawn is that IX will result in XIa with retention of *cis* configuration and XIb with inversion of the substituent at the C–2 carbon atom of IX during the process of the ring closure–reaction. In order to certify the presumption, chemical correlation between one imide (XIa) and the other (XIb) was investigated and the following experiments resulted as expected. Thus, the imide (XIa) was treated with sodium ethoxide in boiling ethanol, followed by acidification and the resulted substance was heated with acetic anhydride to give an O-acetylated imide (XIIa), mp 114—116°, which was identical with the O-acetylated one derived from XIb and moreover, XIIa resulted in the *trans* alcoholic base (XIIIc) on reduction with $LiAlH_4$.

Furthermore, the above–mentioned high pressure–hydrogenation product, that is, the diester (XIX) separated from the lactone carboxylic acid (IX) by way of hydrazide–formation showed no γ-lactone absorption band in the IR spectrum and still seemed to be a mixture of various isomers. Fortunately, *p*-nitrobenzoylation of XIX afforded the corresponding crystalline *p*-nitrobenzoate (XIV), mp 80—81°, which was converted to the O-acetylated anhydride (XV), mp 145—146° (IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1822, 1776 (six–membered ring anhydride)), at first by removal of the *p*-nitrobenzoyl group of XIV, followed by heating with acetic anhydride. According to the synthetic method of cyclic imides by Bachmann, *et al.*,[8] the O-acetyl-

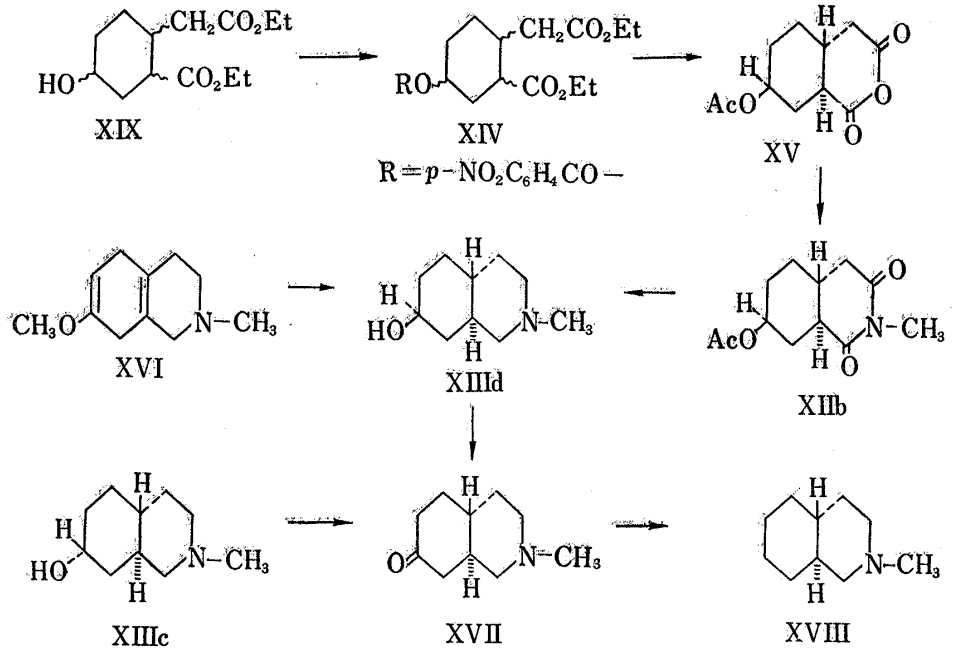

Chart 3

ated anhydride (XV) was converted to the corresponding imide (XIIb), mp 103—104° (IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 ($OCOCH_3$), 1670 (imide)), the IR spectrum of which was not superimposable on that of the epimeric cyclic imide (XIIa) as above. Reduction of the imide (XIIb) with $LiAlH_4$ afforded the epimeric *trans*-2-methyldecahydro-7-isoquinolinol (XIIId) that was identical with the alcoholic base prepared by Durand, *et al.*[5] On oxidation with chromic acid, the alcoholic base (XIIId) was converted to the same corresponding ketone (XVII) which was derived from the epimeric alcohol (XIIIc) as above. Thus, four isomers of the 7-hydroxy alcoholic bases (XIIIa, XIIIb, XIIIc, and XIIId), which are theoretically possible to exist, have been prepared.

