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74. Tetsuji Kametani and Kazumi Ohkubo: The Structure of Sendaverine and Its Total Synthesis.*1

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Re-examination of the experimental data for corpaverine by chemical methods previously reported and the structural elucidation of sendaverine by physical methods led to propose the structure of I. A total synthesis of sendaverine is finally described, confirming the structure for the alkaloid.

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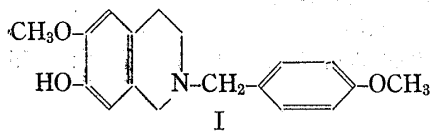
In the previous papers[1~3] sendaverine, m.p. 140~141.5°, was found to be identical with alkaloid F-28 which was isolated from *Corydalis aurea* Willd. by Manske.[4] However, the structure of sendaverine has not yet been elucidated, and its total synthesis has also not been accomplished.

The purpose of the present investigation was to re-examine the experimental data by chemical methods previously reported by Manske[5] and to reveal its structure by physical methods and its total synthesis, leading eventually to confirm formula (I) for the sendaverine, a new structural type of benzylisoquinoline alkaloid.



I

Chart 1.

Manske[5] already revealed that mild oxidation of corpaverine gave *p*-anisic acid which melted sharply at 184°. This fact reveals that one part of the corpaverne, namely, sendaverine, is oxidized to give *p*-anisic acid and it is, therefore, obvious that this alkaloid has a *p*-methoxybenzyl group. Furthermore, since analytical data of alkaloid F-28 (Found: C, 72.17; H, 7.03; N, 5.09; 2OMe, 20.64) was previously given by Manske, its empirical formula must be $C_{18}H_{21}O_3N$ (*Anal.* Calcd., C, 72.21; H, 7.07; N, 4.68) instead of $C_{17}H_{19}O_3N$, the analytical figures being about equally good for both. Attempted recrystallization from *n*-hexane of alkaloid F-28, m.p. 135°, donated by Dr. Manske gave the compound (I) as colorless prisms, m.p. 139~140°.

The infrared spectrum of I showed a hydroxylic band at 3546 cm^{-1} and the characteristic absorption band which was similar to Bohlmann's absorption[6] was observed at 2761, 2801 and 2841 cm^{-1} in chloroform.[3] The ultraviolet spectrum also showed 1,2,3,4-tetrahydroisoquinoline type.[7]

In the NMR spectrum*3 of I, the AA'BB' type at 2.76τ (2H) and 3.19τ (2H) (J_{AB}= $J_{A'B'}$ =8.5 c.p.s.) was assigned to the aromatic protons as doublet signal respectively. The doublet at 3.19τ is presumably due to the protons adjacent to the 4'-methoxyl

*1 This forms Part CLXXVIII of "Studies on the Syntheses of Heterocyclic Compounds" by T. Kametani; Part CLXXVII, Yakugaku Zasshi, **87**, 467 (1967).

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*3 Nuclear magnetic resonance spectrum was determined on a Varian A-60 spectrophotometer with deuterochloroform as solvent and tetramethylsilane as internal reference.

1) T. Kametani, K. Ohkubo, I. Noguchi, R.H.F. Manske: Tetrahedron Letters, **1965**, 3345.
2) T. Kametani, K. Ohkubo: *Ibid.*, **1965**, 4317.
3) T. Kametani, K. Ohkubo, R.H.F. Manske: *Ibid.*, **1966**, 985; T. Kametani, K. Ohkubo, I. Noguchi: J. Chem. Soc., 1966 (c), 715.
4) R.H.F. Manske: Can. J. Research, **B16**, 81 (1938).
5) *Idem*: J. Am. Chem. Soc., **74**, 2864 (1952).
6) F. Bohlmann: Ber., **91**, 2157 (1958).
7) Y. Ban, O. Yonemitsu, M. Terashima: This Bulletin, **8**, 194 (1960).

group. Two singlet signals at 3.50τ (1H) and 3.55τ (1H) due to aromatic ring protons at 5- and 8-positions were observed. Two singlet signls at 6.22τ (3H) and 6.25τ (3H) were assigned to the protons of 6- and 4'-methoxyl groups. The methylene protons at 1-position and 2-benzyl group were also observed at 6.45τ (2H) and 6.56τ (2H). Furthermore, the protons of the 3- and 4-methylene groups were observed at 7.20~7.38τ (4H). These facts reveal that sendaverine has two methoxyl group and lacks N-methyl group.

