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57. Shoshichiro Kimoto and Masao Okamoto : Stereochemistry of Decahydroisoquinolines and Related Compounds.*2 II.*3

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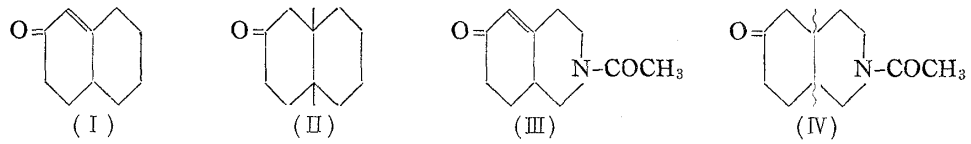
In the preceding paper*2, it was reported that 2-methyldecahydro-5-isoquinolinone and two isomeric 2-methyldecahydro-5-isoquinolinols were prepared and they had *trans* ring juncture.

Tamelen and Proost[1] reported that 4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (I) was hydrogenated with palladium-charcoal as a catalyst to give only *cis*-octahydro-2(1*H*)-naphthalenone (II) in either neutral, acidic, or basic solution. Recently, McElvain and Parker[2] established that hydrogenation of 2-methyl-1,2,3,4,8,8a-hexahydro-6(7*H*)-isoquinolinone (X) with 10% palladium-charcoal in acidic solution gave exclusively the corresponding saturated *cis*-ketone (XII) and in the same year, Merchant and Pinder[3] showed



(I) (II) (III) (IV)

that hydrogenation product of (X) in neutral solution gave presumably the *trans*-ketone (XI) without reliable evidence. Most recently, however, McElvain and Remy[4] found that hydrogenation of 2-acetyl-1,2,3,4,8,8a-hexahydro-6(7*H*)-isoquinolinone (III) in weakly acidic methanol afforded approximately equal amounts of corresponding *cis*- and *trans*-saturated ketones (IV) and consequently it failed to proceed stereospecifically. Accordingly, it was thought that investigations for the stereospecific hydrogenation of such an α,β-unsaturated ketone as (I) were of much interest, and especially it seemed to be important to establish the exact configuration of the so-called *trans*-2-methyloctahydro-6(5*H*)-isoquinolinone by Merchant and Pinder.

The present paper was independently undertaken to obtain each of two isomeric 2-methyloctahydro-6(5*H*)-isoquinolinones by way of exclusively stereospecific hydrogenation and four isomeric 2-methyldecahydro-6-isoquinolinols.

Although several procedures for the synthesis of 2-methyl-1,2,3,4,8,8a-hexahydro-6(7*H*)-isoquinolinone[2,3,5] (X) were available, the following modification was adopted. N-(3-methoxyphenethyl)formamide (VI) was prepared in 81% yield from 3-methoxyphenethylamine (V) and formamide according to the method of Sugazawa and Shigehara,[6] and ring closure of the formamide (VI) with phosphoryl chloride in toluene afforded 6-methoxy-3,4-dihydroisoquinoline (VII) in 85% yield and this methiodide (VIII) was reduced with sodium borohydride in methanol according to Mirza's method[7] to give 2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IX) in 81% yield (total yield, 55% from starting

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*2 Part I : This Bulletin, **9**, 480 (1961).

*3 This work was reported at the Kinki Local Meeting of the Pharmaceutiacl Society of Japan, October 20, 1960.

1) E. E. van Tamelen, W. C. Proost : J. Am. Chem. Soc., **76**, 3632 (1954).
2) S. M. McElvain, P. H. Parker : *Ibid.*, **78**, 5312 (1956).
3) A. Merchant, A. R. Pinder : J. Chem. Soc., **1956**, 327.
4) S. M. McElvain, D. C. Remy : J, Am. Chem. Soc., **82**, 3960 (1960).
5) V. Georgian : Chem. and Ind. (London), **1954**, 930.
6) S. Sugazawa, H. Shigehara : Yakugaku Zasshi, **62**, 531 (1942).
7) R. Mirza : J. Chem. Soc., **1957**, 4400.

material (V)). The unsaturated ketone (X) was prepared in the similar fashion of Merchant and Pinder.[3]

Next, interesting stereospecific hydrogenation was carried out over 5% palladium-charcoal at 20 kg./cm^2 and room temperature, in ethanol solution, the ketone (X) gave exclusively *trans*-saturated ketone (XI) (the methiodide, m.p. 244~246°, which corresponded with that of Merchant and Pinder.) and in 5% hydrochloric acid solution exclusively the *cis*-ketone (XII) (the methiodide, m.p. 257~258°)[8] in satisfactory yield in each case. Furtheremore, these two isomeric saturated ketones were, by the reduction procedure of Wolff-Kishner, converted to *trans*- and *cis*-2-methyldecahydroisoquinoline (XIII and XIV), respectively. Consequently, it was successful to be confirmed that it resulted in *trans*-hydrogenation in neutral solution[9] and in *cis*-hydrogenation in acidic solution.