On the basis of formation of the *trans* alcohol (XIIId) from diethyl 4-hydroxyhexahydrohomophthalate (XIX) purified *via* the *p*-nitrobenzoate (XIV), it seems reasonable to assume

8) W.E. Bachmann, A. Ross, A.S. Dreiding and P.A. Smith, *J. Org. Chem.*, **19**, 222 (1954).

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that the diester (XIX) has probably all *equatorial* substituents at C-1, C-2 and C-4 positions. Confirmation of configuration of XIX is now progressed.

Experimental[9]

4-Hydroxyhomophthalic Acid (I)——This acid was prepared starting from indene according to the synthetic method reported by Ungnade, *et al.*[6] mp 216° (decomp.) (reported mp 214—215° (decomp.)).

Diethyl 4-Hydroxyhomophthalate (II)——A solution of 4-hydroxyhomophthalic acid (13 g) in EtOH (100 ml) was saturated with dry HCl gas and kept standing for 4 days. The reaction mixture was treated in usual manner. Colorless viscous liquid (10.6 g), bp 160—180° (5 mmHg), which was on cooling solidified and recrystallized from C_6H_6 to give colorless needles, mp 70°. *Anal.* Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.52; H, 6.42.

Dimethyl 4-Hydroxyhomophthalate (XX)——This was prepared with the same method as the foregoing diethyl ester. bp 174—177° (2 mmHg), mp 80—81°. Colorless needles (recrystallized from C_6H_6). *Anal.* Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.42. Found: C, 59.05; H, 5.32.

Diethyl 4-Acetoxyhomophthalate (IV)——A mixture of II (1.2 g), Ac_2O (0.62 g) and pyridine (2 drops) was kept standing overnight and then solidified. The reaction mixture was treated in usual manner. Colorless long needles (1.35 g, 96.8%), mp 67° (recrystallized from petr. benzine). *Anal.* Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.05; H, 6.22.

Hydrogenation of Diethyl 4-Acetoxyhomophthalate (IV)——The ester (IV) (1.3 g) in AcOH (20 ml) was catalytically hydrogenated over $PtO_2 \cdot H_2O$ (400 mg) at room temp. and atmospheric pressure for 4 hr. H_2 uptake, 430 ml. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* and the residual oil was distilled at 110—115° (3 mmHg) to give V (850 mg) as a colorless oil, the IR spectrum of which showed no OH absorption.

A solution of the ester (V) (400 mg) in KOH–EtOH (3 ml) was kept standing for 20 hr at room temperature and the Na salt was formed. The salt was dissolved in water and the solution was shaken with ether. Acidification of the aq. solution with conc. HCl gave colorless crystals (100 mg), mp 145—148°, which was identical with the authentic sample of VII[10] by mixed melting point test.

Hydrogenation of Diethyl 4-Hydroxyhomophthalate (II)——i) Over PtO_2: The ester (II) (1.0 g) in AcOH (20 ml) was catalytically hydrogenated over $PtO_2 \cdot H_2O$ (420 mg) at room temperature and atmospheric pressure for 6 hr. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. The residual oil was dissolved in ether and the solution was shaken with 3% NaOH, washed with water and dried over Na_2SO_4. After removal of the solvent, reduced distillation of the residual oil gave 2 fractions, boiling at 104—105° and 145—146° (2 mmHg). The former fraction (V) was hydrolysed in usual manner to give VII. The latter one was diethyl *cis*-4-hydroxyhexahydrohomophthalate (VI). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (free OH), 3400 (associated OH), 1725 (ester C=O), 1099 (C–O). Treatment of VI with hydrazine hydrate in EtOH afforded quantitatively a dihydrazide (VIIIa), mp 198—200°, which was described later.

ii) Over Raney Ni: The ester (II) (5.0 g) in EtOH (100 ml) was catalytically hydrogenated at 162° and 146 kg/cm^2 (initial H_2 pressure, 110 kg/cm^2/24°) over Raney Ni prepared from Ni–Al alloy (12.5 g) for 6.5 hr. H_2 uptake, 1.64 liters. After cooling and removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* and the residual oil was distilled. The above operation was worked up 4 times and an oil (III) (32 g), bp 150—160° (5 mmHg) was obtained from the starting material (41 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1778 (γ-lactone C=O), 1725 (ester C=O).

