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75. Shoshichiro Kimoto and Masao Okamoto: Stereochemistry of Decahydroisoquinolines and Related Compounds. I.

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Fundamental and elaborate investigations on stereochemistry of perhydronaphthalene series have been carried out in parallel with the development of extensive studies on steroids, but fundamental works on simple perhydroisoquinoline series have scarcely been found. For such reasons, syntheses and clarifications of the stereochemistry of decahydroisoquinoline series were undertaken.

Previous reports concerning oxo- and hydroxy-decahydroisoquinolines are as follows: 2-Methyldecahydroisoquinoline was reported by Witkop,[1] who obtained *cis*- and *trans*-isomers from the corresponding decahydroisoquinolines which had been described by Helfer,[2] and Witkop[3] also reported that *trans*-decahydroisoquinoline was prepared in a very good yield by hydrogenation of isoquinoline in the presence of Raney nickel under a high pressure. 2-Methyl-octahydro-6(2*H*)-isoquinolone, a key compound to two isomeric 2-methyldecahydro-6-isoquinolinols, was reported independently by Merchant and Pinder,[4] and by McElvain and Parker[5] in 1956. The octahydro-7(1*H*)-isoquinolone series were reported by Ochiai and Nakagome,[6] and by Clarke and Pinder.[7] In the researches described above, however, configuration of the ring juncture was not clarified at all except by McElvain and Parker. For a series of octahydro-5(1*H*)-isoquinolones, Birch reduction of 2-methyl-5-methoxy-1,2,3,4-tetrahydroisoquinoline, followed by hydrolysis, was carried out by Ochiai and Nakagome,[6] but without success.

In the present series of experiments, 2-methyl-octahydro-5(1*H*)-isoquinolone and two isomers of 2-methyldecahydro-5-isoquinolinols were prepared and they were proved to have *trans* structure at the ring juncture. 2-Methyl-5-amino-1,2,3,4-tetrahydroisoquinoline (IV), $b.p_3$ 125°, m.p. 50~55° (dipicrate, m.p. 176~178°), was obtained by two procedures; (a) reduction of 2-methyl-5-nitroisoquinolinium iodide (II) with sodium borohydride in methanol according to Mirza's procedure[8] gave 2-methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline (III), $b.p_3$ 123~125° (hydrochloride, m.p. 260° (sintering at 200°)), followed by hydrogenation in the presence of Raney nickel in methanol, and (b) directly by hydrogenation of the iodide (II) over platinum oxide in dilute acetic acid. The base (IV) was diazotized with sodium nitrite and followed by hydrolysis into a corresponding phenolic base (V), m.p. 185~187°, which afforded a colorless viscous liquid on hydrogenation over Raney nickel in methanol at 160 kg./cm^2 and at 170°. This hydrogenation product was chromatographed on alumina with chloroform as a solvent in order to separate the isomers, but only 2-methyl-decahydro-5-isoquinolinol (VIa) was lonely obtained as a colorless viscous liquid, $b.p_7$ 115~119° (methiodide, m.p. 260~262°). For the purpose of establishing the steric configuration at the ring juncture by diminishing the asymmetric center at C-5 position, the base was oxidized with chromic acid in acetic acid into 2-methyl-octahydro-5(1*H*)-isoquinolone (VII) as a colorless liquid, $b.p_3$ 85° (picrate, m.p. 211~213°), which was

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1) B. Witkop: J. Am. Chem. Soc., **70**, 2617 (1948).
2) L. Helfer: Helv. Chim. Acta, **9**, 814 (1926).
3) B. Witkop: J. Am. Chem. Soc., **71**, 2559 (1949).
4) A. Merchant, A. R. Pinder: J. Chem. Soc., **1956**, 327.
5) S. M. McElvain, P. H. Parker: J. Am. Chem. Soc., **78**, 5312 (1956).
6) E. Ochiai, T. Nakagome: Yakugaku Zasshi, **78**, 1438 (1958).
7) C. B. Clarke, A. R. Pinder: J. Chem. Soc., **1958**, 1967.
8) R. Mirza: *Ibid.*, **1957**, 4400.