Reductions of saturated ketones (XI and XII) with sodium borohydride in dilute methanol solution gave four isomeric 6-hydroxy bases, that is, from *trans*-ketone (XI), b.p$_5$ 100~103° (XVa) (the methiodide, m.p. 256~258°) and m.p. 35~38° (XVb) (the methiodide, m.p. 261~263°)[10] and, from *cis*-ketone (XII), b.p$_3$ 110~115° (XVIa) (the methiodide, m.p. 259~261°) and b.p$_3$ 85~86° (XVIb) (the methiodide, m.p. 265~266°). Any one of the infrared spectra of these four isomeric alcohols was not superimposable with that of the others, and all the mixed melting point determinations of any pair of methiodides of these bases showed depression. In addition to the above-mentioned facts, two isomeric alcohols (XVa) and (XVb) were oxidized with chromic acid to the original *trans*-ketone (XI) and similar oxidation of

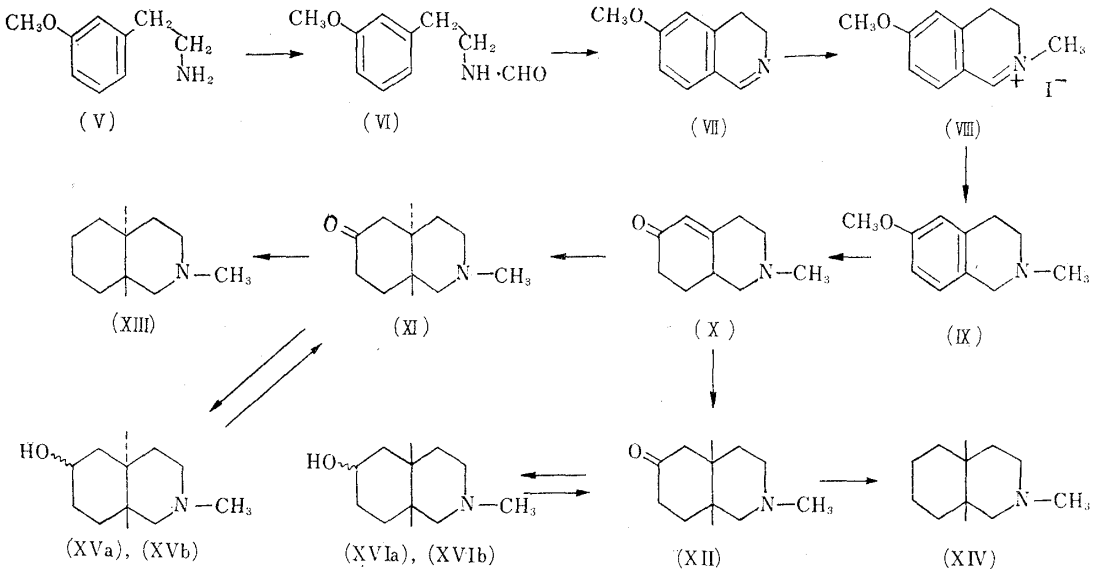
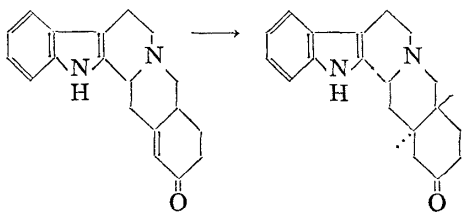


Chart 1.

8) It could not be confirmed to be identical with a methiodide, m.p. 271~273° obtained by McElvain and Parker[2] as they had no sample at hand.

9) P. G. Philipott and A. M. Parson (J. Chem. Soc., **1958**, 3018) reported *trans*-hydrogenation with Pd-$SrCO_3$ in ethanol as below.



10) Either of these methiodides should be identical with that of 2-methyldecahydro-6-isoquinolinol prepared by Merchant and Pinder,[3] but it could not be confirmed by admixture as they had no sample at hand.

two other alcohols (XVIa) and (XVIb) reproduced the original *cis*-ketone (XII). Accordingly, on the basis of these facts, it was convinced to answer the expected purpose, however, it was unsatisfactory at all to discuss the conformational analysis of these four alcohols. It would be thought advisable to investigate other useful stereospecific reductions and further informations.

