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An Alternative Synthesis of So-called Corpaverine (Studies on the Syntheses of Heterocyclic Compounds. CCXXXI[1])

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Brossi and Teitel have recently reported a synthesis of so-called corpaverine (I), mp 115—117°, whose IR and NMR spectra were identical with those of our sample, but the melting points of both specimens were not identical. Therefore, we have re-examined the synthesis of so-called corpaverine. Cyclization of N-(3-benzyloxy-4,5-dimethoxyphenethyl)-4-methoxyphenylacetamide with phosphoryl chloride afforded two isomers, one of which was isolated as its crystals, mp 84—86°, identical with our sample (I) reported previously. Furthermore, the synthesis of 7,8-dimethoxy-1-(4-methoxybenzyl)-2-methyl-3,4-dihydroisoquinolin-6-ol (IV) by Grignard reaction was carried out in order to compare our sample with Brossi's sample.

At first the cyclization of the formyl derivative (VI) with phosphoryl chloride afforded a mixture of VII and VIII, which was separated by recrystallization of its perchlorates. After reduction with sodium borohydride, 8-benzyloxy-derivative (IX) was obtained as its hydrochloride, mp 188—190°, whose debenzylation gave the anhalamine hydrochloride. Secondly Grignard reaction of the methobromide (XIII) with 4-methoxybenzylmagnesium chloride afforded the benzyl-derivative (XV), whose debenzylation with acid gave a phenolic base, mp 84—86°. The IR (in $CHCl_3$) and NMR (in $CDCl_3$) spectra of this sample were not only identical with those of our authentic sample reported by us previously, but also with those of Brossi's sample, mp 115—117°. Accordingly we have concluded to confirm the identity between both specimens and suggesting polymorphism.

In the previous papers,[3-6] we have reported the synthesis of so-called corpaverine (I)[3,4] and revealed that the corpaverine[7] proposed by R.H.F. Manske was found to be a molecular compound of sendaverine (II) with capaurine (III).[5,6,8,9] Recently, Brossi and Teitel[9] have reported that the Grignard reaction of 8-benzyloxy-6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium bromide with an excess of 4-methoxybenzylmagnesium chloride, followed by debenzylation of the corresponding product (XI) by catalytical hydrogenation, afforded (±)-so-called corpaverine (I), mp 115—117° and that the preceding sample was not identical with our sample,[4] mp 136—139° from the point of its melting point, but the NMR and IR spectra (in $CHCl_3$) of both specimens were identical each other. Furthermore, Fujitani and Kishimoto[10] have also reported that Bischler-Napieralski reaction of N-(3-benzyloxy-4,5-dimethoxyphenethyl)-4-methoxyphenylacetamide has proceeded only at the *para*-position of benzyloxy group, but one of the authors,[11] recently reported that cyclization of the above amide with phosphoryl chloride has occurred at both positions of *para* and *ortho*

1) Part CCXXX: *Chem. Pharm. Bull.* (Tokyo), **16**, 936 (1968).
2) Location: *Kita-4-bancho, Sendai.*
3) T. Kametani, K. Ohkubo, and R. H. F. Manske, *Tetrahedron Letters*, **1965**, 3345.
4) T. Kametani, K. Ohkubo, and I. Noguchi, *J. Chem. Soc.* (C), **1966**, 715.
5) T. Kametani and K. Ohkubo, *Tetrahedron Letters*, **1965**, 4317; *idem*, *Chem. Pharm. Bull.* (Tokyo), **15**, 612 (1967).
6) T. Kametani, K. Ohkubo, and R. H. F. Manske, *Tetrahedron Letters*, **1966**, 985.
7) R. H. F. Manske, *J. Am. Chem. Soc.*, **74**, 2864 (1952).
8) R. H. F. Manske and H. L. Holmes, *J. Am. Chem. Soc.*, **67**, 95 (1945).
9) A. Brossi and S. Teitel, *Helv. Chim. Acta*, **49**, 1757 (1966).
10) K. Fujitani and T. Kishimoto, *Yakugaku Zasshi*, **84**, 329 (1964).
11) T. Kametani and T. Kikuchi, *Chem. Pharm. Bull.* (Tokyo), **15**, 879 (1967).

directions to give our objective compound (I) having mp 84—86° as one of two isomers. In this case, the crystals having mp 115—117° could not be obtained as reported by Brossi and Teitel.[9] Accordingly, we have investigated an alternative synthesis of so-called corpaverine (I) according to Brossi's method, but only the substance, mp 84—86°, was also obtained, and the compound, mp 115—117°, could not be obtained. Furthermore, although the chloroform adduct[4] which had been reported previously as crystals of mp 136—139° could not be obtained, the free base (I) was obtained as the crystlas of mp 84—86°, but the mp of its hydrochloride was again recognized as the crystals of mp 136—137°[12] by elementary analysis. Furthermore, since the synthesis of 7,8-dimethoxy-1-(4-methoxybenzyl)-2-methyl-3,4-dihydroisoquinolin-6-ol (IV) by Grignard reaction has been achieved, these results will be reported in this paper.