reduced by the Wolff-Kishner method modified by Huang-Minlon[6,9] to *trans*-2-methyl-decahydroisoquinoline which was found to be identical by admixture of its picrate, m.p. 228~230°,*2 with an authentic sample. However, since it is well known that *cis* ring-juncture attached to a carbonyl group easily converted to the stable *trans* form under mild conditions,[10,11] it was thought advisable to transfer the hydroxyl base to 2-methyl-decahydroisoquinoline without passing through the keto base, using a procedure described by Schmidt and Karrer,[12] who had reported that menthyl tosylate and cholesteryl tosylate were reduced with lithium aluminium hydride into menthane and cholestene, respectively. Thus, the base (VIa) was treated with tosyl chloride in pyridine and the resulting substance, on purification by alumina chromatography, boiled at 50°/3mm. Hg(picrate, m.p. 212~214°) and was found to be not the expected tosylate, but 2-methyl-1,2,3,4,6,7,8,8a-octahydroisoquinoline (IX) which had been prepared by the modified Wolff-Kishner reduction of 2-methyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolone[5] (X). The reason that the tosylate could not be obtained and dehydration took place will be described in detail in later papers.

As attempts to obtain the tosylate of hydroxyl base (VIa) was unsuccessful, oxidation of (VIa) to keto base (VII) using chromium trioxide-pyridine complex, which does not cause ring conversion in oxidation process,[10] was carried out but the reaction product was found to be the same ketone as that obtained by chromium trioxide-acetic acid. Moreover, it was found that the keto base (VII) was recovered without conversion after refluxing with alcoholic potassium hydoxide which might be considered as an enolization agent. As will be described below, the keto base (VII) was reduced to the hydroxyl base (VIa) and it might be concluded from these results that the ring conversion would not take place during the above-mentioned reactions of (VIa)⇄(VII) and (VII)→(VIII).

In order to obtain an isomeric alcoholic base of (VIa), the ketone (VII) was hydrogenated in the presence of platinum oxide in ethanol and the resulting base was separated by alumina chromatography using chloroform as a solvent. The first fraction was a colorless

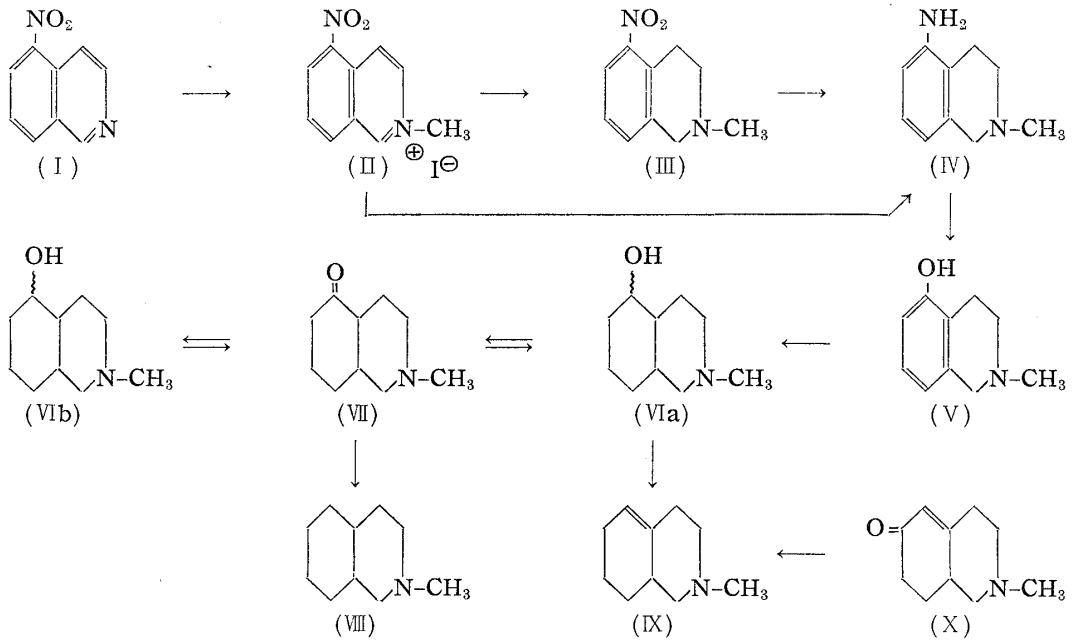

Chart 1.

