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On the Syntheses of 2-Methyl-7-decahydroisoquinolinols starting from Diethyl 4-Hydroxyhexahydrohomophthalate and Their Configurational Analysis on Their Structure

In 1963, the authors reported that high temperature-high pressure hydrogenation of 7-isoquinolinol and 2-methyl-1,2,3,4-tetrahydro-7-isoquinolinol gave two titled compounds possessing *cis* steric configuration at the ring juncture.[1] In the same year, Durand, *et al.*[2] reported in their communication synthesis of only one (Xd) of the *trans* isomers possessing an equatorial hydroxyl group by Birch reduction of 2,3,4,4a,5,6-hexahydro-7(1*H*)-isoquinolinone(I) with lithium in liquid ammonia but unfortunately it was not clear in details. The authors reinvestigated the Birch reduction of I according to the Durand method and the similar result was obtained. On the other hand, synthetic

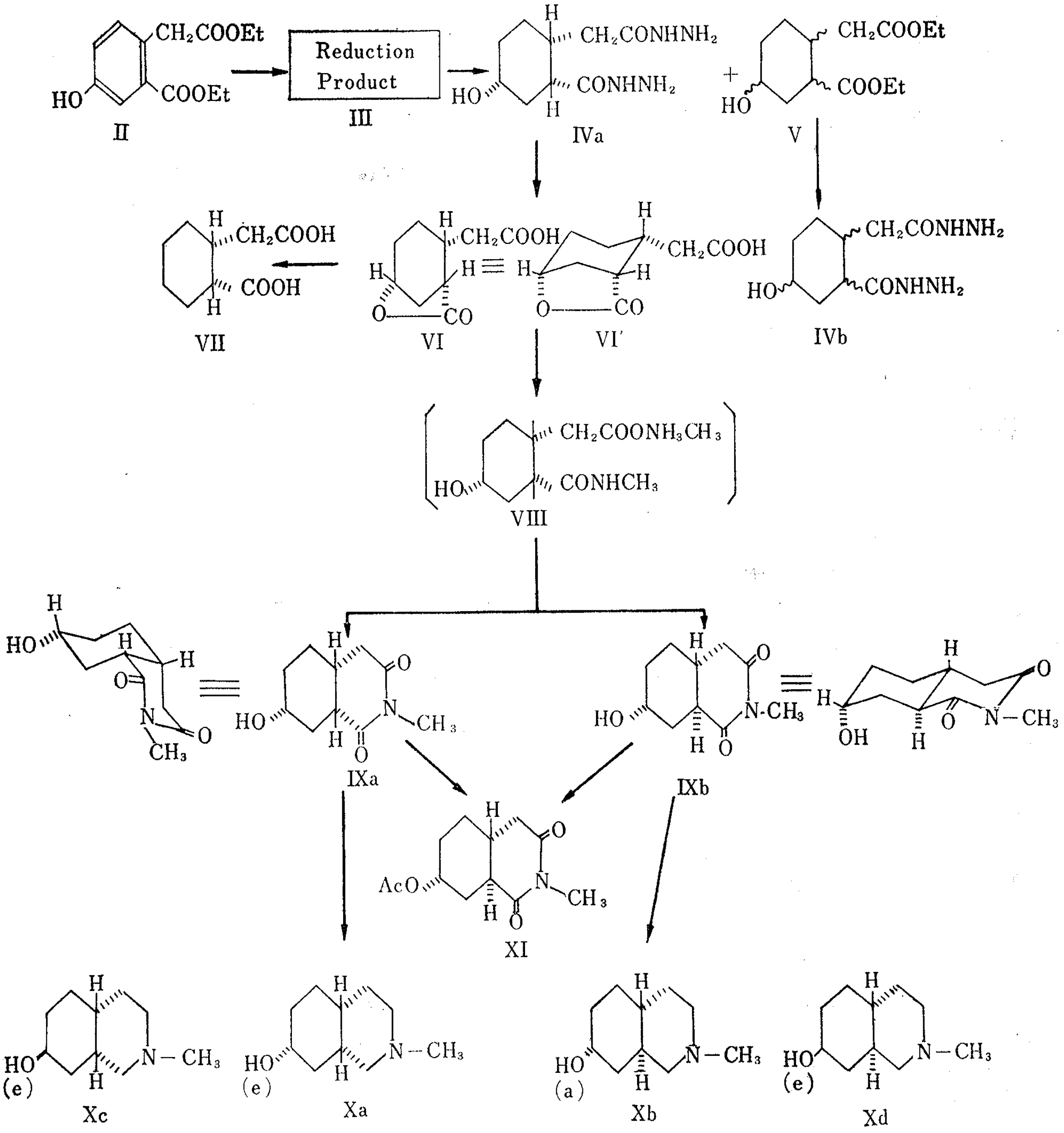

Chart 1.

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[1] M. Okamoto, M. Yamada: This Bulletin, **11**, 554 (1963).
[2] S. Durand, R.C. Moreau: Cr., **257**, 2673 (1963).

trials of the titled compounds by ring closure-reaction of 4-hydroxyhexahydro homophthalic acid derivatives possessing definite steric configuration at C_1 and C_2 position have been undertaken in our laboratory.

High temperature-high pressure hydrogenation of diethyl ester (Ⅱ) (m.p. 70°) of 4-hydroxyhomophthalic acid over Raney nickel afforded an oily mixture of neutral reduction products (Ⅲ) which is suggested to have γ-lactone and ester groups from the fact that two absorption bands were observed at 1770 cm^{-1} and 1710 cm^{-1} in the infrared spectrum. A reaction of Ⅲ with hydrazine hydrate in ethanol at room temperature gave a hydrazide (Ⅳa), m.p. 198~200°, and unreacted diester (Ⅴ), which showed no lactone band in the infrared spectrum, but afforded an isomeric dihydrazide (Ⅳb), m.p. 250~252°, on treatment with hydrazine hydrate in ethanol at 110° in a sealed tube. Hydrolysis of the former dihydrazide (Ⅳa) with boiling diluted hydrochloric acid gave a lactonic carboxylic acid (Ⅵ), m.p. 117~120°, IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1770 (γ-lactone). For the purpose of confirmation of the steric configuration at C_1 and C_2 positions of Ⅵ, hydrogenolysis of Ⅵ over platinum oxide in acetic acid solution containing a little quantity of perhydrochloric acid afforded *cis*-hexahydrohomophthalic acid (Ⅶ), m.p. 146°, which was identical with the authentic sample. Therefore, it is clarified that Ⅵ possesses all *cis* configuration formulated as Ⅵ′. The lactonic carboxylic acid (Ⅵ) was reacted with methylamine in methanolic solution at room temperature for a few days and the resulted solution was evaporated to give oily substance (Ⅷ). Ring closure-reaction of Ⅷ by heating at 160° and following distillation afforded, after separation by recrystallization from ether, two kinds of the imides (Ⅸa, Ⅸb) which melted at 115° and 129° in ratio of 1:2, respectively. On reduction of the former imide (Ⅸa) with lithium aluminum hydride was obtained one of *cis*-2-methyl-7-decahydroisoquinolinol (Xa) (methiodide, m.p. 266°; picrate, m.p. 154~156°) which was already reported[1)], and on similar reduction of the latter (Ⅸb) was obtained one of *trans*-2-methyl-7-decahydroisoquinolinol (Xb) (methiodide, m.p. 251~252°; picrate, m.p. 189~191°), which had been never known and the *trans* ring juncture of which was decided by conversion of the corresponding ketone to *trans*-2-methyl-decahydroisoquinoline. In view of the synthetical facts that the *cis* alcoholic base (Xa) and the *trans* alcoholic base (Xb) are obtained from the lactonic carboxylic acid (Ⅵ), the reasonable presumption to be drawn is that Ⅷ would result in Ⅸa with retention of configuration and Ⅸb with inversion of substituent at C_2 during the process of the ring closure. In order to certify the presumption it is thought advisable to investigate chemical correlation between the imide (Ⅸa) and the other (Ⅸb), and the following experiments give such a result as expected. Thus the imide (Ⅸa) 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, m.p. 114~116°, which was identical with O-acetylated imide (Ⅺ) derived from Ⅸb.

