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132. **Shoshichiro Kimoto and Masao Okamoto:** Stereochemistry of Decahydroisoquinolines and Related Compounds. VI.[*1] Conformations of 2-Methyl -5-, -6-, -7-, and -8-decahydroisoquinolinols.[*2]

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For 2-methyldecahydroisoquinolinols having a hydroxyl group at C_5, C_6, C_7, and C_8 position (presence of sixteen isomers is considered theoretically possible), the authors have prepared all eight isomers having *trans* ring juncture and six isomers having *cis* ring juncture, lacking of one of *cis*-5-hydroxy isomers and one of *cis*-8-hydroxy isomers. Using chemical evidences, NMR and IR spectroscopy, pKa′ values and rates of chromic acid oxidation, conformations of these fourteen isomers of 2-methyldecahydroisoquinolinols are discussed in detail.

Previously, fourteen stereoisomers of 2-methyldecahydroisoquinolinols having a hydroxyl group at C_5, C_6, C_7, and C_8 positions, that is, three of the 5-isoquinolinols (two of *trans*- and one of *cis*-isomers[*4]), four of the 6-isoquinolinols (one pair of *trans*-isomers and *cis*-isomers), four of the 7-isoquinolinols (one pair of *trans*-isomers and *cis*-isomers) and three of the 8-isoquinolinols (two of *trans*- and one of *cis*-isomers) were already synthesized and steric configurations of their ring junctures were determined by chemical means of transformations of their isomers to the known *cis*- and *trans*-2-methyldecahydroisoquinolins.[*5,1)]

In this paper, it deals with discussion of steric configuration and conformation of the above mentioned fourteen isomeric alcohols prepared in our hands (although existence of sixteen isomers is theoretically considered except isomerism at the ring nitrogen atom in this case) by determining rates of chromic acid-oxidation, nuclear magnetic resonance spectroscopy (Abbr.: NMR), infrared spectroscopy (Abbr.: IR), pKa′ value and so on.

[*1] Part V. M. Okamoto: This Bulletin, 15, 168 (1967).

[*2] A large part of this work was presented at the Annual Meeting of Pharmaceutical Society of Japan, Sendai on 22nd of October 1966.

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[*4] Prefixes "*cis*" and "*trans*" mean steric configuration at the ring juncture. All configurational assignment of hydroxyl groups ("α" and "β") are arbitrarily in terms of the relative configuration to the hydrogen atom at C_{10} which is always placed above the plane of the molecule and depicted in solid line.

[*5] Very recently, Wohl obtained six isomers of ***trans***-2-methyldecahydroisoquinolinols having a hydroxyl group at C_5, C_6, and C_7 position on isomerization of *cis*-2-methyl-10-decahydroisoquinolinol with boiling perchloric acid. (R.A. Wohl: Helv. Chim. Acta, **47**, 2162 (1966)). On the other hand, Durand, *et al.* prepared five isomers of ***trans***-2-methyldecahydroisoquinolinols having a hydroxyl group at the same positions lacking of one of 7-alcohols and five isomers of the ***cis***-alcohols lacking of one of 5-alcohols, and in comparison of chemical behavior on hydrogenation, NMR, and IR of these alcohols with those of decalols, their conformations are suggested (Durand-Henchoz, R.C. Moreau: Bull. soc. chim. Fr., **1966**, 3428). The present work is carried out independently to these works, and melting points of these alcohols and derivatives such as picrates or methiodides are almost identical with the corresponding alcohols in our hands.

1) *a*) S. Kimoto, M. Okamoto: This Bulletin, **9**, 480 (1961). *b*) ***Idem*: *Ibid.***, **10**, 362 (1962). *c*) M. Okamoto, M. Yamada: ***Ibid.***, **11**, 554 (1963). *d*) S. Kimoto, M. Okamoto: Yakugaku Zasshi, **85**, 371 (1965). M. Okamoto: This Bulletin, **15**, 168 (1967).