*2 This melting point is uncorrected but that given by B. Witkop, of m.p. 237°, is corrected.

9) Huang-Minlon : J. Am. Chem. Soc., **68**, 2487 (1946).
10) G. Poos, G. E. Arth, R. E. Beyler, L. H. Sarett : *Ibid.*, **75**, 422 (1953).
11) R. P. Linstead, R. R. Whetstone : J. Chem. Soc., **1950**, 1428.
12) H. Schmidt, P. Karrer : Helv. Chim. Acta, **32**, 1371 (1949).

viscous liquid, b.p_3 103° (methiodide, m.p. 260~262°), which was identical with the base (VIa) described above and the second fraction gave a small amount of colorless crystals (VIb), m.p. 124~126.5°, in a low yield. The infrared absorption of this base (VIb) showed a hydroxyl band but no carbonyl band, and was, of course, different from that of the base (VIa). Its analytical values agreed well with $C_{10}H_{19}ON$ and it seemed reasonable to consider that the base (VIb) was an epimer of the base (VIa) at C-5 position. To obtain a larger amount of the base (VIb), the ketone (VII) was reduced with sodium in ethanol, but the yield could not be increased. Therefore, the keto base was hydrogenated over platinum oxide in dilute acetic acid solution and the crystalline hydroxyl base was successfully obtained in higher yield than by the above-described method. The hydroxyl base (VIb) also reverted on oxidation with chromium trioxide to the original ketone. On the basis of these facts, it seemed reasonable to conclude that a series of 5-oxo compounds (VII, VIa, and VIb) have a *trans* configuration at the ring juncture and it is interesting that one of the isomeric hydroxyl bases was predominantly obtained by selection of the reaction conditions and it might be possible to apply this method to other series of perhydroisoquinoline. The conformation of hydroxyl groups in the base (VI) will be discussed in later papers.

Experimental*3

2-Methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline (III)——To a solution of 5-nitroisoquinolinium iodide*4 (II) (11.7 g.) in MeOH (210 cc.) and H_2O (21 cc.), $NaBH_4$ (5 g.) was added with stirring and cooling with water, and the mixture was gently refluxed for 1 hr. After cool, it was poured into H_2O (1 L.) and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residual oil distilled at 123~125°/2 mm. Hg into a wine-red oil. Yield, 6.4 g. or 90%. Its hydrochloride was recrystallized from EtOH to colorless needles, m.p. 260° (sintering at 200°). *Anal.* Calcd. for $C_{10}H_{13}O_2N_2Cl$: C, 52.51; H, 5.73. Found: C, 52.65; H, 5.90.

2-Methyl-5-amino-1,2,3,4-tetrahydroisoquinoline (IV)——i) The foregoing base (III) (9.6 g.) in MeOH (100 cc.) was catalytically hydrogenated over Raney Ni W-4[13] (prepared from 6 g. of Ni-Al alloy) at a room temperature and in a high pressure, and H_2 absorption (3 moles) ceased after approx. 2 hr. The filtered solution was strongly basified with NaOH and extracted with Et_2O. The Et_2O solution was dried over NaOH and evaporated. The residual oil distilled at 125°/3 mm. Hg solidified after standing overnight and melted at 50~55°. Yield, 7.7 g. or 95%. IR: ν_{NH}^{liquid} 2.98 μ, vicinal trisubstituted benzene band in 12 μ region.

