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Stereochemistry of Decahydroisoquinolines and Related Compounds. X.[1] Configurational Assignment of Epimeric 4-Hydroxy-2-methyl-*cis*-decahydroisoquinolines

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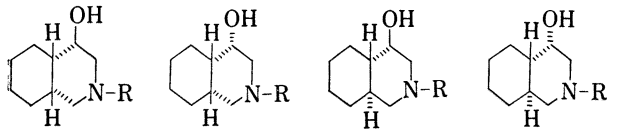
Two isomers of 4-hydroxy-2-methyl-*cis*-decahydroisoquinoline were prepared and the conformations of these compounds were discussed by means of infrared spectroscopy.

In the earlier papers, the authors have reported syntheses of three diastereomeric isomers of 4-hydroxy-2-methyldecahydroisoquinoline, *i.e.* two epimeric alcohols of 2-methyl-*trans*-decahydroisoquinoline and one of two epimeric alcohols of *cis*-ring fused isomer.[1,3] Now, the fourth alcohol having a *cis* ring juncture could be prepared by the catalytic hydrogenation of benzene-tetrahydro-4-isoquinolinol (II). In this paper, it deals with the preparative method of the new epimer and configurational discussion of these two epimeric alcohols having *cis* ring juncture.



IIIa: R=H IIIb: R=H IIIc: R=H IIId: R=H
IXa: R=CH_3 IXb: R=CH_3 IXc: R=CH_3 IXd: R=CH_3

Fig. 1. Configurational Isomers of 4-Hydroxydecahydroisoquinolines

II, obtained from 4-isoquinolinol (I) according to the method reported by Ochiai,[4] was hydrogenated over Adams catalyst in the presence of perchloric acid to afford a new isomer (IIIb), mp 162°, of 4-hydroxydecahydroisoquinoline in 13% yield and *cis*-decahydroisoquinoline (IV) (picrate, mp 151°) in 80% yield. The base (IIIb) has an empirical formula $C_9H_{17}ON$ and is different from the known three isomers[1,3] (IIIa, IIIc and IIId), which have been synthesized from the materials having the stereochemically decided structures, by their physicochemical properties, respectively. Therefore, the base (IIIb) is an epimer of IIIa having *cis* ring juncture (presence of four isomers is considered theoretically possible for 4-hydroxydecahydroisoquinoline). Methylation of IIIb with formalin and formic acid gave the corresponding N-methyl compound (IXb), mp 65° (methiodide, mp 252°; picrate, mp 168°).

Next, catalytic hydrogenation of I over Raney nickel catalyst in methanol at 150—160° and under high pressure resulted in various products, accompanying partial reduction with hydrogenolysis. That is, II, pyridine-tetrahydroisoquinoline (VIII), IV, *cis*-2-methyldecahydroisoquinoline (X) and a mixture (III) (mp 146—147°) of the expected 4-hydroxydecahydroisoquinoline isomers were separated from the reaction mixture. The alcoholic base mixture (III) was produced in 8% yield and apparently seemed to be pure crystal, but it

1) Part IX: S. Kimoto, M. Okamoto, M. Nakamura, and T. Baba, *Yakugaku Zasshi*, **90**, 1538 (1970).
2) Location: *a) Nakauchi-cho, Yamashina-Misasagi, Higashiyama-ku, Kyoto; b) Nishioji-hachijo, Minami-ku, Kyoto.*
3) S. Kimoto, M. Okamoto, M. Uneo, S. Ohta, M. Nakamura, and T. Niiya, *Chem. Pharm. Bull.* (Tokyo), **18, 2141 (1970).**
4) E. Ochiai and M. Ikehara, *Pharm. Bull.* (Japan), 3, 454 (1955).

was found to be a mixture of isomers by thin-layer chromatography (TLC) and further purification was difficult as a free base at this stage. Moreover, it is interesting that II was not hydrogenated over Raney nickel catalyst under the above-mentioned reaction conditions.