Experimental*4

N-(3-Methoxyphenethyl)formamide (VI)——A mixture of 3-methoxyphenethylamine (V) (26.0g.) and freshly distilled formamide (b.p_{26} 116~118°) (11.5 g.) was slowly heated on a water bath until the evolution of NH_3 ceased (5 hr.) and the mixture was dissolved in Et_2O and the Et_2O solution was washed with 5% HCl and H_2O, and then dried over anhyd. Na_2SO_4. After evaporation of Et_2O, the residue distilled at 178° (6 mm. Hg) to give colorless viscous liquid (reported b.p_{17} 216°).[11]

6-Methoxy-3,4-dihydroisoquinoline (VII)——Phosphoryl chloride (2.3 g.) was cautiously dropped into a water-cooled solution of the foregoing formamide (VI) (2.3 g.) and dry toluene (6.5 cc.) under stirring for 16 min. The yellowish reaction mixture was heated on a water bath for 2 hr., then it became dark red and was poured into H_2O (150 cc.). After the toluene layer was discarded, the water solution was made strongly alkaline with NaOH and extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4 and evaporated. The residual oil distilled at 122~128° (3 mm. Hg) as a colorless liquid (reported b.p_{16} 155°).[11] Yield, 2.28 g. (85%). It gave, on treating with MeI in EtOH, quantitatively the methiodide (VIII), which was recrystallized from EtOH to yellow needles, m.p. 195~196° (reported m.p. 199°).[11]

2-Methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IX)——To a solution of the foregoing methiodide (VIII) (5.5 g.) in MeOH (120 cc.) and H_2O (12 cc.) was added $NaBH_4$ (3.0 g.) in small portions under stirring for 50 min. The reaction mixture was refluxed on a water bath for 30 min. and cooled and then poured into H_2O (300 cc.) and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated. The oily residue distilled at 100~105° (3 mm. Hg) as a colorless oil, having slightly violet fluorescence. Yield, 2.6 g. (81 %). n_D^{16} 1.5473. Its picrate, which was recrystallized from MeOH to yellow needles, melted at 130~132° (reported m.p. 130~131°).[11]

2-Methyl-1,2,3,4,8,8a-hexahydro-6(7*H*)-isoquinolinone (X)——This base (X) was prepared from the foregoing base (IX) in a similar manner to that of Merchant and Pinder. The physical properties followed below: b.p_2 110~115°. n_D^{17} 1.5223. The methiodide separated from EtOH to colorless needles, m.p. 208~210°. (Merchant and Pinder[3] give b.p_{12} 150~160° (bath temp.), the methiodide, m.p. 208° and also Georgian[5] gives the methiodide, m.p. 209~210°).

***trans*-2-Methyloctahydro-6(5*H*)-isoquinolinone (XI)**——a) The foregoing base (X) (1.0 g.) in EtOH (100 cc.) was hydrogenated at a room temperature and 20 kg./cm.[2] of H_2 pressure over 5% Pd-C (1.0 g.) for 3 hr. The filtered solution was evaporated *in vacuo*. The residual oil distilled at 92~98° (4 mm. Hg). IR $\nu_{co}^{CHCl_3}$: 5.88 μ. Yield, 0.7 g. The methiodide separated from EtOH to colorless needles, m.p. 244~246° (reported b.$p_{0.5}$ 120~130° (bath temp.) and the methiodide, m.p. 243°).[3] On reduction by Wolff-Kishner method, modified by Huang-Minlon, the keto-base (XI) was transformed into *trans*-2-methyldecahydroisoquinoline (XIII), b.p_4 48~49°, the picrate (m.p. 228~230°) of which was undepressed on admixture with an authentic sample.

b) To a solution of oily *trans*-2-methyldecahydro-6-isoquinolinol (mentioned later) (XVa) (0.1 g.) and AcOH (1.0 cc.) CrO_3 (80 mg.) was added. The reaction mixture was warmed at 60~70° for 1 hr. The cooled solution was basified with Na_2CO_3 and extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4 and evaporated. The residual oil was treated with MeI in EtOH to give the methiodide, m.p. 244°, which was identical with the sample obtained in (a).

c) The similar oxidation of crystalline *trans*-2-methyldecahydro-6-isoquinolinol (XVb) (mentioned later) afforded the same keto-base that was obtained in (a) and (b).

***cis*-2-Methyl-octahydro-6(5*H*)-isoquinolinone (XII)**——a) The unsaturated keto-base (X) (1.0 g.) in 5% HCl (60 cc.) was hydrogenated over 5% Pd-C at the similar condition as before. The filtered solution was concentrated *in vacuo*, basified with NaOH, and extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4 and evaporated. The residual oil distilled at 95~98° (3 mm. Hg). Yield, 0.8 g. n_D^{20} 1.4917. IR $\nu_{co}^{CHCl_3}$: 5.88 μ. The methiodide separated from EtOH to colorless needles, m.p. 257~258°. *Anal.* Calcd. for $C_{11}H_{20}NOI$: C, 42.72; H, 6.52. Found: C, 42.86; H, 6.78.