Dipicrate: Orange-yellow needles (from EtOH), m.p. 176~178°. *Anal.* Calcd. for $C_{10}H_{14}N_2 \cdot 2C_6H_3O_7N_3$: C, 42.59; H, 3.25. Found: C, 42.49; H, 3.27.

ii) A solution of 5-nitroisoquinolinium iodide (II) (11.5 g.), H_2O (150 cc.), and AcOH (10 cc.) was shaken in H_2 at a room temperature in the presence of Adams PtO_2. After 80 hr., H_2 absorption (5 moles) ceased. The filtered solution was treated as described above. Yield, 4.5 g. or 76%. Its dipicrate, m.p. 176~178°, was found by admixture to be identical with the above dipicrate.

2-Methyl-1,2,3,4-tetrahydro-5-isoquinolinol (V)——A solution of the foregoing base (IV) (3.2 g.) and 10% H_2SO_4 (50 cc.) was cooled to 0° and to the mixture a solution of $NaNO_2$ (1.4 g.) and H_2O (7 g.) was added drop by drop with stirring. The reaction mixture was poured into a boiling solution of Na_2SO_4 (16 g.), conc. H_2SO_4 (22 g.), and H_2O (12 cc.). After cool, the mixture was basified with Na_2CO_3, the resulting precipitate was collected by suction, washed with H_2O, and dried. It was recrystallized from a mixture of dehyd. EtOH and benzene to colorless cubes, m.p. 185~187°. Yield, 2.3 g. or 70%. *Anal.* Calcd. for $C_{10}H_{13}ON$: C, 73.59; H, 8.03. Found: C, 73.44; H, 8.29.

Hydrogenation of 2-Methyl-1,2,3,4-tetrahydro-5-isoquinolinol (V)——The foregoing base (V) (3.8 g.) in MeOH (100 cc.) was catalytically hydrogenated at 170° and 160 kg./cm^2 (initial H_2 pressure, 119 kg./cm^2) over Raney Ni (prepared from 5 g. of Ni-Al alloy) for 6 hr. After cool, the filtered solution was evaporated *in vacuo*. The residual oil was dissolved in Et_2O, Et_2O solution was shaken with NaOH solution, washed with H_2O, dried over Na_2SO_4, and evaporated. The residual oil (3.5 g.) was dissolved in $CHCl_3$ and chromatographed through a column (35 × 2 cm.) of alumina (100 g.), eluted with $CHCl_3$ and MeOH. Evaporation of the eluates gave *trans*-2-methyl-decahydro-5-isoquinolinol

*3 All melting points are uncorrected.

*4 The methiodide, m.p. 188~190°, was prepared by treatment of 5-nitroisoquinoline (I) (Le Fevre: J. Chem. Soc., **1935**, 1470) with MeI in dehyd. EtOH.

13) A. A. Pavlic, H. Adkins: J. Am. Chem. Soc., **68**, 1471 (1946).

(VIa), b.p_7 115～119°, n_D^{20} 1.5008. IR : $\nu_{OH}^{CCl_4}$ 3300 cm^{-1}. It gave, on treatment with MeI in dehyd. EtOH, the methiodide which was recrystallized from EtOH to colorless needles, m.p. 260～262°. *Anal.* Calcd. for $C_{10}H_{19}ON \cdot CH_3I$: C, 42.45; H, 7.13. Found : C, 42.48; H, 7.32.

***trans*-2-Methyl-octahydro-5(1*H*)-isoquinolone (VII)**——i) To a solution of the foregoing hydroxyl base (VIa) (3 g.) and AcOH (10 cc.) a solution of CrO_3 (2.4 g.) and H_2O (5 cc.) was added and the mixture was maintained at 60～70° for 7 hr. After cool, the mixture was cautiously basified with Na_2CO_3 and extracted with Et_2O. The Et_2O solution was washed with H_2O, dried over Na_2SO_4, and evaporated. The residual oil, the expected ketone (2 g.), distilled at 85°/3 mm. Hg. n_D^{18} 1.4929. IR : $\nu_{CO}^{CHCl_3}$ 1700 cm^{-1}. It gave on treatment with picric acid in MeOH, a picrate which was recrystallized from MeOH to yellow plates, m.p. 211～213°. *Anal.* Calcd. for $C_{10}H_{17}ON \cdot C_6H_3O_7N_3$: C, 48.48; H, 5.09. Found : C, 48.61; H, 5.32.