Separation of the Foregoing High Pressure-hydrogenation Product with Hydrazine Hydrate——A mixture of the oil (5.3 g), 80% hydrazine hydrate (3.0 g) and EtOH (45 ml) was kept standing for 3 days. White crystals formed were collected by suction and evaporation of the filtrate afforded a mixture of crystals and oil. This oil was separated from crystals with dissolving into ether. Recrystallization of the crystals from EtOH gave a dihydrazide (VIIIa) (2.05 g) mp 198—200°. IR ν_{max}^{Nujol} cm^{-1}: 3350 (associated OH), 3210 3300 (NH), 1640, 1570, 1550 (CONH). *Anal.* Calcd. for $C_9H_{18}O_3N_4$: C, 46.94; H, 7.88; N, 24.33. Found: C, 47.34; H, 7.99; N, 24.11.

The oil which dissolved in ether was distilled *in vacuo* to give colorless liquid (2.0 g), bp 158—160° (5 mmHg) (XIX). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (ester C=O), no absorption bands of γ-lactone near 1780 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.31; H, 8.90. A solution of XIX (0.5 g) and 100% hydrazine hydrate (0.3 g) in EtOH was sealed in a glass tube and the solution was heated at 110° for 6 hr. After cooling, the crystals formed were collected and recrystallized from water to give colorless needles (VIIIb) (150 mg, 3%), mp 250—252°. *Anal.* Calcd. for $C_9H_{18}O_3N_4$: C, 46.94; H, 7.88; N, 24.33. Found: C, 47.07; H, 7.88; N, 24.26.

9) All melting points are not corrected. NMR spectra were determined on a Varian A-60 spectrophotometer with $CDCl_3$ as solvent and tetramethylsilane as an internal reference.

10) E. Berner and O. Steffensen, *Acta Chem. Scand.*, **8**, 64 (1954).

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High Pressure-hydrogenation of Dimethyl 4-Hydroxyhomophthalate (XX)——The ester (XX) (1.5 g) in MeOH (50 ml) was catalytically hydrogenated at 180° and 180 kg/cm² (initial H_2 pressure, 111 kg/cm²) over Raney Ni, prepared from Ni–Al alloy (5.0 g) for 5 hr. After cooling and removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. The residual oil was dissolved into ether and the ethereal solution was shaken with 10% Na_2CO_3, washed with water and dried over Na_2SO_4. After removal of the solvent, the residual oil was distilled at 145—155° (5 mmHg). Colorless viscous liquid (700 mg). This solidified on cooling. Recrystallization from ether afforded the methyl ester (X) as colorless prisms, mp 87—88°. *Anal.* Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.61; H, 7.09.

4-Hydroxyhexahydrohomophthalic Acid 2,4-Lactone (IX)——i) The dihydrazide (VIIIa) (10.5 g) in 10% HCl (155 ml) was heated for 4.5 hr. Then the solvent was evaporated *in vacuo* and the residual mass was extracted with ether. Removal of the solvent gave crystals, which were recrystallized from ether to give colorless prisms, mp 117—120°. *Anal.* Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.94; H, 6.84. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1778 (γ-lactone C=O).

ii) A mixture of VI (700 mg) and 10% KOH–MeOH (10 ml) was refluxed for 1 hr. After removal of the solvent, the residual mass was dissolved in water. The aq. solution was acidified with dil. HCl and extracted with ether. The ethereal solution was dried over Na_2SO_4 and evaporated to give the residual mass, which was distilled at 203—206° (bath temp.) (2 mmHg). The distillate was solidified on cooling and recrystallized from ether to give colorless prisms, mp 117—120°, which were identical with the foregoing lactone (IX).

The lactone (IX) (100 mg) in AcOH (20 ml) containing a few drops of perchloric acid was catalytically hydrogenated over $PtO_2 \cdot H_2O$ (100 mg) at room temperature and atmospheric pressure for 50 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residual mass was recrystallized from water to give VII (50 mg) as colorless needles, mp 148°, which were identified by admixture with an authentic sample.