On benzoylation of III using benzoyl chloride and sodium hydroxide, N-benzoyl-4-hydroxy-*cis*-decahydroisoquinoline (VI), mp 136°, and N-benzoyl-4-benzoyloxy-*cis*-decahydroisoquinoline (V), mp 160°, were obtained and the former (VI) was converted to the latter (V) using benzoyl chloride and pyridine. Furthermore, benzoylation of IIIb obtained by hydrogenation of II using Adams catalyst afforded the corresponding O,N-dibenzoate, mp 159°, which was identical with the sample prepared from III mentioned above. Therefore, it can be concluded that the alcoholic base (III) obtained by hydrogenation of I using Raney nickel catalyst is mainly composed of IIIb.

Hydrogenation of 4-methoxyisoquinoline (VII), obtained from I with diazomethane, over Raney nickel catalyst at elevated temperature and under high pressure was carried out and resulted in a mixture of benzene-tetrahydro-4-methoxyisoquinoline (XI), VIII, IV and X (Chart 1).

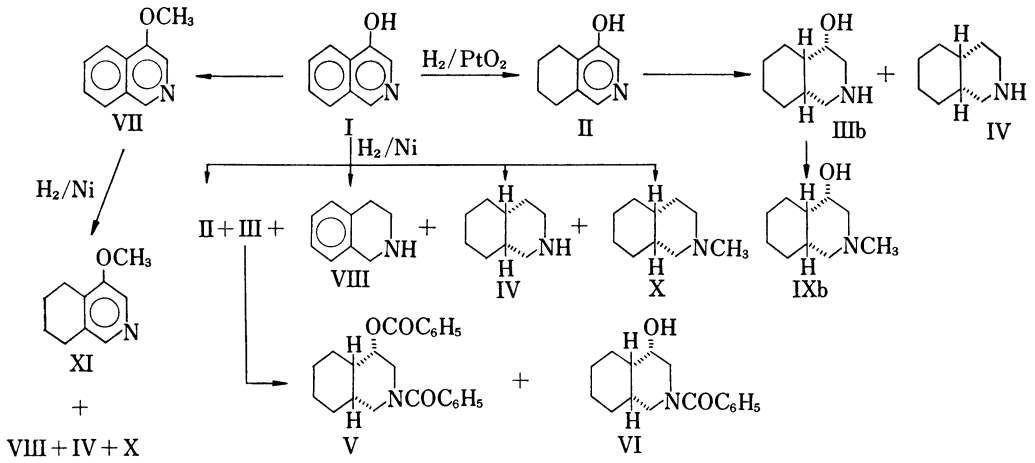


Chart 1

Previously, Witkop[5] reported that hydrogenation of isoquinoline over Raney nickel catalyst at elevated temperature and under high pressure yielded a mixture of *cis*- and *trans*-decahydroisoquinolines, and comparing his result with our experiment mentioned above, it is surprising that *cis*-decahydro derivatives were exclusively produced on hydrogenation of I and its O-methyl derivative (VII) under similar reaction condition.

Physicochemical data of two isomeric 4-hydroxy-*cis*-decahydroisoquinolines (IIIa[1]: 4β-OH; IIIb: 4α-OH) and their N-methyl derivatives (IXa and IXb) are listed in Table I. It is well known that half-band width of the signal of the axial proton adjacent to a hydroxyl group is more than about 15 cps and half-band width of the equatorial proton is less than 8 cps in nuclear magnetic resonance (NMR) spectra.[6,7] It is evident from Table I that each hydroxyl group in the compounds of a-series (IIIa and IXa)[1] or b-series (IIIb and IXb) appears to occupy mainly equatorial position.

Taking into consideration of ring conversion in a conformational equilibrium as shown in Chart 2, the following discussion will be delineated that the intramolecular hydrogen bond-

5) B. Witkop, *J. Am. Chem. Soc.*, **71**, 2559 (1949).
6) R.U. Lemiux, R.K. Kullnig, H.J. Bernstein, and W.G. Scheider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).
7) Y. Kawazoe, Y. Sato, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 328 (1963).