ii) A solution of the foregoing base (VIa) (2.2 g.) and pyridine (10 cc.) was combined with CrO_3-pyridine complex[10] (a mixture of CrO_3 (3.7 g.) and pyridine (30 cc.)), sealed in a glass tube, and allowed to stand at room temperature for 2 days. The mixture was poured into ice-water. The resulting brown precipitate was collected by suction, basified cautiously with saturated Na_2CO_3 solution, and extracted with $CHCl_3$. The $CHCl_3$ solution, concentrated *in vacuo*, afforded an oil, which distilled at 85～89°/2 mm. Hg. The IR absorption spectrum was well superimposable with that of the keto base (VII). Its picrate, recrystallized from MeOH, melted at 210～213°, undepressed on admixture with that of the keto base (VII).

iii) To a solution of the hydroxyl base (VIb) (3 g.) and AcOH (10 cc.) a solution of CrO_3 (2.4 g.) and H_2O (5 cc.) was added and the reaction mixture was maintained at 60～70° for 6 hr. After cool, it was worked up in the usual manner. The IR absorption spectrum of the resulting base was well superimposable with that of the keto base (VII). Its picrate, m.p. 210～213°, was identical by admixture with that of the base (VII).

Reduction of *trans*-2-Methyl-octahydro-5(1*H*)-isoquinolone (VII) by the Wolff-Kishner Method modified by Huang-Minlon——A mixture of the foregoing ketone (VII) (1 g.), 81% hydrazine hydrate (5 cc.), and triethylene glycol (5 cc.) was refluxed at 135～140° for 24 hr., cooled, and the reaction mixture was transferred to a small distillation flask. To the mixture, KOH (5 g.) was added, the temperature was gradually raised to 210° during 3 hr., and the distillate was extracted with Et_2O. The Et_2O solution was washed with a small amount of H_2O, dried over Na_2SO_4, and evaporation of Et_2O gave *trans*-2-methyl-decahydroisoquinoline (VIII), b.p_4 48～49° (0.5 g.). Its picrate recrystallized from MeOH to yellow needles, m.p. 228～230° and was found on admixture to be identical with an authentic sample.

Reduction of *trans*-2-Methyl-octahydro-5(1*H*)-isoquinolone (VII) by Another Method——i) Catalytic hydrogenation over PtO_2 in EtOH : A solution of the base (VII) (1 g.) in EtOH (30 cc.) was shaken with PtO_2 (0.6 g.) in H_2 at a room temperature. H_2 absorption (1 mole) ceased after 3 hr. The filtered solution was evaporated, the residual oil (0.8 g.) was dissolved in $CHCl_3$ (2 cc.), and passed through a column (30 × 1 cm.) of alumina (20 g.). The column was eluted with $CHCl_3$ and the result was as follows :

Fr. No.	Eluting solvent (cc.)		Eluate (mg.)	
1～6 (A)	$CHCl_3$	120	oily	500
7～9 (B)	$CHCl_3$	60	crystalline	50

The oil in (A) distilled at 103°/3 mm. Hg. n_D^{20} 1.5006. Its methiodide melted at 260～262°, undepressed on admixture with that of the base (VIa).

Crystals in (B) were treated with petr. ether (b.p. 35～60°) and a small amount of colorless thin plates, m.p. 124～126.5°, was obtained. This substance was readily soluble in usual organic solvents except petr. ether. *Anal.* Calcd. for $C_{10}H_{19}ON$: C, 70.96; H, 11.32. Found : C, 71.01; H, 11.25. The IR spetrum showed free OH band at 2.72 μ but no carbonyl band. Its crystalline methiodide was too soluble in alcohol and hygroscopic to be obtained in a pure state.