Table I. 2-Methyldecahydroisoquinolinols[a]

	Free base		Methiodide m.p. (°C)	Picrate m.p. (°C)
	b.p. (°C/mm.)	m.p. (°C)		
Va		90~92	210~212	—
Vb	111~112/4	oil	260~262	—
Vc		130~131	187~188.5	—
Ⅵa	85~86/4	oil	282	178
Ⅵb	115~117/5	oil	251	190~191
Ⅵc		68	263	228
Ⅵd		64	259	180~181
Ⅶa	117.5~118/5	oil	279~280	173.5~175.5
Ⅶb	95/4	oil	264~266	154~156
Ⅶc		70~71	268~269	206~207.5
Ⅶd		45	251~253	189~191
Ⅷa		78~80	229~231	181~183
Ⅷb		115	183~185	235
Ⅷc		84	235	147~150

a) All melting points are uncorrected.

Table Ⅱ. Nuclear Magnetic Resonance Spectra,[b] Rate Constants of Chromic Acid Oxidation (K_4),[c] Infrared Spectra[d] and pKa′ Values of *trans*-2-Methyldecahydroisoquinolinols

	NMR			K_4 $(m./L.)^{-3}$ min^{-1}	IR (cm^{-1})	pKa′
	N-CH_3 (τ)	>C$\underline{H}$OH (τ)	W/2 of >C$\underline{H}$OH(c/s)			
Vb	7.77	6.29	16	1.09	1044, 1016	9.72
Vc	7.77	6.21	5	2.66	980	9.70
Ⅵc	7.77	5.86	5	2.50	1000	9.60
Ⅵd	7.78	6.45	16	1.02	1056, 1023	9.54
Ⅶc	7.78	6.50	16	0.51	1050, 1019	9.45
Ⅶd	7.82	5.96	7	2.15	1008	9.23
Ⅷb	7.77	6.15	5	2.81	1004	9.48
Ⅷc	7.77	6.08	16	1.14	1059, 1014	9.54

b) NMR spectra are determined on a Varian A-60 Spectrophotometer with deuterochloroform as solvent and tetramethylsilane as internal reference.

c) Rate constants, according to Westheimer's method, are calculated from consumption value of dichromate ion at 350 mμ in ultraviolet spectra determined at 40° using Model QV-50, Shimadzu as a spectrophotometer (F.H. Westheimer, A. Novick : J. Chem. Phys., **11**, 505 (1943). cf. H.G. Kuivila, W.J. Becker : J. Am. Chem. Soc., **74**, 5329 (1952)).

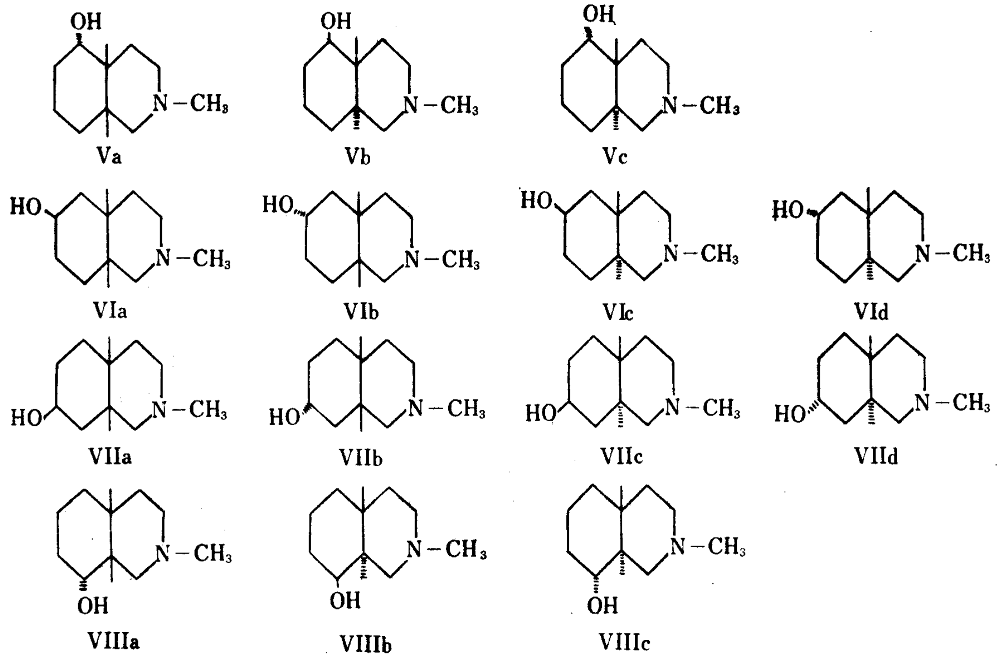
d) Relatively strong peaks in the region of 1060 cm^{-1} to 960 cm^{-1} determined in chloroform solution.

