CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 18, No. 11 November 1970

Regular Articles

[Chem. Pharm. Bull.
18(11)2141—2145(1970)] UDC 547.833.3.02.07

Stereochemistry of Decahydroisoquinolines and Related Compounds. VIII.[1] Syntheses of *trans*-4-Hydroxy-2-methyldecahydroisoquinolines[2]

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(Received December 22, 1969)

Two isomers of *trans*-4-hydroxy-2-methyldecahydroisoquinoline were prepared and the conformation of these compounds was discussed.

In the earlier papers, the authors have reported the syntheses of decahydroisoquinolinols having a hydroxyl group at C_5, C_6, C_7, and C_8 position and clarified their steric configurations including conformations. At this time, syntheses of decahydro-bases of isoquinolines having a hydroxyl group at piperidine ring are undertaken and they succeeded in preparations of four isomers of 4-hydroxy-2-methyldecahydroisoquinolines (each two isomers belong to *trans* and *cis* ring-fused compounds). In this paper, it deals with preparations and discussion of steric configuration concerning a pair of the *trans* ring-fused decahydroisoquinolinols.

trans-1-Carbomethoxycyclohexane-2-carboxylic acid chloride (III), obtained from *trans*-hexahydrophthalic acid anhydride (I) according to the method reported by Nazarov,[4] was treated with diazomethane in ether, followed by decomposition of resulted diazoketone with dry hydrogen chloride to afford ω-chloromethyl ketone (IV), mp 65—66° in 89% yield. Phthalimidation of IV with potassium phthalimide in N,N-dimethylformamide (DMF) and successive hydrolysis of resulted ω-phthalimide (V), mp 122° in boiling solution of hydrochloric acid–acetic acid afforded the corresponding ω-aminoketone hydrochloride (VI) as colorless prisms, mp 208° (decomp.) in 67.2% overall-yield. Esterification of VI with ethanol and dry hydrogen chloride in usual manner gave an ester hydrochloride (VII), mp 171° as colorless needles in 88.8% yield. Then catalytic hydrogenation of VII over platinum oxide in ethanol at room temperature and under atmospheric pressure afforded corresponding alcoholic intermediate (VIII) in oily form which, without purification, was dissolved into a small amount of

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[1] Part VII: S. Kimoto, M. Okamoto, T. Mizumoto and Y. Fujiwara, *Chem. Pharm. Bull.* (Tokyo), **16**, 2390 (1968).

[2] A part of this work was presented at the Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968.

[3] Location: *Nakauchi-cho, Yamashina-Misasagi, Higashiyama-ku, Kyoto.*

[4] I.N. Nazarov and V.F. Kucherov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk,* **1954**, 329; *Chem. Abstr.*, **49**, 5328 (1955).