Table I. Physicochmical Data of Isomeric *cis*-Decahydro-basic Alcohols

	Free base mp (°C)	Methiodide mp (°C)	pK_a'[a] (20°)	NMR -NCH_3 (τ)	NMR >CHOH (τ)	NMR W/2 of >CHOH (cps)
IIIa[1]	136	—	10.20	—	6.39, broad	14
IXa[1]	oil	242	9.11	7.75	6.32, broad	12
IIIb	162	—	9.68	—	6.32, broad	17
IXb	65	252	8.82	7.71	6.31, broad	16

a) pK_a' values were measured using H_2O as solvent.

Table II. Infrared Spectral Data of Two Isomeric 4-Hydroxy-*cis*-2-methyldecahydroisoquinolines and 4-Hydroxypiperidine in Tetrachloroethylene

Compound	Free OH (cm^{-1})	Bonded OH (cm^{-1})	% of free OH
cis-trans (IIIa)	3624	3531	56
cis-cis (IIIb)	3624	3531	84
4-Hydroxypiperidine	3622	—	100

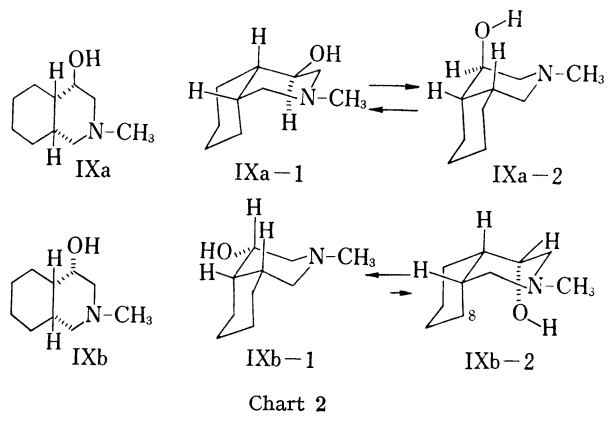


Chart 2

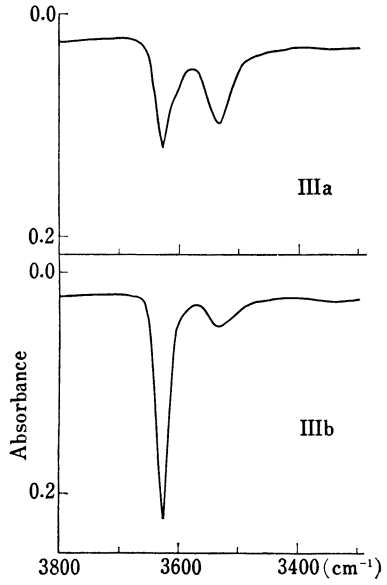


Fig. 2. IR Spectra of 4β-and 4α-Hydroxy-2-methyl-*cis*-decahydroisoquinolines (IIIa and IIIb)

concentration: IIIa, 2.7×10^{-3} mole/liter
IIIb, 3.1×10^{-3} mole/liter

ing between the hydroxyl group and the ring nitrogen atom should be present to the same extent in IXa-2 and IXb-2, if one assumes the compounds of a-series exist in the *cis-trans* configuration and the others (b-series) *cis-cis* form. However, 1,3-diaxial interaction between 4-OH and 8-CH_2 in IXb-2[8] may be employed to diminish the stabilization of IXb-2 based on hydrogen bonding and it will be quite rational that the equilibrium seems to be displaced in favor of the form IXb-1.