Table Ⅲ. Nuclear Magnetic Resonance Spectra,[b] Rate Constants of Chromic Acid Oxidation (K_4),[c] Infrared Spectra[d] and pKa′ Values of *cis*-2-Methyldecahydroisoquinolinols

	NMR			K_4 $(m./L.)^{-3}$ min^{-1}	IR (cm^{-1})	pKa′
	N-CH_3 (τ)	>C$\underline{H}$OH (τ)	W/2 of >C$\underline{H}$OH(c/s)			
Va	7.75	6.29	16	0.57	1058, 1014	9.60
Ⅵa	7.75	6.40	16	1.62	1056, 1022	9.37
Ⅵb	7.75	6.33	16	1.11	1050, 1022	9.44
Ⅶa	7.78	6.26	16	0.85	1054, 1018	9.48
Ⅶb	7.75	6.48	16	0.96	1050, 1019	9.65
Ⅷa	7.77	5.92	5	2.73	965	9.82

b, c, d) Similar to those in the case of Table Ⅱ.

These data are listed in Table I, Table Ⅱ and Table Ⅲ.


Va Vb Vc

VIa VIb VIc VId

VIIa VIIb VIIc VIId

VIIIa VIIIb VIIIc

Chart 1.

Discussion

Generally it is well known that saturated six-membered ring systems exist in energetically stable chair forms and therefore it may be considered that simple 2-methyldecahydroisoquinolines have fused ring systems which are composed of chair forms of cyclohexane and N-methylpiperidine as in the case of decalins. On the other hand, for N-methylpiperidine it was suggested that the methyl group would be axial in about half the molecules and equatorial in the other half. This seems, however, to be incorrect and recently it was indicated that the N-methyl group is similar to the methyl group in methylcyclohexane and prefers the equatorial disposition by various physical methods[2] and for N-methyl-4-piperidinol it was reported the inversion of the methyl group around the nitrogen atom occurs more rapidly than that of ring interconversion and the relatively large free energy needed for the N-methyl group to assume an axial disposition, consequently it seems most reasonable to rule out any appreciable participation of conformations possessing axial N-methyl disposition.[3] On the base of these facts, consideration concerning dispositions of axial N-methyl groups in the free fourteen alcoholic bases is therefore ruled out from this discussion.

Conformation of *trans*-2-Methyldecahydroisoquinolinols

Since in the case of *trans* compounds it is not necessary to take ring inversion into consideration, the steric disposition of hydroxyl groups can be easily decided from consideration of rate constants of chromic acid-oxidation and NMR. Generally it is well known that alicyclic alcohols possessing axial hydroxyl groups are oxidized with chromic acid more rapidly than those possessing equatorial hydroxyl groups[4] and that the half-widths of the signals of the axial protons adjacent to hydroxyl groups are more than about 15 c.p.s. and half-widths of the equatorial protons are less than

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2) *a*) M. Aroney, R.J.W. Le Fevre: Proc. Chem. Soc., **1958**, 82. *b*) *Idem*: J. Chem. Soc., **1958**, 3002.

3) C.Y. Chen, R.J.W. Le Fevre: Tetrahedron Letters, **45**, 4057 (1965). *rf.* N.L. Allinger, J.C.D. Carpenter, F.M. Karkowski: J. Am. Chem. Soc., **87**, 1232 (1965).

4) J. Schreiber, A. Eschenmoser: Helv. Chim. Acta, **38**, 1529 (1955).