Methyl Ester (X) of 4-Hydroxyhexahydrohomophthalic Acid 2,4-Lactone (IX)——The lactone carboxylic acid (IX) (100 mg) was methylated with CH_2N_2 in ether as a solvent in usual manner. Colorless prisms, mp 87—88°. Yield, 50 mg. This was identical with the ester, obtained on high pressure-hydrogenation of XX.

Ring Closure-Reaction of The Lactone Carboxylic Acid (IX) to Cyclic Imides——i) A solution of IX (5.3 g) and 28% CH_3NH_2–MeOH (31.2 ml) was kept standing in a sealed tube for 5 days. Removal of the solvent afforded a viscous liquid, which was dissolved in water and neutralized with conc. HCl. After removal of the solvent, the residual mass was heated at 200—205° and distilled *in vacuo*. The distillate was extracted with ether and the ethereal extract was distilled at 210—220° (5 mmHg) to be a colorless viscous liquid, which was soon solidified and recrystallized from ether to give *cis*-7*a*-hydroxy-2-methyl-1,2,3,4-4a,5,6,7,8,8a-decahydroisoquinoline-1,3-dione (XIa) as colorless prisms (2.0 g), mp 115°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1739, 1670 (six-membered imide C=O). *Anal.* Calcd. for $C_{10}H_{15}O_3N$ (XIa): C, 60.89; H, 7.67; N, 7.10. Found: C, 60.62; H, 7.91; N, 7.03.

From the mother liquor of the recrystallization, another imide (20 mg), *trans*-7*a*-hydroxy-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-1,3-dione (XIb) was obtained as colorless needles, mp 128—129°, recrystallized from ether. *Anal.* Calcd. for $C_{10}H_{15}O_3N$: C, 60.89; H, 7.67; N, 7.10. Found: C, 61.05; H, 7.78; N, 7.05.

ii) A solution of IX (1.5 g) and 40% CH_3NH_2–EtOH (66 ml) was kept standing in a sealed tube for 5 days and warmed at 75° for 40 min. After removal of the solvent and the excess CH_3NH_2, the residual liquid was heated at 180° for 20 min and distilled *in vacuo*. The distillate, bp 164—167° (1 mmHg), solidified on standing, was fractionally recrystallized from ether to give the foregoing imides, XIa (100 mg) and XIb (600 mg), which were identified by admixture or with comparison of IR spectra with the authentic samples.

***trans*-7*a*-Acetoxy-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-isoquinoline-1,3-dione (XIIa)**——i) Acetylation of XIb with Ac_2O and pyridine in usual manner afforded the O-acetate (XIIa), bp 180—185° (3 mmHg), which was recrystallized from ether to give colorless plates, mp 114—116°. *Anal.* Calcd. for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.65; H, 7.20; N, 6.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (ester C=O), 1680 (six-membered imide C=O).

ii) A solution of XIa (500 mg) and NaOEt–EtOH, prepared with Na (50 mg) and EtOH (3 ml), was refluxed for 4 hr. After removal of the solvent, the residual mass was diluted with water, acidified with conc. HCl and the solvent was evaporated. The residual mass was extracted with acetone and, after removal of acetone, the residue was treated once with ether. A mixture of the ether-insoluble substance and Ac_2O (4 ml) was heated at 154—160° for 4 hr. After removal of excess of Ac_2O *in vacuo*, the residual mass was distilled at 180—185° (3 mmHg) and the distillate was recrystallized from ether to give colorless plates (100 mg), mp 114—116°. This was identical to XIIa with comparison of IR spectra.

***cis*-2-Methyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-7*a*-isoquinolinol (XIIIa)**——A solution of XIa (1.0 g) in ether (230 ml) was added dropwise into a mixture of $LiAlH_4$ (660 mg) in ether (18 ml) under stirring, and the mixture was refluxed for 20 hr. After cooling, the excess of the reagent was decomposed with water the ethereal solution was decanted off and the aq. layer was extracted with ether several times. The combined ethereal solution was shaken with 10% HCl (30 ml), the acidic solution was basified with NaOH, and extracted

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with ether. The ethereal extract was washed with sat.NaCl, dried over Na_2SO_4 and evaporated. Distillation of the residual oil afforded a colorless viscous oil (300 mg), bp 95° (4 mmHg). Methiodide, mp 266° (recrystallized from EtOH). Picrate, mp 154—156° (recrystallized from MeOH). This was identified by admixture with an authentic sample. NMR τ: 7.75 (3H, singlet, N-C$\underline{H}_3$), 6.48 (1H, multiplet, =C$\underline{H}$OH, $W/2=16$ cps).