In order to confirm validity of the assumption, the infrared (IR) spectral study in dilute solution was undertaken. The solutions of *cis-trans*- and *cis-cis*-4-hydroxydecahydroisoquinolines in tetrachloroethylene at about 0.003 M concentration were measured, using 2 cm IR-grade quartz cells. At the dilution method used, no intermolecular hydrogen bonding is evident and the N-H absorption is clearly revealed in the 3350 cm^{-1} region (Fig. 2). The calculated percentage of free OH was obtained from the integrated intensity of the free OH

8) E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc. New York, N.Y., 1962, p. 237.

stretching bands relative to that of 4-hydroxypiperidine as the 100% free OH model.[9] The pertinent data and results are summarized in Table II.

From the data in Table II, it seems to be reasonable that the configuration of IIIa is the *cis-trans* form and that of IIIb is *cis-cis*.

In agreement with this assignment, pKa′ of IIIa is larger than that of IIIb (Δ pKa′ 0.52) as shown in Table I and it is generally accepted that hydrogen bonding between the OH group and the nitrogen atom increases basicity.[10] Further, it was reported that catalytic hydrogenation of naphthol and tetralol over platinum catalyst gives *cis-cis* alcohols predominantly[11] and the experimental result which only IIIb was obtained by a similar method is in accord with the above-mentioned assignment.

Experimental

All melting and boiling points are uncorrected. IR spectra were taken on Shimadzu IR-spectrophotometer, except the dilute solution spectra were recorded on a Perkin Elmer Model 521 and NMR spectra, on Varian A-60A Analytical spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal reference.

Hydrogenation of 4-Hydroxy-benzene-tetrahydroisoquinoline (II) over Platinum Oxide——The tetrahydroisoquinolinol(II) (1 g) in AcOH (60 ml) was catalytically hydrogenated over $PtO_2 \cdot 2H_2O$ (0.67 g) at room temperature and under atmospheric pressure for 32 hr. An amount of absorption of hydrogen was 700 ml. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. To the residual oil was added 15% NaOH solution and the mixture was extracted with ether. The ethereal layer was shaken with saturated NaCl solution and dried on Na_2SO_4. Evaporation of the solvent gave crystalline mass, which was recrystallized from iso-Pr_2O to form colorless needles, mp 162—163°. Yield, 0.147 g (13.5%). *Anal.* Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.76; H, 10.78; N, 9.06. NMR τ: 6.32 (1H, broad, >CHOH, $W/2=17$ cps) p$K_a'=9.68$. Picrate, yellow needles, mp 149—151° (recrystallized from MeOH). Picrolonate, long yellow prisms, mp 251—254° (recrystallized from EtOH).

Evaporation of the mother liquor of the above recrystallization gave colorless oil, bp 40—45°/3 mmHg. Yield, 0.8 g (80%). The oil was found to be *cis*-decahydroisoquinoline (IV) by mixed melting point determination of the picrate, mp 149—151°, with the authentic sample.

4-Hydroxy-2-methyl-*cis*-decahydroisoquinoline (IXb)——A mixture of IIIb (0.15 g), 36% formalin (0.3 ml), 85% formic acid (0.081 ml) and sodium formate (0.24 g) was heated at 100° for 2 hr and then at 120° for 1 hr. After being cooled, the mixture was basified with 15% NaOH and shaken with ether. The ethereal layer was washed with saturated NaCl solution, dried on Na_2SO_4 and evaporated. The residual oil soon solidified and was recrystallized from ether to give colorless prisms, mp 63—65°. Yield, 0.12 g (73%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3625 (OH), 2782 (N-CH_3). NMR τ: 6.31 (1H, broad, >CHOH, $W/2=16$ cps), 7.71 (3H, singlet, N-CH_3). p$K_a'=8.82$. Picrate, yellow prisms, mp 167—168° (recrystallized from MeOH). Methiodide, colorless prisms, mp 252—254° (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.

