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72. Masao Okamoto: Stereochemistry of Decahydroisoquinolines and Related Compounds. V.[*1] Syntheses of Decahydro-2-methyl-8-isoquinolinols. (Supplement continued from page 172)

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Experimental[*4]

8-Acetamino-5-chloroisoquinoline (V)——A solution of IV (26.0 g.)5) and Ac_2O (130 ml.) was heated for 5 hr. in a boiling water bath. After decomposition of the excess Ac_2O by adding H_2O to the solution, was basified the resulted solution with Na_2CO_3. The precipitate was collected by suction, washed with H_2O and recrystallized from dil. CH_3OH to form colorless needles, m.p. 208~210° (lit.6): m.p. 209~210°). Yield, 30.5 g. (95%). *Anal.* Calcd. for $C_{11}H_9ON_2Cl$: C, 59.86; H, 4.11. Found: C, 60.06; H, 4.36. Gentle boiling a mixture of V and CH_3I in C_2H_5OH gave methiodide, which was recrystallized from C_2H_5OH to form colorless needles, m.p. 245°, in 90% yield.

8-Acetamino-5-chloro-2-methyl-1,2,3,4,-tetrahydroisoquinoline (VI)——To a solution of the methiodide of V (11.3 g.), CH_3OH (500 ml.) and H_2O (50 ml.) was added $NaBH_4$ (5.0 g.) in small portions with stirring and the solution was gently refluxed for 1 hr. and poured into H_2O (2.5 L.) and then extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated. The residual solid was recrystallized from Me_2CO to form colorless needles, m.p. 190~191°. Yield, 6.5 g. (87.8%). *Anal.* Calcd. for $C_{12}H_{15}ON_2Cl$: C, 60.38; H, 6.33. Found: C, 60.39; H, 6.22.

8-Amino-5-chloro-2-methyl-1,2,3,4-tetrahydroisoquinoline (VII)——A solution of VI (6.5 g.) and 10% HCl (130 ml.) was heated on the steam bath for 9 hr. and after cool, strongly basified with NaOH. The precipitate was collected by suction, washed with water, dried and upon recrystallization from petr. ether, formed colorless prisms, m.p. 80~82°. Yield, 4.5 g. (85%).

5-Chloro-2-methyl-1,2,3,4-tetrahydro-8-isoquinolinol (VIII)——A solution of $NaNO_2$ (0.88 g.) and H_2O (9 ml.) was added to a solution of VII (2.5 g.) and 10% H_2SO_4 (50 ml.) cooled at 0° drop by drop with stirring. The reaction mixture was poured into a boiling solution of Na_2SO_4 (30.0 g.), H_2SO_4 (50 g.), and H_2O (50 ml.) and refluxed until gas evolution ceased. After cool, the mixture was basified with Na_2CO_3, and the resulting precipitate together with dark resinous material was collected by suction and dissolved in ether and ether-insoluble inorganic compounds were discarded. On evaporating the dried ether extract, yellow crystalline mass, m.p. 168~171°, remained and recrystallization from $CHCl_3$ afforded colorless cubes, m.p. 171.5~172.5°. Yield, 1.9 g. (75.8%). *Anal.* Calcd. for $C_{10}H_{12}ONCl$: C, 60.75; H, 6.12. Found: C, 60.87; H, 6.12.

2-Methyl-1,2,3,4-tetrahydro-8-isoquinolinol (XIII)——a) A mixture of VIII (3.9 g.) and KOH (0.6 g.) in CH_3OH (100 ml.) was catalytically hydrogenated over Raney Ni prepared from Ni-Al alloy (5.0 g.) at 140 kg./cm² (initial H_2 pressure, 110 kg./cm²) and 150° for 4 hr. The filtered solution was evaporated and the residual mass was dissolved into a small amount of water, weakly acidified with 10% HCl, then basified with Na_2CO_3, and extracted with ether. The ether extract was dried over Na_2SO_4 and evaporated. The resulted crystalline mass was recrystallized from C_6H_6 to form colorless cubes, m.p. 177~178°. Yield, 2.1 g. (52%). Beilstein test, negative. *Anal.* Calcd. for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.89; N, 8.46.