***trans*-2-Methyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-7*α*-isoquinolinol (XIIIc)**——i) A solution of XIb (600 mg) in ether (100 ml) was added dropwise into a stirred mixture of $LiAlH_4$ (350 mg) in ether (10 ml) within 50 min and then the mixture was refluxed for 30 hr under stirring. After cooling, the excess of the reagent was decomposed with water. The mixture was treated in the same way as in case of the foregoing reduction. A colorless viscous liquid, bp 99—101° (3 mmHg). After cooling, it solidified and melted at 45°. Methiodide, mp 251—253°, as colorless needles (recrystallized from EtOH). *Anal.* Calcd. for $C_{10}H_{22}ONI$: C, 42.45; H, 7.13. Found: C, 42.45; H, 7.12. Picrate, mp 189—191°, as yellow needles (recrystallized from MeOH). NMR τ: 7.82 (3H, singlet, N-C$\underline{H}_3$), 5.96 (1H, multiplet, =C$\underline{H}$OH, $W/2=7$ cps).

ii) The same reduction of XIIa (800 mg) with $LiAlH_4$ (470 mg) as in case of the foregoing reduction gave XIIIc (300 mg), which was identified with comparison of IR spectra.

Diethyl *trans*-4-(*p*-Nitrobenzoyloxy)-1,2,3,4,5,6-hexahydrohomophthalate (XIV)——A solution of *p*-nitrobenzoyl chloride (3.5 g) in ether (100 ml) was added dropwise into a stirred solution of XIX (4.8 g) in pyridine (20 ml) in an ice–bath and the mixture was stirred at 10° for 50 hr. After removal of pyridine. HCl(mp 163°) by suction, the ethereal solution was washed with sat. NaCl and dried on Na_2SO_4. Removal of the solvent gave crystals (7.1 g), which were recrystallized from EtOH to give pale yellow plates (1.0 g), mp 80—81°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1530, 1350 (NO_2). *Anal.* Calcd. for $C_{20}H_{25}O_{10}N$: C, 58.96; H, 6.18; N, 3.40. Found: C, 58.67; H, 6.04; N, 3.40.

***trans*-4-Acetoxy-1,2,3,4,5,6-hexahydrohomophthalic Acid Anhydride (XV)**——A solution of XIV (500 mg) and 10% KOH–EtOH (15 ml) was kept on standing at 50° for 30 hr. After removal of EtOH, the residual mass was dissolved into water and acidified to pH 4.2 with HCl. *p*-Nitrobenzoic acid formed was removed by suction and the filtrate was evaporated to dryness *in vacuo*. The residual mass was dissolved into acetone. Removal of the solvent gave a viscous oil. A solution of the oil and Ac_2O (5 ml) was refluxed at 155° for 5 hr. After removal of excess of Ac_2O, the residual oil was distilled at 70—150° (bath temp.) (3 mmHg) to give crystals, which were recrystallized from $CHCl_3$–ether to afford colorless plates, mp 145—147°. *Anal.* Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.65; H, 6.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1822, 1776 (six–membered anhydride C=O), 1742 (ester C=O).

***trans*-4-Acetoxy-1,2,3,4,5,6-hexahydrohomophthalic Acid N-Methyl Imide (XIIb)**——A solution of XV (500 mg) in $CHCl_3$ was saturated with methylamine and the mixture was kept on standing overnight to afford precipitates. The upper $CHCl_3$ layer, on evaporation, gave also the precipitates. The combined precipitates were heated at 160—170° for 0.5 hr and distilled at 140—145° (bath temp.) (7 mmHg) to give a viscous liquid, which on standing solidified. As the IR spectrum of this solid (mp 75—86°) showed a weak absorption band of a free OH at 3590 cm^{-1}, a mixture of the solid in Ac_2O (1.5 ml) and a few drops of pyridine was kept on standing overnight, and treated with water. After evaporation of water and AcOH *in vacuo*, the residual oil was dissolved in ether (80 ml), the ethereal solution was shaken with 10% Na_2CO_3, dried over Na_2SO_4 and evaporated. The residual mass was recrystallized from ether to give colorless prisms or needles (300 mg), mp 103—104°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester C=O), 1670 (imide C=O). *Anal.* Calcd. for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.41; H, 7.30; N, 6.03.