8 c.p.s. in NMR.[5~7] At first, in comparison with the rate constants of oxidations, values of K_{Vc}, $K_{\text{Ⅵc}}$, $K_{\text{Ⅶd}}$, and $K_{\text{Ⅷb}}$ are 2.45~4.2 times larger than that of K_{Vb}, $K_{\text{Ⅵd}}$, $K_{\text{Ⅶc}}$, $K_{\text{Ⅷc}}$ respectively (Table Ⅱ). Therefore, even only with these data it can be easily presumed that Vc, Ⅵc, Ⅶd, and Ⅷb correspond to axial alcohols and Vb, Ⅵd, Ⅶc, and Ⅷc to equatorial alcohols according to the general rule. Furthermore, the results obtained from consideration of NMR make good agreement with the above presumption especially on a point of the half-width of the proton of $\rangle C\underline{H}OH$. From these evidences, it is concluded that Vb, Vc, Ⅵc, Ⅵd, Ⅶc, Ⅶd, Ⅷb, Ⅷc correspond to 5*β*(*e*)-, 5*α*(*a*)-, 6*β*(*a*)-, 6*α*(*e*)-, 7*β*(*e*)-, 7*α*(*a*)-, 8*β*(*a*)-, and 8*α*(*e*)-alcohols respectively.[*4] In addition to this, differences between the chemical shifts of the protons of $\rangle C\underline{H}OH$ in the epimeric alcohols are as follows. Thus differences between Ⅵd and Ⅵc, and between Ⅶc and Ⅶd are 0.59 and 0.54 p.p.m. respectively but differences Vb and Vc, and between Ⅷc and Ⅷb are very small. From these results the differences for the 6- and 7-alcohols make a good agreement with the well-known difference between chemical shifts of the axial and the equatorial protons (approximately 0.5 p.p.m.),[5,6] whereas the differences for the 5- and 8-alcohols do not consist with the established fact. However, since the signals of the protons are relatively broad and is to be influenced with the adjacent substituents or environments, it is presumably considered that this fact is dependent on the influence of the adjacent ring juncture.

Since it is questionable to determine the C-O stretching bands exactly in the IR spectra of these alcohols, the remarkable bands in the region of 950~1060 cm^{-1} are picked up in the Table Ⅱ, although the spectra should be compared with those of decalols.[*5]

They are parallel to the fact that the C-O stretching frequencies of a number of equatorial steroid alcohols are found around 1040 cm^{-1}, whereas the corresponding stretching frequencies for axial epimers occurs at about 1000 cm^{-1} at least when A/B ring juncture is *trans*.[8]

Of pKa′ values, which involve experimental errors properly at least to the extent of ±0.02, characteristic relations seems not to be observed since the hydroxyl groups exist in far from the ring nitrogen atom. This is the same in the following *cis* compounds with exception of Ⅷa.

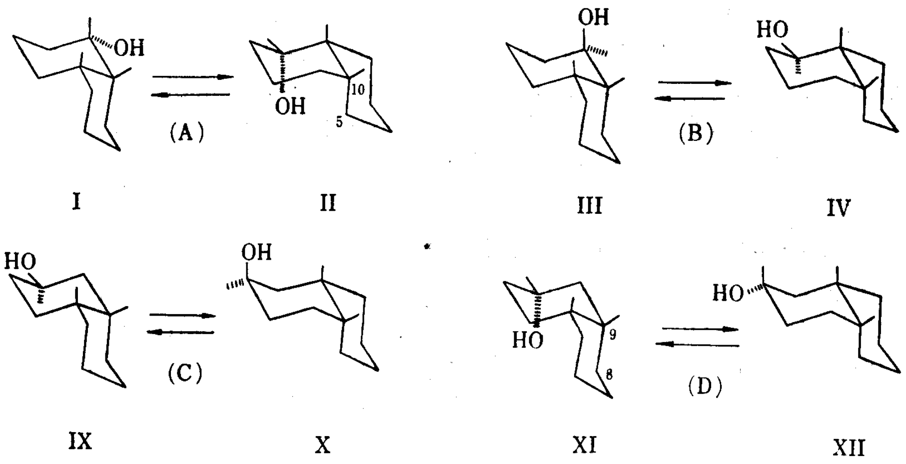

Chart 2.