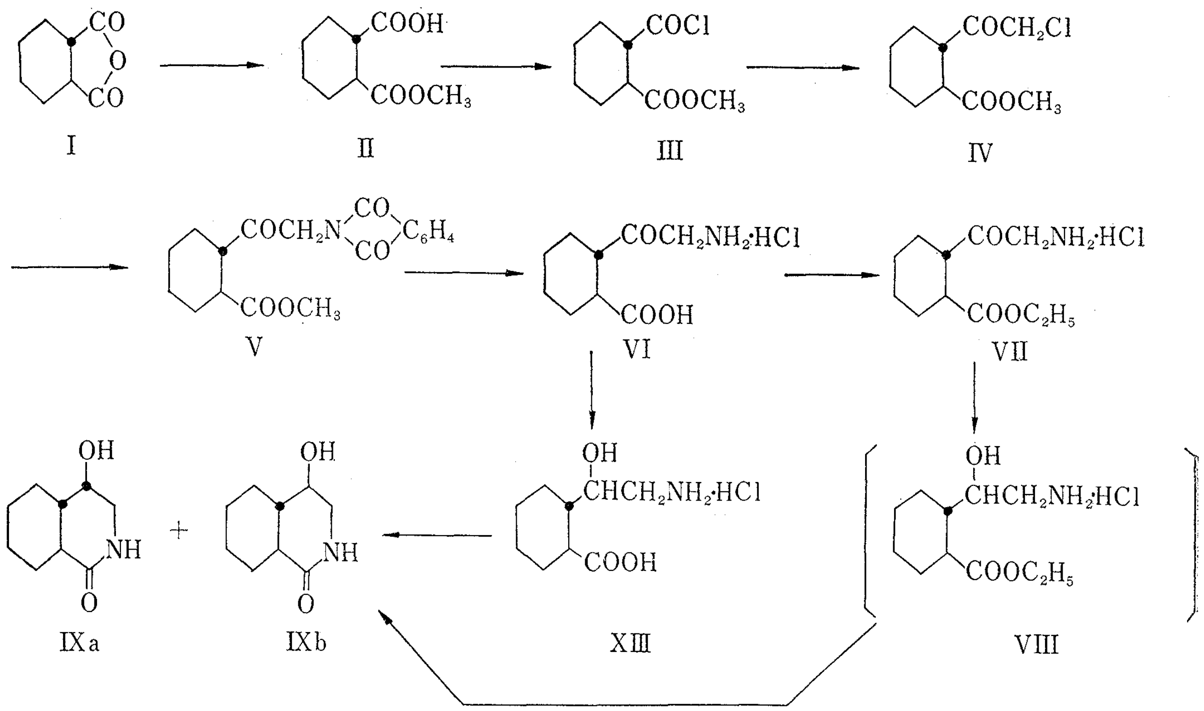

Chart 1

water and basified with conc. sodium hydroxide solution to result in crystalline precipitate and it was recrystallized from methanol to give a lactam (IXa) as colorless prisms, mp 241°, in 76% yield. The lactam (IXa) was slightly soluble in sodium hydroxide solution and dil. hydrochloric acid, 6,7,8,8a-octahydro-1(2*H*)isoquinolinone (IXa) on the basis of following data, that is, IXa showed satisfactory elementary analysis for $C_9H_{15}O_2N$ and in mass spectrum, parent peak appeared at 169 *m/e* and also in infrared spectrum (IR), broad NH band and amide band appeared at 3410 and 1640 cm^{-1}, respectively.

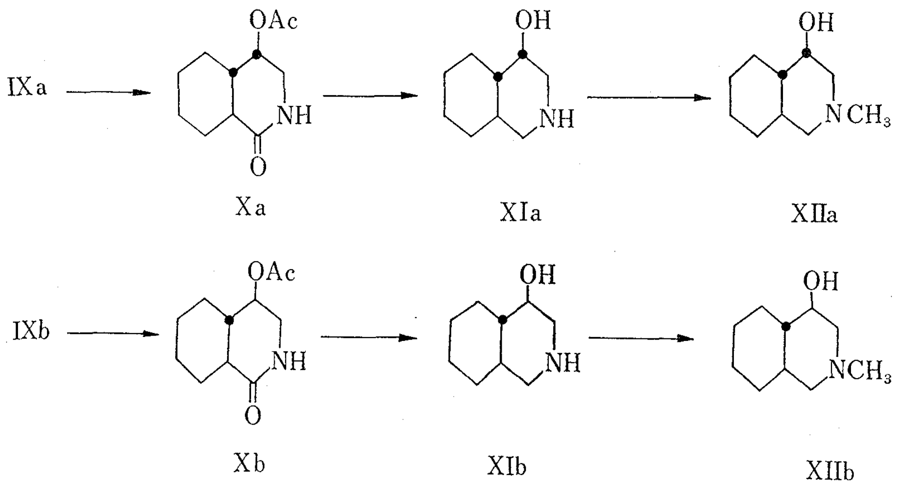

Chart 2

Moreover, concentration of methanolic mother liquor on recrystallization of IXa gave clearly different crystalline form of a compound (IXb), mp 196—201°, from IXa. As it was very difficult to separate IXb in pure state from a mixture of IXa and IXb, crude IXb was converted to the corresponding acetate (Xb) and successively to an expected 4-decahydroisoquinolinol (XIb) by lithium aluminium hydride reduction as schemed in Chart 2, and XIb, mp 167°, could be separated in pure state by recrystallization of crude XIb from ether using difference of solubilities between XIb and XIa, the latter of which was prepared from the corresponding acetate (Xa), mp 180°, in the same manner as in the case of XIb. Further, catalytic hydrogenation of the keto-base hydrochloride (VI) and subsequent treatment of resulting alcoholic base hydrochloride (XIII), mp 169°, with excess of diazomethane afforded the lactam (IXa), mp 241°, and this lactam was also formed by heating an amino acid, which was obtained with neutralization of XIII with sodium carbonate, on free flame.