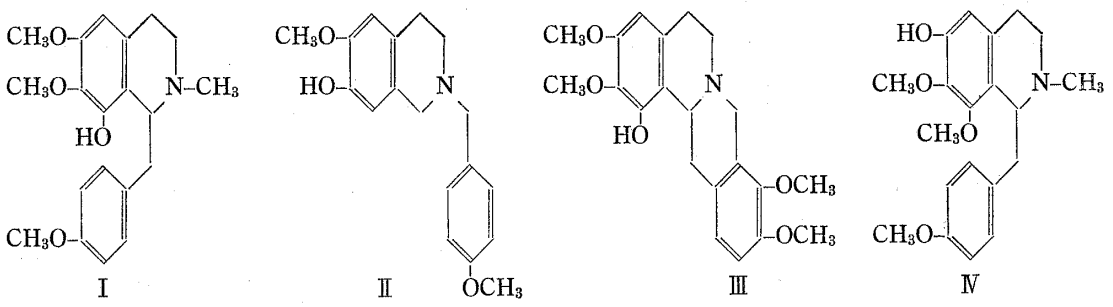


Chart 1

At first, conversion of phenethylamine derivative (V) into the corresponding formate, followed by dehydration on heating, afforded the formyl derivative (VI),[13] which was cyclized with phosphoryl chloride to give a mixture of both 3,4-dihydroisoquinoline derivatives (VII and VIII). Separation of the perchlorates by recrystllization from methanol and ether has been achieved successfully to give yellow needles, mp 142—144° and yellow prisms, mp 167—169°. This fact supports that Grignard reaction of the above both compounds (VII and VIII) with 4-methoxybenzylmagnesium chloride would afford the corresponding 6- and 8-hydroxy-1,2,3,4-tetrahydroisoquinoline derivatives (XV) and (XVI), respectively. Therefore, reduction of both perchlorates of VII and VIII with sodium borohydride was carried out, to give the corresponding 1,2,3,4-tetrahydroisoquinoline derivatives, (IX) and (X), respectively.

8-Benzyloxy-derivative (IX) obtained from the latter perchlorate was characterized as its hydrochloride,[14] mp 188—190°, whose debenzylation with ethanol and concentrated

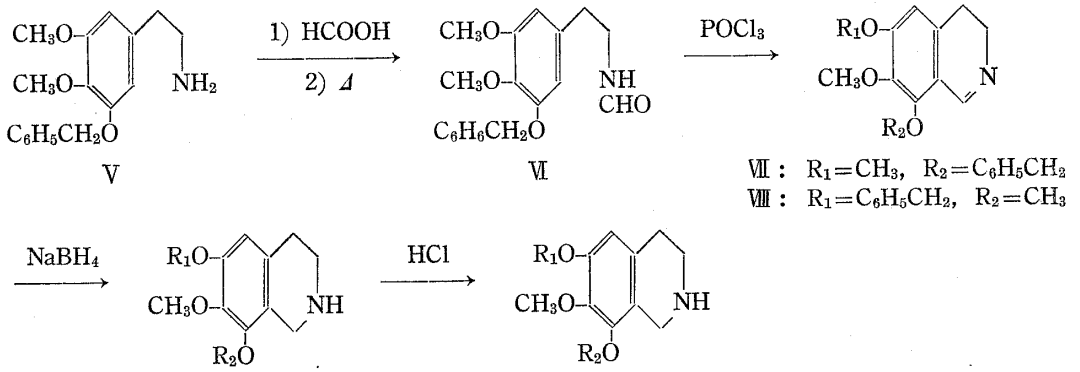


Chart 2

12) Brossi, *et al.*[9] reported that this hydrochloride melted at 192—194°.
13) A. Brossi, F. Schenker, R. Schmidt, R. Banziger, and W. Leimgruber, *Helv. Chim. Acta*, **49**, 403 (1966).
14) A. Brossi, F. Schenker, and W. Leimgruber, *Helv. Chim. Acta*, **47**, 2089 (1964).

hydrochloric acid (1:1) to give the anhalamine as its hydrochloride.[13-15] Therefore, the structure of VII was found to be 8-benzyloxy-6,7-dimethoxy-3,4-dihydroisoquinoline.