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5) R.U. Lemiux, R.K. Kullnig, H.J. Bernstein, W.G. Schneider: J. Am. Chem. Soc., **80**, 6098 (1958).
6) J. Musher, R.E. Richards: Proc. Chem. Soc., **1958**, 230.
7) Y. Kawazoe, Y. Sato, T. Okamoto, K. Tsuda: This Bulletin, **11**, 328 (1963).
8) E.L. Eliel, "Stereochemistry of Carbon Compounds," p. 217. McGraw-Hill Book Co., Inc. (1958).

Conformation of *cis*-2-Methyldecahydroisoquinolinols

It is properly presumed that the *cis*-2-methyldecahydroisoquinolinols will, in principle, have the similar behavior as *cis* decalols, in which 1β- and 2β-decalols exist in the following equilibrium (B) and (C), whereas 1α- and 2α-decalols exist in predominantly the conformations as I and XII having equatorial hydroxyl groups, for the conformations as II and XI will be excluded with considerable magnitude of the steric interaction between the axial OH and the axial C-C bondings, namely, C_5-C_{10} in II and C_8-C_9 in XI.[9] Since it is considered, however, that in the case of the *cis*-2-methyldecahydroisoquinolinols there should be some differences from *cis*-decalols because of the presence of the N-methyl group attached to the ring nitrogen, the following are discussed in detail.

1) *cis*-2-Methyl-8-decahydroisoquinolinol (VIIIa). The fact that this alcohol has an axial hydroxyl group and the steric structure possessing an intramolecular hydrogen bond is indicated with the half-width of the proton of $\rangle\mathrm{C\underline{H}OH}$ (5 c.p.s.), the highest pKa′ value of the all bases and the IR absorption of an associated hydroxyl group at 3200 cm^{-1}. Therefore, the steric structure is indicated in Fig. 1.[*1]

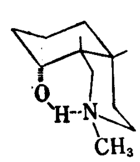

Fig. 1.

2) *cis*-2-Methyl-7-decahydroisoquinolinols (VIIa, VIIb). Taking the concept of ring inversion as in *cis*-2-decalol, it is necessary to consider the following equilibria between the extreme conformations. The disposition of the N-methyl group was already discussed. From examination of molecular models and roughly calculated energetic consideration, it is presumed that inversion of E_1 to A_1 *via* A_2 in the case of the 7α-alcohol is considerably difficult while the reverse inversion of A_1 to E_1 is possible as in the case of 2α-decalols, therefore that the equilibrium should be inclined predominantly toward E_1. On the other hand, in the equilibrium of the conformers of the 7β-alcohol there is no interaction between the hydroxyl group and any C-C bond at all in E_2, E_3, A_3 and the energy differences among these conformers will be small. Therefore, in the case of the 7β-alcohol the equilibrium will exist between E_2 and A_3 *via* E_3 as in the case of 2β-decalol and the disposition of the β-hydroxyl group may be depicted as (*e*-*a*). Accordingly, it is thought that if one of these bases (VIIa, VIIb) is an α(*e*)-alcohol, the other is a β(*e*-*a*)-alcohol. From the experimental data of chromic acid-oxidation and NMR (w/2 of $\rangle\mathrm{C\underline{H}OH}$, 16 c.p.s.), it is

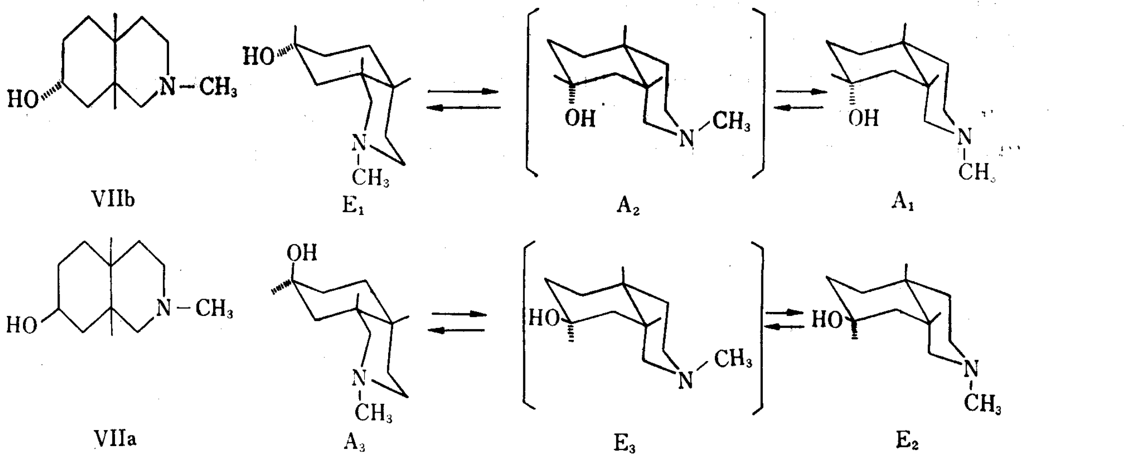

Chart 3.