The base ion peak in the mass spectrum*4 of compound (I) (molecular ion at m/e 226) occurs at m/e 121 and is presumably due to the loss of isoquinoline unit by β-cleavage to form ion (a).[3] The presence of a metastable ion at m/e 49.3 ($121^2/299$ = 49.0) seems to substantiate such a process. The peak at m/e 178 is due to the loss of C_8H_9O unit (ion a) from the molecular ion to form ion (b), which is supported by

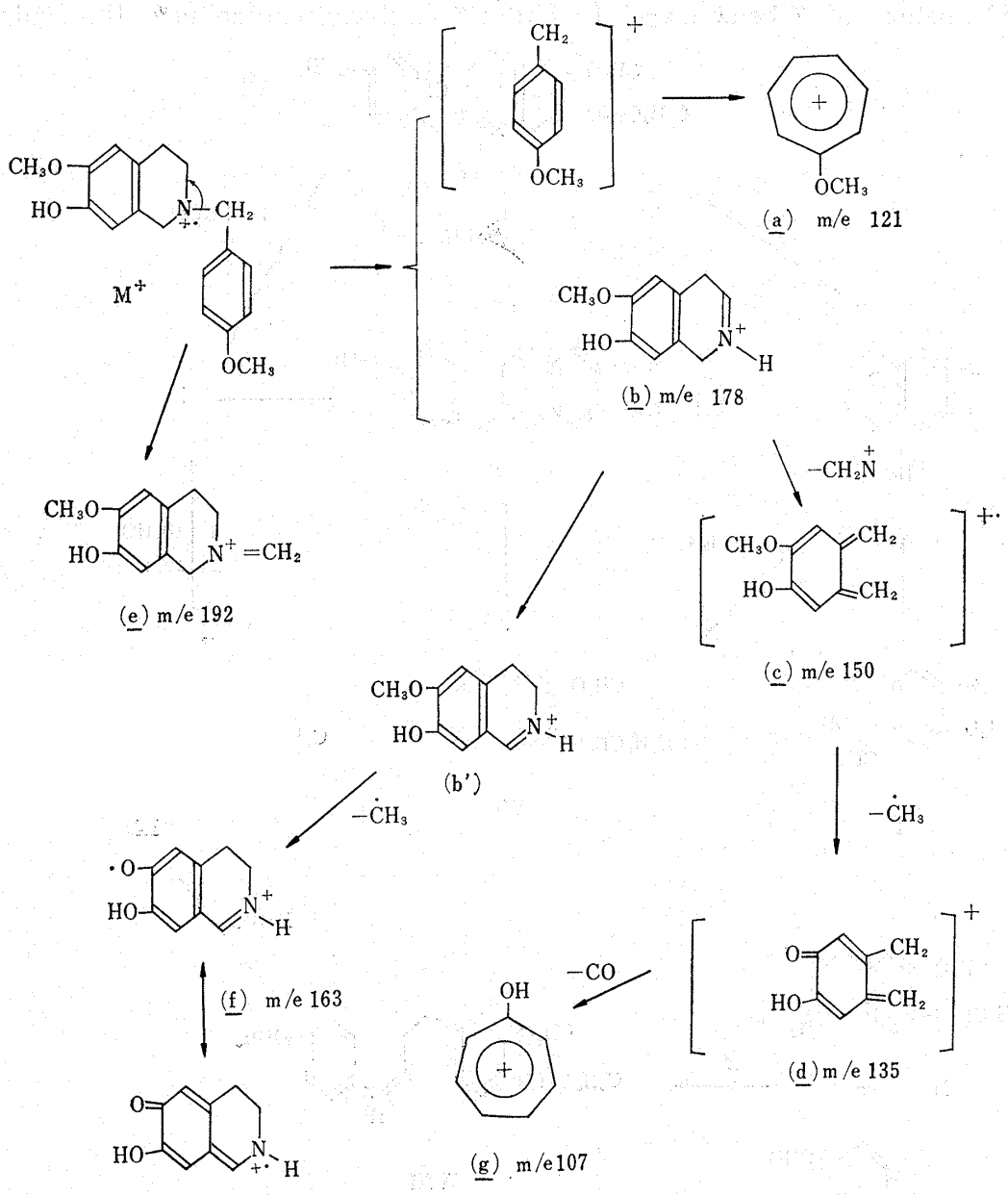

Chart 2.

*4 The mass spectrum was measured with a Hitachi mass spectrometer equipped with a direct inlet system; Accel. voltage, 1800 V; Chamber voltage, 70 V; Total emission, 80 μA; Targer current, 60 μA; Evaporation/Source Temp. 150°C/200°C.

the existence of a metastable ion at 106.0 ($178^2/299 = 106.0$). A retro-Diels-Alder decomposition of ion (b) can again be invoked to explain the genesis of ion (c) (m/e 150), which decompose further through expulsion of a methyl radical to ion (d) (m/e 135). The operation of this process is supported by the existence of a metastable ion at 121.5 ($135^2/150 = 121.5$). Furthermore, the ion (e) (m/e 192) is also formed from the molecular ion through β-cleavage. This fragmentation seems to support the existence of benzyl group at 2-position. Loss of CO radical from ion (d) gave the ion (g) (m/e 107). The only other ion of appreciable intensity is associated with the further expulsion of a methyl radical from ion (b') to give the mesomeric ion radical (f) (m/e 163), but it is only of very low abundance. This fact reveals that the possibility of the existence of ion (b') is scarcely considered and this fragmentation is not analogous to the other 1-substituted-1,2,3,4-tetrahydroisoquinoline derivatives.[8]

Condensation of 7-benzyloxy-3,4-dihydro-6-methoxyisoquinoline[9] (III), which was