The base (XII), on reduction by the modified Wolff-Kishner method, was transformed into *cis*-2-methyldecahydroisoquinoline (XIV), b.p_7 71~78°, the picrate (m.p. 204~206°) of which was found to be identical by admixture with an authentic sample.

*4 All melting and boiling points are not corrected.

11) J. M. Gulland, C. J. Virden: J. Chem. Soc., **1929**, 1791.

b) Either similar oxidation of *cis*-2-methyl decahydro-6-isoquinolinol (XVIa) and (XVIb) (mentioned later) as described in (b) of *trans*-saturated ketone (XI) afforded the same keto-base that was obtained in (a), respectively.

Reduction of *trans*-2-Methyl-octahydro-6(5*H*)-isoquinolinone (XI)——To a solution of the *trans*-keto-base (XI) (0.7 g.) in MeOH (20 cc.), and H_2O (0.5 cc.) was added $NaBH_4$ (0.17 g.) in small portions under stirring and the mixture was refluxed on a water bath for 4 hr. and then poured into H_2O (50 cc.). The solution was extracted with $CHCl_3$ and the extract was dried over anhyd. Na_2SO_4 and evaporated. The residual *trans*-2-methyldecahydro-6-isoquinolinols were chromatographed through a column (1×15 cm.) of alumina (14.0 g.). The column was eluted with $CHCl_3$.

Fr. No.	Solvent (cc.)	Eluate
1～2(A)	30	oily
3	15	〃
4 (B)	15	crystalline

The oil (XVa) in (A)-fraction distilled at 100～103° (5 mm. Hg), was a colorless and viscous liquid and not crystallized under allowing it to stand in a refrigerator for a few days. n_D^{20} 1.5200. The methiodide separated from EtOH to colorless needles, m.p. 256～258°. *Anal.* Calcd. for $C_{11}H_{22}NOI$: C, 42.45; H, 7.13. Found : C, 42.58; H, 7.21. The colorless crystals (XVb) in (B)-fraction melted at 35～38°. The methiodide separated from EtOH to colorless needles, m.p. 261～263°. *Anal.* Calcd. for $C_{11}H_{22}NOI$: C, 42.45; 7.13. Found : C, 42.11; H, 7.17. The either infrared spectrum of the bases (XVa) and (XVb) showed a hydroxyl group near 2.7 μ and no carbonyl group but was not superimposable mutually. A mixed melting point determination of the methiodide of (XVa) with that of (XVb) showed depression.

Reduction of *cis*-2-Methyloctahydro-6(5*H*)-isoquinolinone (XII)——This base (XII) (0.7 g.) was reduced with $NaBH_4$ and the product was chromatographed as described in the foregoing experiment.

Fr. No.	Solvent (cc.)	Eluate
1～2(A)	30	oily
3	15	oily
4 (B)	15	oily

The oil (XVIa) in (A)-fraction distilled at 110～115° (3 mm. Hg), was a colorless and viscous liquid. n_D^{20} 1.5000. The methiodide separated from EtOH to colorless needles, m.p. 259～261°. *Anal.* Calcd. for $C_{11}H_{22}NOI$: C, 42.45; H, 7.13. Found : C, 42.20; H, 7.34. The oil (XVIb) in (B)-fraction distilled at 85～86° (4 mm. Hg), was a colorless and viscous liquid. The methiodide separated from EtOH to colorless needles, m.p. 265～266°. *Anal.* Calcd. for $C_{11}H_{22}NOI$: C, 42.45; H, 7.13. Found : C, 42.22; H, 7.38. The either infrared spectrum of these bases (XVIa) and (XVIb) showed a hydroxyl group near 2.7 μ and no carbonyl group but was not superimposable mutually. And a mixed melting point determination of the methiodide of the base (XVIa) with that of (XVIb) showed depression.

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Summary

It was shown that stereospecific hydrogenation of 2-methyl-1,2,3,4,8,8a-hexahydro-6(7*H*)-isoquinolinone (X) over palladium-charcoal proceeded in *trans* in neutral solution and in *cis* in acidic solution. Moreover, reduction of *trans*- and *cis*-2-methyloctahydro-6(5*H*)-isoquinolinone gave two epimeric 6-isoquinolinol bases, respectively, that is, four isomeric alcohols in all.

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