b) A solution of $NaNO_2$ (2.9 g.) and H_2O (24 ml.) was dropped little by little into a solution of XII (6.9 g.) and 20% H_2SO_4, previously cooled at 0°, under stirring (30 min.) and then stirring was continued for 30 min. further. The orange diazonium salt solution was poured in small portions into a boiling solution of H_2O (27 ml.), H_2SO_4 (50 g.), and Na_2SO_4 (36.4 g.), and vigorous evolution of N_2 took place. After cool, upon basification of the solution, was collected the precipitate by suction, dried and extracted with hot dehyd. C_2H_5OH. The C_2H_5OH extract was decolorized with Norit, and evaporated. The residual solid was recrystallized from ether or C_6H_6 to colorless cubes, m.p. 176~178°. Yield, 4.9 g. (70%).

8-Acetaminoisoquinoline (X)——According to the method of Ahmad, *et al.*,6) 100% $NH_2NH_2 \cdot H_2O$ (87 ml.) was added to a boiling suspension of IV (10.7 g.), Pd-C (3.6 g.) and dehyd. C_2H_5OH (600 ml.) drop by drop during 1.5 hr. In a course of addition of $NH_2NH_2 \cdot H_2O$ took place vigorous gas evolution and gentle boiling was continued for 6 hr. The filtered solution, after removal of the solvent, gave yellow crystals, which

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[*1] Part IV. S. Kimoto, M. Okamoto: Yakugaku Zasshi, 85, 371 (1965).

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[*4] All melting points are uncorrected. In column chromatograph, aluminum oxide standardized (Merck) was used. Thin-layer chromatography (TLC) was worked on aluminum oxide G (Merck) by using $CHCl_3$-CH_3OH (45:4) as a developer and the spots were detected by spraying with the Dragendorff reagent.

were washed with water, dried, and recrystallized from C_6H_6 to give 8-aminoisoquinoline (V) as slightly yellow needles, m.p. 168~170° (lit.[6]: m.p. 173~174°). Yield, 7.6 g. (88%). V was converted quantitatively to the acetate (X), m.p. 166~168° (lit.[6]: 168~169°) as colorless needles according to usual method. The methiodide, colorless needles, m.p. 252~254°.

8-Acetamino-2-methyl-1,2,3,4-tetrahydroisoquinoline (XI)——To a solution of the methiodide of X (22.2 g.), CH_3OH (700 ml.) and H_2O (70 ml.) was added $NaBH_4$ (10 g.) with stirring under cooling with cold water and the mixture was gently refluxed for 1 hr. After removal of the solvent, a mixture of the residual mass and H_2O (1 L.) was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated. The residual solid was recrystallized from C_6H_6 to form colorless needles, m.p. 122~123°. Yield, 11.0 g. (80%). *Anal.* Calcd. for $C_{12}H_{16}ON_2$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.08; H, 8.00; N, 14.06.

8-Amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (XII)——A solution of XI (10.7 g.) and 10% HCl (220 ml.) was gently refluxed for 6 hr., and then became gradually red. After cool, the solution was strongly basified with NaOH and extracted with ether. The ether extract, having light green fluorescence, was dried over Na_2SO_4 and evaporated. Distillation of the residual oil afforded light yellow liquid, b.p$_3$ 120~122°. Yield, 6.9 g. (81%).

Hydrogenation of 2-Methyl-1,2,3,4-tetrahydro-8-isoquinolinol (XIII) over Platinum Oxide——XIII (1.0 g.) in AcOH (20 ml.) was catalytically hydrogenated over $PtO_2 \cdot H_2O$ (0.5 g.) at a room temperature and an atmospheric pressure and H_2 uptake (630 ml.) ceased after 2.5 hr. The filtered solution was evaporated *in vacuo*. The residual mass was dissolved in a small amount of water, basified cautiously with a cold NaOH solution under cooling, and extracted with ether. The ether solution was shaken with saturated NaCl solution, dried over Na_2SO_4 and evaporated *in vacuo*. The resulting crystalline mass was recrystallized from petr. ether to give *cis*-2-methyldecahydro-8-isoquinolinol (XIVa) as colorless prisms, m.p. 78~80°. Yield, 0.8 g. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3200 (intramolecular associated OH). TLC: Rf, 0.79. The picrate, recrystallized from CH_3OH and the methiodide, recrystallized from EtOH, formed respectively yellow needles, m.p. 181~183° and colorless plates, m.p. 229~231°. *Anal.* Calcd. for $C_{10}H_{19}ON \cdot CH_3I$: C, 42.45; H, 7.13. Found: C, 42.60; H, 7.21. Evaporation of the mother liquor of recrystallization of the free base left a very small amount of basic oil, and any further examination could not be done at all.