Table I. Physicochemical Data of Four Isomeric Decahydro-basic Alcohols

	Free base mp (°C)	Methiodide mp (°C)	$pK_a'^{a)}$ (20°)	NMR		IR (cm^{-1})
				$-NC\underline{H}_3$ (τ)	$\rangle C\underline{H}OH$ (τ)	
XIa	115	—	10.54	—	6.47, broad $W/2=6$ cps	3325, 1015, 995
XIIa	80	208	9.89	7.77 singlet	6.45, broad $W/2=6$ cps	3450, 1004, 960
XIb	167	—	9.66	—	6.67, broad $W/2=22$ cps	3550, 1000
XIIb	64	241	8.66	7.75 singlet	6.67, broad $W/2=22$ cps	3600, 1015

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

On the other hand, J.W. Wilson, *et al.*[5] and H. Baer, *et al.*[6] reported that 1-amino-1-(3-phthalidyl)alkanes could be rearranged to give substituted 4-hydroxy-1,2,3,4-tetrahydroisoquinolones on heating with 40% sodium hydroxide solution. However, it could not be clarified if the above mentioned cyclization-reaction (VIII or XIII to IXa) would depend upon the same mechanism as in the case of J.W. Wilson, *et al.* and H. Baer, *et al.* or not. Decahydro-base (XIa) melted at 115°, the hydrochloride mp 188°, the picrate mp 206° and the other isomeric decahydro-base (XIb) melted at 167°. XIa and XIb on N-methylation with formic acid-formalin converted into two isomers of the desired compounds, that is, *trans*-2-methyl-4-hydroxydecahydroisoquinolines (XIIa and XIIb), respectively. From the physicochemical data of the isomeric compounds (in Table I), the following facts are summarized.

i) pK_a' values of a-series (XIa and XIIa) are larger than those of the corresponding b-series (XIb and XIIb) and therefore the hydroxyl group of XIa may be assumed to be of α-type and axial disposition (formation of an intramolecular hydrogen bonding between OH group and nitrogen atom is possible). ii) In IR spectra, stretching vibration bands of free OH in b-series appear near 3600 cm^{-1}, while those of strongly bonded OH in a-series appear at 3300—3400 cm^{-1}. iii) In nuclear magnetic resonance (NMR) spectra, signals of protons attached to secondary carbon atoms in a-series shift strongly to lower field than those in b-series and half-widths of the protons are 6 cps in a-series and 22 cps in b-series.

From these evidences mentioned above, it seems reasonable to assume that hydroxyl groups of XIa and XIIa in a-series are of α-type and must be axial, while those of XIb and XIIb in b-series are of β-type and have equatorial conformation.

Experimental

All melting and boiling points are uncorrected. IR spectra were taken on Shimadzu IR-spectrophotometer and NMR spectra, on Varian A-60A Analytical Spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal reference.

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[5] J.W. Wilson, E.L. Anderson and G.E. Ullyit, *J. Org. Chem.*, **16**, 800 (1951).
[6] H.H. Baer and B. Achmatowicz, *J. Org. Chem.*, **29**, 3180 (1964).

Methyl *trans*-2-Chloroacetylcyclohexane-1-carboxylate (IV)——Into a stirred and ice-cooled etherial solution containing excess CH_2N_2 was dropped a solution of *trans*-1-carbomethoxycyclohexane-2-carboxylic acid chloride (III) (12.4 g) in ether and the mixture was kept standing at room temperature overnight, then saturated with dry HCl under cooling. After gas evolution ceased, the solvent was removed. The brown residual oil was distilled at 100° (6 mmHg) to give solid mass when cooled, which was recrystallized from ether–petr. ether to give colorless prisms, mp 65—66°. Yield, 11.8 g (88.9%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720 (CO). *Anal.* Calcd. for $C_{10}H_{15}O_3Cl$: C, 54.91; H, 6.91. Found: C, 54.50; H, 6.98.

Methyl *trans*-2-Phthalimidoacetylcyclohexane-1-carboxylate (V)——A mixture of the ester (IV) (4.5 g), potassium phthalimide (4.0 g) and DMF (20 ml) was heated at 60—70° for 1 hr. To the dark brown reaction mixture was added water and extracted with $CHCl_3$, the $CHCl_3$ solution was washed with H_2O, 5% KOH solution and dried over Na_2SO_4. After removal of $CHCl_3$, the residue was treated with hot EtOH to form colorless prisms, which were recrystallized from EtOH to give prisms, mp 122—123°. Yield, 5.5 g (82.0%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1770 (five-membered ring imide CO), 1720 (ester CO). *Anal.* Calcd. for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.87; H, 5.87; N, 4.11.