High Pressure-Hydrogenation of 4-Hydroxyisoquinoline (I)——A solution of I(5.0 g) in MeOH (100 ml) was catalytically hydrogenated over Raney Ni(prepared from 5.0 g of the alloy) at 150—160° and 150—160 kg/cm² for 9 hr. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to afford brown oily residue, which was dissolved in ether. The ethereal layer was shaken with 30% NaOH and CO_2 gas was bubbled into the alkaline solution. The precipitated phenol was collected by filtration and recrystallized from MeOH to form colorless flakes (0.6 g), mp 194—196°, which was found to be identical with II by mixed melting point determination with the authentic sample. The ethereal layer, separated from the NaOH solution, was washed with saturated NaCl solution, dried on Na_2SO_4 and evaporated. On cooling, the residual oil solidified and recrystallized from iso-Pr_2O to form colorless needles (0.4 g, 8%), mp 146—147°, which seemed to be a mixture of stereoisomers of 4-hydroxydecahydroisoquinoline by TLC. *Anal.* Calcd. for $C_9H_{17}ON$: C, 69.62; H, 11.04; N, 9.02. Found: C, 69.42; H, 10.87; N, 9.26. Picrolonate, mp 249—252°, which was identical with the authentic sample prepared from the *cis*-alcoholic base (IIIb). Distillation of the oil (3.6 g) separated from the crystalline base (III) resulted in two fractions, boiling at 55—60° and 84—100°/4 mmHg. The low-boiling fraction on treating with picric acid in MeOH gave a mixture of two picrates, mp 147—151° and mp 202—205°, which were separated by fractional recrystallization from MeOH. They were found to be identical with picrates of known *cis*-decahydroisoquinoline (IV) and *cis*-2-methyldecahydroisoquinoline (X), respectively, by mixed melting point determina-

9) H.S. Aaron, C.P. Ferguson, and C.P. Rader, *J. Am. Chem. Soc.*, **89**, 1431 (1967).
10) E.A. Braude and F.C. Nachod, "Determination of Organic Structures by Physical Methods," Academic Press Inc., Publishers, New York, N.Y., 1955, p. 654.
11) W. Hückel, *Ann.*, **441**, 1 (1925); *idem*, *ibid.*, **451**, 109 (1927).

tion. High-boiling fraction in the same manner formed a picrate as yellow prisms, mp 197—200°, which was identical with the picrate of Py-tetrahydroisoquinoline (VIII).

Benzoylation of 4-Hydroxy-*cis*-decahydroisoquinoline(III)——To a solution of the mixed *cis* alcohol(III), mp 147°, (0.5 g) and water (50 ml) was added benzoyl chloride (1.36 g) and 10% aqueous solution of NaOH (2.58 g) alternately under cooling and stirring to precipitate a brown oil, which was taken up with ether. The ethereal layer was washed with water, dried on Na_2SO_4 and evaporated to afford a colorless oil, which was rinsed in *n*-hexane. The resulting crystalline mass was recrystallized from EtOH to give 2-benzoyl-4-hydroxy-*cis*-decahydroisoquinoline(VI) as colorless prisms, mp 135—136°. *Anal.* Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.24; H, 8.38; N, 5.32. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620, 1280 (amide CO), 3560(OH).

The mother liquor, separated from recrystallization of the monobenzoate (VI), was concentrated and kept standing to give O,N-dibenzoate(V) of IIIb as colorless prisms, mp 159—160°(recrystallized from EtOH). *Anal.* Calcd. for $C_{23}H_{25}O_3N$: C, 76.00; H, 6.93; N, 3.85. Found: C, 75.96; H, 6.97; N, 3.86.

4-Methoxyisoquinoline (VII)——To a solution of 4-hydroxyisoquinoline (I) (5.0 g) in MeOH (500 ml) was added first an ethereal solution of CH_2N_2 prepared from N-nitrosomethylurea (50 g) and in order to complete the reaction, an additional amount of CH_2N_2 prepared from N-nitrosomethylurea (25 g) was necessary. The mixture was kept standing at room temperature for 3 days and treated with a small amount of AcOH to decompose excess CH_2N_2. After removal of the solvent, to the residue was added 20% NaOH solution. The alkali-insoluble portion was dissolved into ether and the ethereal solution was shaken with water, dried on Na_2SO_4 and evaporated. Residual oil distilled at 130—132°/4 mmHg to form on cooling crystalline mass, which was recrystallized from ether to afford colorless prisms, mp 72—73°. *Anal.* Calcd. for $C_{10}H_9ON$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.58; H, 5.69; N, 8.86.