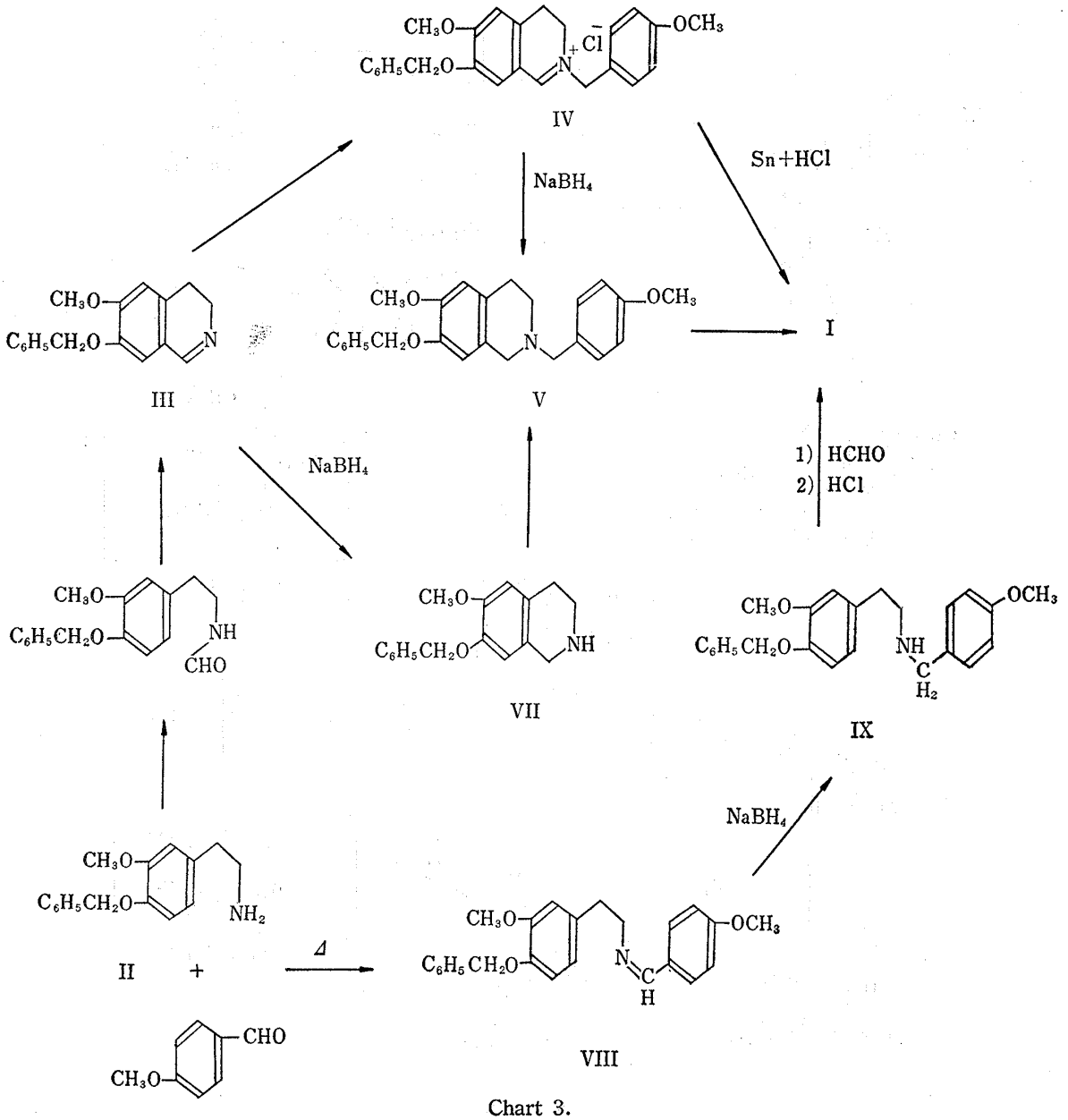

Chart 3.

8) H. Budzikiewicz, C. Djerassi, D.H. Williams: "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1, Alkaloids, p. 174, Holden-Day, Inc., 1964.
9) M. Tomita, H. Watanabe: Yakugaku Zasshi, 58, 783 (1938).

obtained by Bischler-Napieralski reaction of the formamido-derivative of Ⅱ, with 4-methoxybenzyl chloride in the presence of toluene gave 2-(4-methoxybenzyl)isoquinolinium chloride (Ⅳ). Hydrolysis of the 1,2,3,4-tetrahydroisoquinoline derivative (Ⅴ), which was obtained by reduction of Ⅳ with sodium borohydride, with an ethanolic hydrochloride solution afforded 1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-(4-methoxybenzyl)isoquinoline (I). This substance showed no depression of melting point on admixture with the natural product, whose infrared spectrum was superimposable on that of synthetic sendaverine (I) in chloroform.

The same product (I) was also obtained by an alternative route. Reduction of Ⅳ with tin and ethanol-concentrated hydrochloric acid gave the above compound (I). Furthermore, Pictet-Spengler reaction of N-(4-methoxybenzyl)-3-methoxy-4-benzyloxyphenethylamine (Ⅸ), which was obtained by reduction of the Schiff base (Ⅷ) between the amine (Ⅱ) and 4-methoxybenzaldehyde, gave the sendaverine (I).

The existence of sendaverine as a minor alkaloid in natural plants seems to be very interesting, and it is indeed surprising that such a simple 2-benzylisoquinoline alkaloid as sendaverine has for so long escaped detection.