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[9] O.R. Rodig, L.C. Ellis: J. Org. Chem., **26**, 2197 (1961). C.A. Grob, S.W. Tam: Helv. Chim. Acta, **48**, 1317 (1965).

obvious that both alcohols exist in predominantly equatorial conformations. On the other hand, since it was clarified that VIIb was an α-alcohol from the result of a stereoselective synthetic route starting from 4-hydroxyhexahydrohomophthalic acid lactone (m.p. 117~120°) which was prepared by hydrogenation of diethyl 4-hydroxyhomophthalate over Raney-Ni catalyst and has all *cis* configuration at each substituent,[10] the other alcohol (VIIa) may be a β-alcohol. Furthermore, in order to clarify the above facts, it is thought advisable that these alcohols are quaternized to the corresponding methiodides, since quaternization of these bases give rise to different aspect in energetic stabilities of the molecules from that in the free bases. Thus, in the NMR spectrum of VIIb methiodide (m.p. 266°) the signal of the equatorial proton (w/2 of $\rangle C\underline{H}OH$, 7 c.p.s.) is observed at 5.95τ, while in the spectrum of VIIa methiodide (m.p. 280°) no signals of protons can be seen in the lower field than 6.20τ, in which a broad signal of the axial proton seems to be veiled in other signals, that is, it seems to be found that there is the difference of chemical shift of more than at least 0.25 p.p.m. between the axial and equatorial protons in these methiodides. These observations will be interpreted as follows, that is, the methiodide of VIIb (E_1 which has axial lone pair electrons inside and the axial proton of $\rangle C\underline{H}OH$) converts preferably to the more stable methiodide corresponding to A_1 or A_2. However in the case of the 7β-alcohol, if VIIa would be regarded as A_3, the methiodide of VIIa should converts to that corresponding to E_3 or E_2, as in the 7α-alcohol, but it could not be observed in NMR as above mentioned. This conclusion seems to be also consistent with the data of determination of dipole moments. Thus, dipole moments of VIIa and VIIb are 1.84 D and 2.29 D, respectively.[*6]

3) *cis*-2-Methyl-6-decahydroisoquinolinols (VIa, VIb). For VIa and VIb, a similar presumtion as for *cis*-7-alcohols will be possible to be made with resemblance of their conformations. That is, in Chart 4, since the equilibrium $E_4 \rightleftarrows A_4$ is inclined