4-Methoxy-benzene-tetrahydroisoquinoline (XI)——i) II (2.65 g) in MeOH (150 ml) was methylated with CH_2N_2–ether in the similar manner as the above method. The alkali-insoluble oil distilled at 104—105°/4 mmHg to form colorless oil. Yield, 1.5 g(52 %). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2870, 1580, 1490, 1300, 1100. Picrate, yellow needles, mp 156—157° (recrystallized from MeOH). *Anal.* Calcd. for $C_{16}H_{16}O_8N_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.82; H, 4.18; N, 14.42. Hydrochloride, colorless prisms, mp 195—197° (recrystallized from acetone).

ii) VII (3.0 g) in AcOH (100 ml) was catalytically hydrogenated over PtO_2(0.3 g) at room temperature and under atmospheric pressure. After absorption of H_2 ceased, the reaction mixture was treated as usual to give the expected base (XI), bp 104—105°/4 mmHg. Yield, 2.0 g(70 %). This was found to be identical with XI at i) by comparison of IR spectrum and mixed melting point determination of picrates.

High Pressure-Hydrogenation of 4-Methoxyisoquinoline (VII)——A solution of VII (4.65 g) in MeOH (100 ml) was catalytically hydrogenated over Raney Ni(prepared from 5 g of the alloy) at 150—160° and 133—163 kg/cm^2 for 10 hr. When 77% of theoretical amount of H_2 was taken up, the reaction was stopped. After treatment as usual, the resulting oil distilled into following 3 fractions. bp 80—84°/11 mmHg (0.71 g), bp 85—130°/11 mmHg (1.45 g), and bp 132—136°/11 mmHg (1.44 g)

The First Fraction: The fraction was benzoylated in usual manner using benzoyl chloride (0.5 g) and pyridine (0.6 ml). The reaction mixture was poured into 15% HCl under cooling and resulting oil was extracted with ether. The ethereal layer was washed with water, dried on Na_2SO_4 and evaporated. Reduced distillation of the resulting oil gave a colorless oily benzoyl derivative, bp 165—170°/5 mmHg, a part of which was hydrolyzed by heating with HCl–EtOH to afford on basification oily *cis*-decahydroisoquinoline (IV), which was identified by mixed melting point determination of its picrate, mp 150—152,° with an authentic sample. The foregoing aqueous acidic solution, which was soluble in 15% HCl as above-mentioned, was basified with NaOH and shaken with ether. The etherel layer was washed with water, dried on Na_2SO_4 and evaporated *in vacuo* to remove thoroughly remaining pyridine. The ether-extract, on treating with picric acid in MeOH, converted to the picrate, mp 199—202,° which was found to be identical with the one of *cis*-2-methyldecahydroisoquinoline(X) by mixed melting point determination.

The 2 nd Fraction: Treatment of the fraction with ether containing HCl gas produced an oil, which was treated with a small amount of acetone to be solidified. The resulting mass was recrystallized from acetone repeatedly to form colorless needles, mp 191—193,° which was found to be identical with VIII hydrochloride by mixed melting point determination. The mother liquor of above-mentioned recrystallization was collected, concentrated and moreover recrystallized from acetone to form colorless prisms, mp 195—197°, which was found to be identical with XI hydrochloride by mixed melting point determinatlon.

The 3 rd Fraction: Into the ethereal solution of the fraction was bubbled dry HCl gas. The resulting crystalline mass was recrystallized from acetone to form colorless prisms, mp 195—197°, which was found to be identical with XI hydrochloride.

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