Experimental*5

7-Benzyloxy-3,4-dihydro-6-methoxyisoquinoline (III)——According to Tomita's procedure,[9] Bischler-Napieralski reaction of 10.9 g. of N-(3-methoxy-4-benzyloxyphenethyl)formamide with 40 g. of $POCl_3$ in the presence of 100 ml. of toluene, followed by treatment as usual, gave 2.9 g. of the compound (Ⅲ), whose recrystallization from *n*-hexane afforded colorless prisms, m.p. 101~101.5°. ν_{max}^{KBr} cm^{-1}: 1629 (C=N), 700 and 759 (mono-substituted benzene). *Anal.* Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.46; H, 6.34; N, 5.15. This melting point was different from that of Tomita's sample (lit.,[9] m.p. 183°). Therefore, this was recognized by elementary analysis as above. NMR (τ) (in $CDCl_3$): 1.89 (1H, triplet, $J_{1,3}=2.0$ c.p.s.) (C_1-H); 3.21 and 3.35 (1H, singlet, respectively) (C_5-H, C_8-H); 4.90 (2H, singlet) (-O-CH_2-Ph); 6.12 (3H, singlet) (C_6-OCH_3); 6.30 (2H, multiplet, $J_{3,4}=8.0$ c.p.s., $J_{1,3}=2$ c.p.s.) (C_3-H); 7.39 (2H, triplet, ($J_{3,4}=8.0$ c.p.s.) (C_4-H).

7-Benzyloxy-3,4-dihydro-6-methoxy-2-(4-methoxybenzyl)isoquinolinium Chloride (IV)——A mixture of 1.5 g. of 3,4-dihydroisoquinoline derivative (Ⅲ)[9] and 1.4 g. of 4-methoxybenzyl chloride in 30 ml. of absolute toluene was heated on a water-bath for 5 hr., and allowed to stand at room temperature overnight. Removal of the solvent by decantation gave a dark reddish-brown viscous syrup which was triturated with ether to afford 1.5 g. of the chloride (Ⅳ) as a yellow powder, m.p. 131~135°. Since recrystallization of this chloride was so difficult, it was characterized as its bromide as follows. To a solution of the preceding chloride in water was added an excess of crystalline KBr, giving yellow needles. Recrystallization from MeOH-ether gave 7-benzyloxy-3,4-dihydro-6-methoxy-2-(4-methoxybenzyl)isoquinolinium bromide as yellow needles, m.p. 141°. *Anal.* Calcd. for $C_{25}H_{26}O_3NBr \cdot H_2O$: C, 61.73; H, 5.80; N, 2.88. Found: C, 61.96; H, 5.60; N, 2.93.

7-Benzyloxy-1,2,3,4-tetrahydro-6-methoxyisoquinoline (VII)——To a suspension of 1 g. of HCl salt of 3,4-dihydroisoquinoline derivative (Ⅲ) in 45 ml. of MeOH was added in small portions 0.8 g. of $NaBH_4$ at room temperature within 20 min., and the mixture was heated under reflux on a water-bath for 30 min. The solvent was distilled off, water was added to the resulting residue, extracted with ether, and dried on K_2CO_3. Removal of the solvent and recrystallization from *n*-hexane gave 0.8 g. of the tetrahydroisoquinoline derivative (Ⅶ) as colorless needles, m.p. 133° (sinters at 107°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3269 (NH). *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.45; H, 6.97; N, 5.00. Recrystallization of its HCl salt from MeOH-ether gave colorless scales, m.p. 219°. *Anal.* Calcd. for $C_{17}H_{19}O_2N \cdot HCl$: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.67; H, 6.50; N, 4.39.