Hydrogenation of 2-Methyl-1,2,3,4-tetrahydro-8-isoquinolinol (XIII) over Raney Ni——XIII (4.9 g.) in MeOH (100 ml.) was catalytically hydrogenated at 165±5° and 140 kg./cm^2 (initial H_2 pressure, 110 kg./cm^2) over Raney Ni "W-4," prepared from Ni-Al alloy (5.0 g.) for 5 hr. After cool, the filtered solution was evaporated *in vacuo*. The residual oil was dissolved in $CHCl_3$. The solution was shaken with a small amount of 40% NaOH, washed with the saturated NaCl solution, dried over Na_2SO_4, and evaporated *in vacuo*. Distillation of the residual oil gave two fractions boiling at 88~93°/4 mm. Hg and at 99~103°/4 mm. Hg. The former fraction solidified after cool and the solid, on recrystallization from a mixture of ether and petr. ether, gave one of *cis*-2-methyldecahydro-8-isoquinolinol (XIVa) (1.3 g.) as colorless prisms, m.p. 78~80°, which was already described above. The latter portion (1.7 g.), b.p$_4$ 99~103°, having three spots of nearly same size in TLC, was chromatographed through a column of alumina and eluted with $CHCl_3$ to give three fractions (TLC: Rf, 0.79, 0.66, 0.59), which on recrystallization from petr. ether, afforded XIVa and two of other *trans*-decahydro-2-methyl-8-isoquinolinol (XIVb, XIVc), characterized as follows. XIVb: Colorless prisms, m.p. 115°. The methiodide, colorless needles, m.p. 183~185°, recrystallized from a small amount of dehyd. C_2H_5OH. The picrate, yellow prisms, m.p. 235° recrystallized from dehyd. C_2H_5OH. *Anal.* Calcd. for $C_{10}H_{19}ON \cdot C_6H_3O_7N_3$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.26; H, 5.55; N, 13.72. XIVc: Colorless crystals, m.p. 84°, which was relatively soluble in petr. ether, b.p. 45~50°. The methiodide, colorless needles, m.p. 235°. *Anal.* Calcd. for $C_{10}H_{19}ON \cdot CH_3I$: C, 42.45; H, 7.13. Found: C, 42.50; H, 7.10. The picrate yellow powders, m.p. 147~150°, recrystallized from a mixture of C_2H_5OH and ether. The approximate ratio of these bases (XIVa, XIVb, XIVc), produced by the hydrogenation, was determined to be 3:1:1 with use of TLC.

Hydrogenation of 5-Chloro-2-methyl-1,2,3,4-tetrahydro-8-isoquinolinol (VIII) over Raney Ni——VIII (4.0 g.) in MeOH (100 ml.) was catalytically hydrogenated at 160±5° and 130 kg./cm^2 (initial H_2 pressure, 94 kg./cm^2) over Raney Ni "W-4," prepared from Ni-Al alloy (4.0 g.) in the presence of KOH (0.56 g.) for 5 hr. After cool, the filtered solution was treated in the same manner as described at hydrogenation of XIII and the similar result was obtained.