***trans*-2-Aminoacetylcyclohexane-1-carboxylic Acid Hydrochloride (VI)**——A solution of the ester (V) (10.0 g) in AcOH–conc. HCl (1:1) (170 ml) was refluxed for 10 hr. After removal of the solvent *in vacuo*, water (100 ml) was added to the residual mass, and on filtration the filtrate was evaporated to dryness to give colorless plates, mp 208—209° (decomp.) (recrystallized from EtOH–ether). Yield, 5.5 g (82.0%). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1724 (COOH), 1715 (CO). *Anal.* Calcd. for $C_9H_{15}O_3N \cdot HCl$: C, 48.76; H, 7.28; N, 6.32. Found: C, 48.80; H, 7.34; N, 6.30.

Ethyl *trans*-2-Aminoacetylcyclohexane-1-carboxylate Hydrochloride (VII)——A solution of the carboxylic acid (VI) (2.0 g) in anhydr. EtOH (70 ml) was saturated with dry HCl and kept standing at room temperature for 2 days. After removal of the solvent *in vacuo*, the residual mass was recrystallized from iso-PrOH to give colorless needles, mp 169—171°. Yield, 2.0 g (88.8%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3420 (NH), 1740 (CO). *Anal.* Calcd. for $C_{11}H_{19}O_3N \cdot HCl$: C, 52.91; H, 8.07; N, 5.61. Found: C, 53.27; H, 8.20; N, 5.62.

***trans*-2-(1-Hydroxy-2-aminoethyl)cyclohexane-1-carboxylic Acid Hydrochloride (XIII)**——The hydrochloride (VI) (1.5 g) in 95% EtOH (40 ml) was hydrogenated over $PtO_2 \cdot 2H_2O$ (300 mg) at room temperature and atmospheric pressure. After theoretical amount of H_2 was absorbed, reduced evaporation of the filtered reaction mixture formed white crystals, which were recrystallized from EtOH–ether to give colorless needles, mp 169° (decomp.). Yield, 1.3 g (86.3%). *Anal.* Calcd. for $C_9H_{17}O_3N \cdot HCl$: C, 48.32; H, 8.11; N, 6.26. Found: C, 48.20; H, 8.10; N, 6.25.

***trans*-4-Hydroxy-3,4,4a,5,6,7,8,8a-octahydro-1(2*H*)-isoquinolinones (IXa and IXb)**——i) A solution of the hydrochloride (VII) (2.5 g) in 95% EtOH (50 ml) was hydrogenated catalytically over $PtO_2 \cdot 2H_2O$ (400 mg) at room temperature and atmospheric pressure. After absorption of theoretical amount of H_2 ceased, the catalyst was filtered off and the filtrate was evaporated *in vacuo* to dryness. The residual oil (VIII) was dissolved in a small amount of H_2O and the solution was basified with conc. NaOH. Crystals formed were collected by suction and recrystallized from MeOH to give colorless prisms (IXa: 1.3 g, 76.3%), mp 241—243°, which were slightly soluble in water, conc. NaOH, 10% Na_2CO_3 and dil. HCl, but soluble in conc. HCl. *Anal.* Calcd. for $C_9H_{15}O_2N$: C, 63.88; H, 8.94; N, 8.28. Found: C, 64.11; H, 9.11; N, 8.43. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3410 (hydrogen bonded band), 1640 (amide). NMR τ: 6.0 (1H, broad, $\rangle C\underline{H}\text{–}OH$, $W/2 = 6$ cps). Mass number, 169 *m/e*.

The mother liquor of above mentioned recrystallization gave another prisms on concentration, mp 196—201° (IXb), which was difficult to purify and without purification, used as starting material to XIb.

ii) The hydrochloride (XIII) (0.1 g) in MeOH (10 ml) was esterified with excess CH_2N_2 in ether. Treated in usual manner, colorless prisms, mp 240—242°, was obtained. It was identical with above mentioned sample of IXa. Yield, 55 mg (72.6%).

iii) Into a solution of the hydrochloride (XIII) (0.1 g) in a small amount of water was added 10% Na_2CO_3, then crystals formed were collected by suction and heated on free flame, the crystals were melted at 170—180° for several minutes, cooled, and followed by recrystallization from MeOH to afford colorless prisms, mp 240—242°, which were identical with authentic sample of IXa. Yield, 45 mg (59.4%).

***trans*-4α-Acetoxyoctahydro-1(2*H*)-isoquinolinone (Xa)**——A solution of the lactam (IXa) (1.0 g), Ac_2O (3.0 g) and BF_3–ether (1.0 ml) was kept standing at room temperature overnight, and added with a small amount of water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and evaporated to dryness to form crystalline mass, which was recrystallized from $CHCl_3$–ether to give colorless needles, mp 179—180°. Yield, 1.2 g (95.6%). *Anal.* Calcd. for $C_{11}H_{17}O_3N$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.68; H, 8.33; N, 6.49. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3485 (NH), 1760 (CO), 1680 (lactam). NMR τ: 7.90 (3H, singlet, $COC\underline{H}_3$), 6.52 (2H, triplet, $NHC\underline{H}_2CH\langle$, $J = 2$ cps), 4.95 (1H, broad, $\rangle C\underline{H}OCOCH_3$, $W/2 = 6$ cps), 3.45 (1H, broad, $N\underline{H}CO$).