7-Benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-(4-methoxybenzyl)isoquinoline (V)——a) $NaBH_4$ (1.5 g.) was added in small portions on cooling within 45 min. to a stirred solution of the preceding chloride (Ⅳ) in 70 ml. of MeOH containing a few drops of water and the mixture was allowed to stand at room temperature for 5 hr. The solvent was removed by evaporation, the residue was treated with water, and extracted with ether. The extract was dried on K_2CO_3. Removal of the solvent gave 1.0 g. of the solid whose recrystallization from *n*-hexane afforded 1,2,3,4-tetrahydroisoquinoline derivative (V) as colorless prisms, m.p. 92~93°. *Anal.* Calcd. for $C_{27}H_{25}O_3N$: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.41; H, 7.20; N, 3.56. NMR (τ) (in $CDCl_3$): 2.75 (2H, doublet J=8.5 c.p.s.) ($C_{2'}$H-$C_{6'}$H); 3.18 (2H, doublet, J=8.5 c.p.s.) ($C_{3'}$H-$C_{5'}$H); 3.42, 3.51

*5 All m.p.s. were not corrected and determined on a Kofler hot stage apparatus.

(1H, singlet, respectively) (C_5-H, C_8-H); 4.99 (2H, singlet) (O-CH_2-Ph); 6.45, 6.56 (2H, singlet, respectively) (C_1-H, N-CH_2-C_6H_4-); 6.21 (3H, singlet) (OMe); 6.25 (3H, singlet) (OMe); 7.20~7.40 (4H) (-CH_2-CH_2-).

b) A mixture of 509 mg. of the above compound (Ⅶ) and 148 mg. of 4-methoxybenzyl chloride in 20 ml. of dried benzene was refluxed on a water-bath for 7 hr., white precipitates being separated. After cooling, 145 ml. of a starting material was recovered as its HCl salt, m.p. 219°. The solvent layer separated was washed with water in order to remove the above salt, dried on K_2CO_3, and distilled off, to give a pale yellow powder, whose recrystallization from *n*-hexane afforded 147 mg. of O-benzyl-derivative (Ⅴ) as colorless prisms, m.p. 92~93°. The infrared spectrum of this compound was superimposable on that of the above authentic sample.

The Schiff Base (Ⅷ)——After a mixture of 5.14 g. of 7-benzyloxy-6-methoxyphenethylamine (Ⅱ) and 2.72 g. of anisaldehyde had been heated on a water-bath for 30 min., the mixture was evaporated to dryness under reduced pressure to give the solid, whose recrystallization from ether afforded 4.8 g. of the Schiff base (Ⅷ) as pale yellow needles, m.p. 75~76°. IR ν_{max}^{KBr} cm^{-1}: 1643 (C=N). *Anal.* Calcd. for $C_{24}H_{25}O_3N$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.84; H, 6.83; N, 3.50.

N-(4-Methoxybenzyl)-4-benzyloxy-3-methoxyphenethylamine (Ⅸ)——To a suspension of 1.3 g. of the preceding base (Ⅷ) in 30 ml. of MeOH was added in small portions 0.8 g. of $NaBH_4$ at room temperature within 30 min., and the mixture was mildly refluxed on a water-bath for 30 min. After MeOH had been distilled off, water was added to the resultant residue, extracted with ether. The extract was dried on K_2CO_3. Removal of the solvent gave 1.2 g. of the solid, whose recrystallization fron *n*-hexane afforded the phenethylamine derivative (Ⅸ) as colorless needles, m.p. 56~57°. *Anal.* Calcd. for $C_{24}H_{27}O_3N$: C, 76.36; H, 7.21; N, 3.71. Found: C, 76.37; H, 7.21; N, 3.65. Recrystallization of HCl salt of Ⅸ from MeOH-ether gave colorless needles, m.p. 196~201°. *Anal.* Calcd. for $C_{24}H_{27}O_3N \cdot HCl$: C, 69.64; H, 6.82; N, 3.38. Found: C, 69.56; H, 6.87; N, 3.42.