ii) Reduction with Na in EtOH : To a solution of the base (VII) (1 g.) in dehyd. EtOH (10 cc.) Na (0.3 g.) was added, the mixture was warmed at 50～60° for 1 hr. with stirring, cooled, diluted with H_2O, and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residual oil was chromatographed on alumina as after the catalytic hydrogenation. The oily fraction (550 mg.) boiled at 115°/3 mm. Hg and its methiodide melted at 260～262°, undepressed on admixture with that of the base (VIa). The crystalline fraction, purified from petr. ether, melted at 123～125°, undepressed on admixture with the base (IVb).

iii) Catalytic hydrogenation over PtO_2 in acid medium : A solution of the base (VII) (660 mg.) in 50% AcOH (20 cc.) was shaken over PtO_2 (0.1 g.) in H_2 at a room temperature. The theoretical H_2 absorption required 2 hr. The filtered solution was basified with Na_2CO_3 and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residual oil (400 mg.) distilled at 103～107°/3 mm. Hg. The distillate, kept standing overnight, solidified. It was dissolved in $CHCl_3$ (3 cc.) and chromatographed through a column (10 × 1 cm.) of alumina (7 g.).

Fr. No.	Eluting solvent (cc.)		Eluate (mg.)
1～7 (A)	$CHCl_3$	21	oily, trace
8～9 (B)	$CHCl_3$	6	oily and crystalline, trace
10～23 (C)	$CHCl_3$	42	crystalline 300

Crystals in (C) melted at 122～124°, undepressed on admixture with the base (VIb).

Formation of 2-Methyl-1,2,3,4,6,7,8,8a-octahydroisoquinoline (IX) from *trans*-2-Methyldecahydro-5-isoquinolinol (VIa) by the Action of Tosyl Chloride——To a solution of the hydroxy base (VIa) (1.0 g.) in dehyd. pyridine (4 cc.), a solution of tosyl chloride (1.3 g.) and pyridine (4 cc.) was added with cooling in ice-water. The reaction mixture was sealed in a glass tube, allowed to stand at a room temperature for 4 days, and poured into ice-water. The mixture was acidified with HCl, shaken with Et_2O to remove excess of tosyl chloride, the aqueous layer was cautiously basified with Na_2CO_3, and extracted with Et_2O. The Et_2O solution was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. Attempts for crystallization and distillation (0.02 mm.) of the viscous residue were unsuccessful. Therefore the oil was dissolved in $CHCl_3$ (5 cc.) and chromatographed through a column of alumina (10 g.) using $CHCl_3$ as an eluting solvent. The viscous liquid obtained from the effluent turned to a fluid oil. This oil, 2-methyl-1,2,3,4,6,7,8,8a-octahydroisoquinoline (IX), boiled at 50°/3 mm. Hg; n_D^{20} 1.4941. Yield, 400 mg. Its IR spectrum showed double-bond at 6.01 μ but no hydroxyl group and was superimposable with that of the base (IX), described below. Its picrate on recrystallization from MeOH melted at 212～214° (sintering at 209°), undepressed on admixture with an authentic sample.

2-Methyl-1,2,3,4,6,7,8,8a-octahydroisoquinoline (IX)——A mixture of 2-methyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolone (X) (1 g.), 81% hydrazine hydrate (5 cc.), and triethylene glycol (5 cc.) was refluxed at 135～140° for 24 hr. and after cool, the reaction mixture was transferred to a small distillation flask. To the mixture KOH (5 g.) was added, the temperature raised to 210° during 3 hr., and the distillate was extracted with Et_2O. The Et_2O solution was washed with a small amount of H_2O, dried over Na_2SO_4, and evaporation of Et_2O gave a colorless liquid (0.7 g.), $b.p_3$ 50°. Its picrate was recrystallized from MeOH to yellow needles, m.p. 212～214° (sintering at 209°). *Anal.* Calcd. for $C_{16}H_{20}O_7N_4$: C, 50.52; H, 5.30. Found : C, 50.26; H, 5.43.

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Summary

trans-2-Methyl-octahydro-5(1*H*)-isoquinolone was prepared and configuration of the ring juncture was discussed. Reduction of this base gave two isomers of *trans*-2-methyl-decahydro-5-isoquinolinol.

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