Oxidation of *cis*-Decahydro-2-methyl-8-isoquinolinol (XIVa) with Sodium Dichromate in Acidic Solution——To a solution of XIVa (800 mg.), $Na_2Cr_2O_7 \cdot 2H_2O$ (500 mg.) and H_2O (2.0 ml.), was cautiously added 30% H_2SO_4 (3.6 ml.) under cooling with ice-water and the solution was kept standing at a room temperature for 3 hr., then the orange red solution changed to deep green. The reaction mixture was cautiously basified and a small amount of oil was floating and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated. The residual oil was chromatographed through a column of Al_2O_3, using $CHCl_3$ as an eluting solvent. The ketonic fractions were combined and evaporated *in vacuo*, while the unchanged alcoholic base was adsorbed on Al_2O_3. The residual *trans*-2-methyl-1,3,4,4a,5,6,7,8a-octahydro-8(2*H*)-isoquinolinone (XV) distilled at 114~116°/11 mm. Hg. and after cool solidified. m.p. 40~42°. Yield, 400 mg. The methiodide, colorless needles, m.p. 288~290°. *Anal.* Calcd. for $C_{10}H_{17}ON \cdot$

CH_3I : C, 42.74; H, 6.52. Found : C, 42.58; H, 6.46. Extraction of Al_2O_3, employed for chromatographic separation with MeOH, recovered the unchanged alcohol (XIVa).

Oxidation of a Mixture of *trans*-Decahydro-2-methyl-8-isoquinolinols (XIVb, XIVc) with Sodium Dichromate in Acidic Solution——A solution of a mixture of XIVb and XIVc (400 mg.), $Na_2Cr_2O_7 \cdot 2H_2O$ (0.26 g.), H_2SO_4 (0.44 g.) and H_2O (5.0 ml.) was kept standing at a room temperature (about 10°) for 4 days. The reaction mixture was treated in the same manner as described at oxidation of XIVa. The ketonic base obtained was converted to the methiodide, m.p. 288~290°, which was identical by admixture with the authentic sample of XVI.

Hydrogenation of *trans*-2-Methyl-1,3,4,4a,5,6,7,8a-octahydro-8(2*H*)-isoquinolinone (XVI)——a) With platinum oxide. A solution of XVI (400 mg.) and EtOH (20 ml.) was shaken with $PtO_2 \cdot H_2O$ (50 mg.) in H_2 at a room temperature and atmospheric pressure. The H_2 uptake (1 mole) ceased after 2 hr. Evaporation of the filtered solution afforded crystalline mass (almost quantitative), m.p. 105~110°, which, upon recrystallization from petr. ether, gave XIVb, m.p. 115°.

b) With $NaBH_4$. To a solution of XVI (50 mg.) and CH_3OH (20 ml.), and H_2O (2 ml.), was added $NaBH_4$ (0.5 g.) with shaking and the mixture was kept standing for 2 hr. After evaporation of the solvent *in vacuo*, was extracted the residual mass with ether several times and the combined extract was evaporated to dryness. A small amount of viscous oil remained. TLC of the oil : Rf, 0.66 (XIVc), 0.59 (XIVb).

***trans*-2-Methyl-1,3,4,4a,5,6,7,8a-octahydro-8-isoquinolinone Dithioethylene Ketal (XVII)**——Into a solution of XVI (400 mg.), dithioethylene glycol (1.0 g.) and AcOH (4.0 ml.) was bubbled dry HCl in a cold water bath. The mixture was kept standing overnight and diluted with H_2O. The separated oil was extracted with ether and the ether extract was discarded. The aqueous layer was cautiously basified with NaOH and extracted with ether. The ether extract, dried over Na_2SO_4, was evaporated and the residual oil, after cool, solidified. m.p. 55~57°. The methiodide, m.p. 232~234°. *Anal.* Calcd. for $C_{12}H_{21}NIS$: C, 40.51; H, 6.28. Found : C, 40.38; H, 6.16.

A mixture of the ketal (XVII) (200 mg.), Raney Ni (prepared from Ni-Al alloy (1.0 g.)), EtOH (20 ml.) was refluxed for 5 hr. The filtered solution was evaporated *in vacuo*. The residual oil distilled at 100° (oil bath temperature)/10 mm. Hg. The distillate was converted to the picrate, m.p. 232°, which was identical with the authentic picrate of *trans*-decahydro-2-methylisoquinoline (XVIII) by admixture.