1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(4-methoxybenzyl)isoquinoline (Sendaverine) (Ⅰ)——a) A mixture of 140 mg. of O-benzyl-derivative (Ⅴ) and 10 ml. of 20% HCl aq. solution was heated on a water-bath for 1.5 hr. The reaction mixture was extracted with ether in order to remove a neutral substance. The above acidic layer was basified with 28% NH_4OH solution and extracted with benzene. The extract was dried on K_2CO_3 and removal of the solvent gave 89 mg. of a solid, whose recrystallization from *n*-hexane for many times afforded the sendaverine (Ⅰ) as colorless needles, m.p. and mixed m.p. 139~140°. (lit.,[1~3] 140~141.5°). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.16; H, 6.91; N, 4.16. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3546 (OH), 2761, 2801, 2841. UV λ_{max}^{EtOH} mμ (log ε): 225 (4.33), 283.5 (3.70). (TLC (WAKOGEL B-5 activated at 110° for 1 hr.): Rf 0.76 (synthetic); Rf 0.76 (natural) [$CHCl_3$-Me_2CO-MeOH (50:40:3) as solvent; the spots were detected by fume HNO_3]. Recrystallization of the HCl salt of Ⅰ from MeOH-ether afforded colorless needles, m.p. 225~230°*6 (decomp.). *Anal.* Calcd. for $C_{18}H_{21}O_3N \cdot HCl$: C, 64.37; H, 6.60; N, 4.17. Found: C, 64.56; H, 6.70; N, 4.36. The infrared and nuclear magnetic resonance spectra of synthetic and natural sendaverine[2] were identical.

b) To a solution of 1 g. of the above chloride (Ⅳ) in 15 ml. of EtOH and 15 ml. of conc. HCl aq. solution was added 4 g. of Sn powder, and the mixture was mildly refluxed on a water-bath for 5 hr. After cooling, the reaction mixture was admixed with 4 g. of Zn powder, and the solvent was distilled off. After the resultant residue had been extracted with benzene, the acidic solution was basified with 28% NH_4OH solution and extracted with ether. The extract was dried on K_2CO_3. Removal of the solvent and recrystallization from *n*-hexane gave 0.5 g. of the sendaverine (Ⅰ) as colorless needles, m.p. 138~139°, whose infrared spectrum was identical with that of natural product.

c) A mixture of 0.65 g. of the amine (Ⅸ) and 2 ml. of 37% formalin in 2 ml. of MeOH was mildly refluxed on a water-bath for 15 min., a pale yellow oil being precipitated and then extracted with benzene. The solvent was washed with water and dried on Na_2SO_4. Removal of the solvent gave a pale brown syrup. A mixture of the preceding syrup, 3 ml. of EtOH and 3 ml. of conc. HCl solution was refluxed on a water-bath for 25 min. After the solvent had been distilled off, the residue was extracted with benzene. The acidic aqueous solution separated was basified with 28% NH_4OH aq. solution and extracted with ether. The ethereal extract was washed with water, dried on K_2CO_3 and distilled, to give 0.25 g. of a pale yellow powder. Recrystallization from *n*-hexane gave the compound (Ⅰ) as colorless needles, whose infrared spectrum was superimposable on that of natural sendaverine.

We express our deep gratitude to Dr. R. H. F. Manske, Dominion Rubber Company, Ltd., Research Laboratories (Guelph, Ontario, Canada), for the gift of natural products, namely, corpaverine, capaurine, and alkaloid F-28. We are also grateful Mrs. F. Seto, Miss N. Nanjo, and Miss R. Kobayashi for microanalyses, to Miss T. Oikawa, Pharmaceutical Institute, Tohoku University School of Medicine, for measurement of infrared spectra, and to Chemical Department, Tohoku University, for nuclear magnetic resonance spectra.

*6 The HCl salt of this synthetic sendaverine showed m.p. 225~230° on measuring in sulfuric acid-bath. The lower m.p. 202~207° previously reported[2] for HCl salt of sendaverine was due to inadequate purification and we now amend it to 225~230°.