***trans*-4αa-Hydroxydecahydroisoquinoline (XIa)**——Into a stirred suspension of $LiAlH_4$ (1.3 g) in tetrahydrofuran (THF) (50 ml) was added dropwise a solution of lactam O-acetate (Xa) (1.5 g) in THF (80 ml) and the mixture was warmed at 50—55° for 50 hr. To the reaction mixture was added a small amount of water, and after removal of the solvent of the filtered solution *in vacuo*, residual mass was rinsed with ether and dil. HCl. The aqueous solution was basified with conc. NaOH and extracted with ether. Etherial solution was dried over Na_2SO_4 and evaporated to dryness to form crystalline mass, which was recrystallized from ether to afford colorless prisms, mp 113—115°. Yield, 600 mg (54.5%). *Anal.* Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.94; H, 11.31; N, 9.20. Hydrochloride; mp 188—189° (recrystallized from EtOH–ether). Picrate, mp 203—206° (recrystallized from MeOH–ether). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 3325 (bonded OH), 1015 (C–O), 995. NMR τ: 6.47 (1H, broad, $\rangle$C$\underline{\mathrm{H}}$OH, $W/2=6$ cps), p$K_a{}'=10.54$.

***trans*-4βe-Hydroxydecahydroisoquinoline (XIb)**——According to the similar manner as mentioned above, this was prepared from crude IXb *via* corresponding O-acetate. Colorless needles, mp 165—167° (recrystallized from ether). *Anal.* Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.28; H, 11.15; N, 9.37. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 3550 (OH), 1000 (C–O). NMR τ: 6.67 (1H, broad, $\rangle$C$\underline{\mathrm{H}}$OH, $W/2=22$ cps). p$K_a{}'=9.66$.

***trans*-2-Methyl-4-αa-hydroxydecahydroisoquinoline (XIIa)**——A solution of XIa (0.2 g), 85% HCOOH (0.12 ml), 36% formalin (0.4 ml) and AcONa (0.32 g) was warmed at 60—70° for 2 hr and then heated at 110° for 15 min. The reaction mixture was basified with NaOH and extracted with ether. The etherial solution was dried over Na_2SO_4 and evaporated to dryness to form crystals, which were recrystallized from anhydr. ether to afford colorless prisms, mp 80—81°. Yield, 200 mg (91.7%). *Anal.* Calcd. for $C_{10}H_{19}ON$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.74; H, 11.79; N, 8.05. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 3450 (bonded, OH), 1004 (C–O), 960. NMR τ: 7.77 (3H, singlet, NC$\underline{\mathrm{H}}_3$), 6.45 (1H, broad, $\rangle$C$\underline{\mathrm{H}}$OH, $W/2=6$ cps). p$K_a{}'=9.89$. Picrate; yellow prisms, mp 166—167° (recrystallized from MeOH–ether). Methiodide; colorless needles, mp 208—209° (recrystallized from EtOH). *Anal.* Calcd. for $C_{10}H_{19}ON \cdot CH_3I$: C, 42.45; H, 7.13; N, 4.50. Found: C, 42.36; H, 7.07; N, 4.44.

***trans*-2-Methyl-4βe-hydroxydecahydroisoquinoline (XIIb)**——According to the similar manner as mentioned above, this was prepared from XIb. Colorless prisms, mp 63—64° (recrystallized from petr. ether (bp 40—50°)). *Anal.* Calcd. for $C_{10}H_{19}ON$: C, 70.96; H, 11.32. Found: C, 71.16; H, 11.39. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 3600 (free, OH), 1015 (C–O). NMR τ: 7.74 (3H, singlet, NC$\underline{\mathrm{H}}_3$), 6.67 (1H, broad, $\rangle$C$\underline{\mathrm{H}}$OH, $W/2=22$ cps). p$K_a{}'=8.66$. Methiodide, mp 239—241°.

Acknowledgement The authors wish to express their deep gratitude to the members of Analysis Room of Nippon Shinyaku Co. Ltd. for elementary analyses and many thanks to Mr. Y. Fujiwara for measurement of NMR spectra.