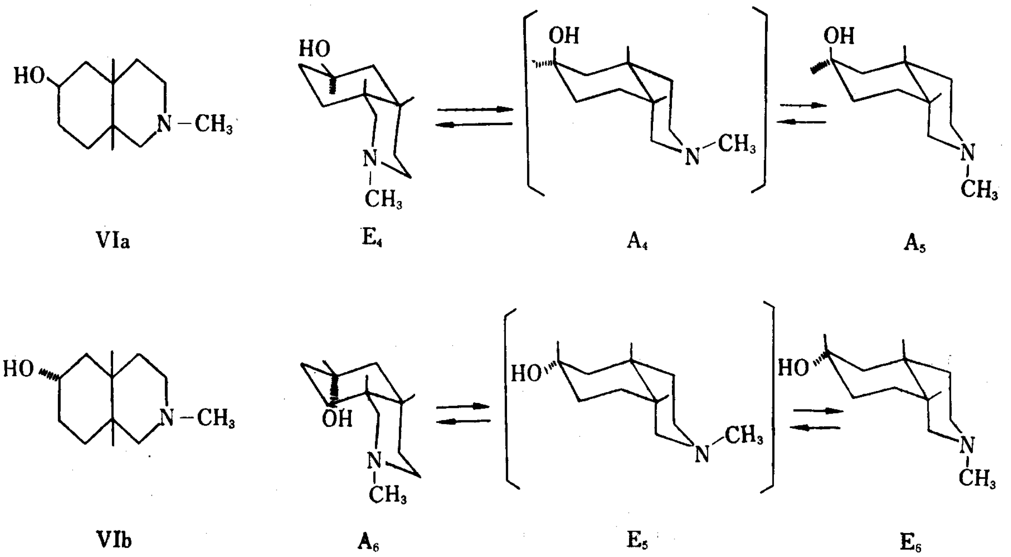

Chart 4.

[*6] The measurements are carried out at 25° on dilute solution in benzene. The dielectric constants are measured by means of a heterodyne beat apparatus provided with a platinum cell (Y. Kurita, M. Kubo: J. Am. Chem. Soc., **79**, 5460 (1957); B. Eda, K. Tsuda M. Kubo: *Ibid.*, **80**, 2426 (1958)).

The graphical plots of the dielectric constants as well as, the density of solutions against the concentration in weight % gave linear dependence within experimental errors. The slopes of these straight lines are evaluated by the least squares method and the molarizations of the solute are calculated by a method similar to that introduced by Halverstadt and Kumler (J. Am. Chem. Soc., **64**, 2988 (1942)).

10) S. Kimoto, M. Okamoto, T. Mizumoto, Y. Fujiwara: This Bulletin, **15**, 340 (1967).

exclusively toward E_4 because the hydroxyl group and the N-methyl group are orientated as axial forms in A_4, the β-alcohol seems to be equatorial in a large number of molecules. On the contrary to it, for the α-alcohol the most energetically stable form seems to be E_6 in the equilibrium $A_6 \rightleftarrows E_5 \rightleftarrows E_6$ and as energy difference between A_6 and E_5 is small, and if a corresponding ketone prepared by oxidation of E_4 or A_6 is reduced to two original epimeric alcohols, theoretically E_4 and A_6 will be reproduced, but the latter form (A_6) will convert to the most stable conformation (E_6) having an equatorial hydroxyl group *via* E_5. On such point of view, this discussion presents different aspect from the conformational treatment for *cis* 2-decalols. Again, there is a similar relationship in NMR spectra between *cis*-7-alcohols and *cis*-6-alcohols, that is, in the NMR spectrum of VIa methiodide (m.p. 282°) the signal of the equatorial proton (w/2 of $\rangle C\underline{H}OH$, 7 c.p.s.) is observed at 5.88τ, while in the spectrum of VIb methiodide (m.p. 251°) no signals of protons can be seen in the lower field than 6.2τ as in the case of *cis*-7(β)-alcohols. On the basis of these results and the data listed in Table III, it seems reasonable to assume that VIa is mostly a $\beta(e)$-alcohol and the great portion of VIb is an $\alpha(e)$-alcohol. But this assumption, of course, must be criticized under further investigation.

4) *cis*-2-Methyl-5-decahydroisoquinolinol (Va). In the case of the *cis*-5-alcohol, the other epimer which is possible to exist theoretically, cannot be isolated and from rough estimation of energetic stabilities of the molecular models, the same conformational analysis with NMR as described in the section (2) and (3) seems to be impossible. However, since on the facts that Va is obtained by hydrolysis of Va O-acetate, which is prepared by catalytic hydrogenation of 2-methyl-1,2,3,4-tetrahydro-5-isoquinolinol (XIV) over platinum using acetic acid as a solvent and moreover on catalytic hydrogenation of 2-methyl-1,2,3,4-tetrahydro-5-acetoxyisoquinoline (XV) over platinum, *cis*-2-methyldecahydroisoquinoline (XVI) is exclusively produced,[14] Va O-acetate and XVI are considered to be produced by all *cis* attack of hydrogen to XIV and XV, therefore Va seems to eb an α-alcohol. In addition to this, considerating estimation of energetic stabilities of the extreme conformations in similar way as in the case of *cis*-1-decalols and data in Table III, it is reasonable to suggest that Va is predominantly an $\alpha(e)$-alcohol.

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