In alicyclic alcohols, it is well known that axial alcohols are more rapidly oxidized than equatorial ones with chromic acid[3)] and that the half-widths of the signals of the axial proton adjacent to hydroxyl groups are more than about 15 c.p.s. and those of the equatorial proton are less than about 8 c.p.s. in the nuclear magnetic resonance.[4~6)] Consequently, in the case of the *trans* pair (Xb, Xd), from the experimental data listed in Table I, it is clarified that Xb has an axial hydroxyl group and Xd has an equatorial one.

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3) J. Schrieber, A. Eschenmoser : Helv. Chim. Acta, **38**, 1529 (1955).
4) R.U. Lemieux, R.K. Kullnig, H.J. Bernstein, W.G. Schneider : J. Am. Chem. Soc., **80**, 6098 (1958).
5) Y. Kawazoe, Y. Sato, T. Okamoto, K. Tsuda : This Bulletin, **11**, 328 (1963).
6) C.A. Grob, H.R. Kiefer : Helv. Chim. Acta, **48**, 808 (1965).

Table I. Nuclear Magnetic Resonance Spectra and Rate Constants (K_4) of Chromic Acid Oxidation of 2-Methyl-7-decahydroisoquinolinols

	NMR Spectra[a]			K_4 ((m./L.)$^{-3}$min^{-1})[c]
	N-C$\underline{H}_3$ (τ)	=C$\underline{H}$OH (τ)	W/2 (c.p.s.)[b]	
Xa	7.75	6.48	16	0.96
Xc	7.78	6.26	16	0.85
Xb	7.82	5.96	7	2.15
Xd	7.78	6.50	16	0.51

a) Nuclear magnetic resonance spectra were determined on a Varian A 60 spectrophotometer with deuterochloroform as solvent and tetramethylsilane as internal reference.
b) Half-width of signals of protons of =C$\underline{H}$OH.
c) Rate constants were calculated from consumption value of dichromate ion at 350 mμ in ultraviolet spectra determined at 40°.

On the other hand, in the case of the *cis* pair (Xa, Xc), it is also shown that both Xa and Xc possess equatorial hydroxyl groups from the data in Table I. If an assumption is made that N-methyl group may be located in equatorial state as in the case of N-methylpiperidine,[7] the presence of the two conformers which have equatorial hydroxyl groups are possible on the examination of molecular models of these *cis* alcoholic bases. Therefore it is thought that if one of these bases is a β-equatorial alcohol, the other is an α-equatorial one.

But it seems reasonable to assume that if these bases are quaternized with methyl iodide, the quaternary base which has an α-equatorial hydroxyl group should be converted to a more thermodynamically stable form which has an α-axial hydroxyl group as a result of the well-known ring conversion in *cis* ring juncture systems, and in the case of the other quaternary base which has an β-equatorial hydroxyl group, such ring conversion should not take place. Thus in the spectrum of methiodide Xa the signal of the equatorial proton (the half-width, 7 c.p.s.) was observed at 5.95τ as expected, while in the spectrum of methiodide Xc no signals of protons could be seen in the lower field than 6.2τ and therefore the broad signal of the axial proton seems to be veiled in other signals.

This conclusion that Xa has an α-equatorial hydroxyl group and Xc has a β-equatorial one is well agreed with the result of the above mentioned stereoselective synthesis starting from the lactonic carboxylic acid (Ⅵ) which has all *cis*-configuration.

On the basis of these above mentioned evidences, it seems to be concluded that steric configurations of the four isomeric alcoholic bases (Xa～Xd) are determined.

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Kyoto College of Pharmacy,
Nakauchi-cho, Yamashina-Misasagi,
Higashiyama-ku, Kyoto

Shoshichiro Kimoto (木本正七郎)
Masao Okamoto (岡本正夫)
Takaaki Mizumoto (水本隆章)
Yasuhiro Fujiwara (藤原靖弘)

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