***trans*-2-Methyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-7*β*-isoquinolinol (XIIId)**——i) A solution of XIIb (480 mg) in ether (80 ml) was added dropwise within 30 min into a mixture of $LiAlH_4$ (350 mg) in ether (10 ml) under stirring and the mixture was refluxed for 36 hr. After cooling, the reaction mixture was treated in usual manner. bp 90—95° (bath temp.) (6 mmHg). Yield, 220 mg. This was soon solidified and recrystallized from petr. ether to give colorless crystals, mp 70—71°. Methiodide, mp 268—269° (recrystallized from EtOH). *Anal.* Calcd. for $C_{11}H_{22}ONI$: C, 42.45; H, 7.13; N, 4.50. Found: C, 42.52; H, 7.22; N, 4.54. Picrate, mp 206—207° (recrystallized from MeOH). NMR τ: 7.78 (3H, singlet, N–C$\underline{H}_3$), 6.50 (1H, multiplet, =C$\underline{H}$OH, $W/2=16$ cps).

ii) 7-Methoxy-2-methyl-1,2,3,4,5,8-hexahydroisoquinoline (XVI) (4.0 g) was dissolved in an aq. sat. oxalic acid and the mixture was kept standing overnight, then basified with sat. $NaHCO_3$ and extracted with ether. The ethereal solution was dried over Na_2SO_4 and the solvent was removed in a stream of N_2. The residual oil distilled at 94—101° (4 mmHg) in a stream of N_2 to give a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1722 (C=O). UV λ_{max}^{EtOH} $m\mu$ (ε): 217 (2400), 278 (447). Into liq. NH_3 (300 ml) cooled at −60° was added dropwise a solution of the above–mentioned oil (2.5 g), ether (70 ml) and MeOH (90 ml) and Li (14.0 g)was added cautiously in small pieces to the above solution with stirring for 2.5 hr. Treatment of this reaction mixture in usual manner afforded the corresponding crude alcoholic base (1.7 g) as an oil, bp 128° (5 mmHg), which was purified by recrystallization of the picrate from MeOH to give yellow needles (3.0 g), mp 206—207°. Basification of the picrate afforded the free base as colorless viscous oil (900 mg), bp 119° (7 mmHg) which was solidified after cooling and recrystallized from petr. ether to give colorless prisms, mp 70—71°.

***trans*-2-Methyl-2,3,4,4a,5,6,8,8a-decahydro-7(1*H*)-isoquinolinone (XVII)**——To a solution of *trans* alcoholic base (XIIIc or XIIId) (1.0 g), conc. H_2SO_4 (800 mg) and H_2O (2 ml), a solution of $Na_2Cr_2O_7 \cdot 2H_2O$

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(400 mg) and H_2O (4 ml) was added cautiously under cooling and the solution was kept on standing at room temperature for 20 hr. The reaction mixture was basified with 40% NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with sat. NaCl, dried over Na_2SO_4 and evaporated. The residual oil was distilled at 94—100° (3 mmHg) as a colorless mobil oil (300 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O). Picrate, mp 215°, yellow needles (recrystallized from MeOH). *Anal.* Calcd. for $C_{16}H_{20}O_8N_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.36; H, 5.07; N, 13.73. Methiodide, mp 246—247°. Colorless needles (recrystallized from EtOH).

Wolff-Kishner-Huang-Minlon Reduction of the Foregoing *trans* Ketone (XVII)——A mixture of the ketone (XVII) (400 mg), 100% hydrazine hydrate (10 ml) and triethylene glycol (10 ml) was refluxed at 140° for 5 hr. To the above mixture was added KOH (2.5 g) and the temperature of the mixture was raised gradually to 210° during 3 hr. The distillate (bp 160—210°) was extracted with ether. The extract was washed with sat.NaCl and dried over Na_2SO_4. Evaporation of ether gave *trans*-2-methyldecahydroisoquinoline (XVIII), bp 71—75° (7mmHg). The picrate of XVIII, mp 230°, was undepressed on admixture with an authentic sample.

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