Secondly, the hydrochloride of benzyloxy-derivative (X) obtained from the former perchlorate was formed as colorless needles, mp 204—207°, whose NMR spectrum ($CDCl_3$) showed the protons of two methoxyl groups at 6.15 τ, the methylene of C_1-position at 6.10 τ as singlet, the methylene of benzyloxy group at 4.95 τ, and one aromatic proton of C_5-position at 3.54 τ. Debenzylation of the compound (X) with the same reagent as above afforded 6-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XII) as colorless cubes, mp 173—175° (lit.,[13] mp 172—174°). Accordingly, the compound obtained as perchlorate of mp 142—144° was found to be 6-benzyloxy-7,8-dimethoxy-3,4-dihydroisoquinoline (VIII).

Methylation of VII with methyl bromide afforded the methobromide (XIII), mp 145—146.5° (lit.,[14] 147—148°), which was reacted with 4-methoxybenzylmagnesium chloride[16,17] by Grignard reaction to give the benzyloxy-derivative (XV), mp 75—76° (lit.,[9] mp 74—76°). The melting point and NMR spectra were identical with an authentic sample. Furthermore, debenzylation of XV with ethanol-hydrochloric acid (1:1) gave a phenolic base, mp 84—86°, which was positive against Gibbs reagents. Although this compound was different from the chloroform-adduct[4] from the point of melting point, the IR ($CHCl_3$) and NMR ($CDCl_3$) spectra of both specimens were completely identical. In this case the compound (I) showing mp 115—117°[9] could not be obtained. Therefore, comparison of the IR and NMR spectra of our sample with Brossi's one was achieved, by the result of which both specimens were found to be identical completely. Furthermore, the IR spectra (KBr) of both specimens showed a difference.[18] These facts show that both exists as one of dimorphorism respectively (Fig. 1—4).

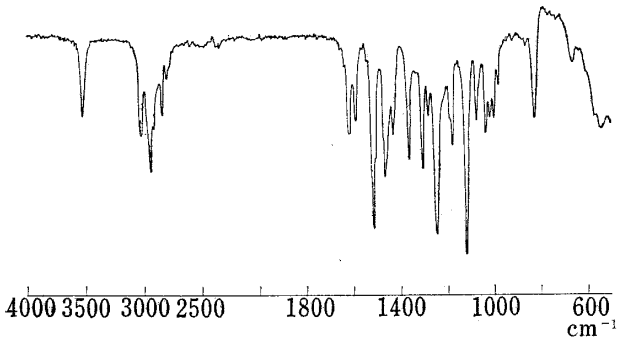


Fig. 1. The Infrared Spectrum (in Chloroform) of Kametani's Sample, mp 84—86°

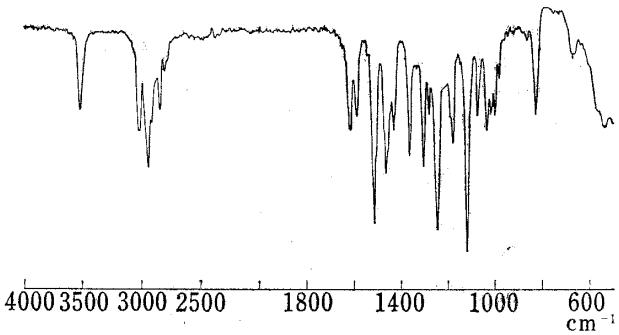


Fig. 2. The Infrared Spectrum (in $CHCl_3$) of Brossi's Sample, mp 115—117°

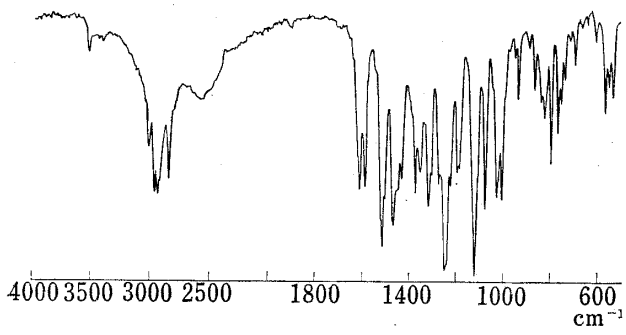


Fig. 3. The Infrared Spectrum (in KBr) of Kametani's Sample

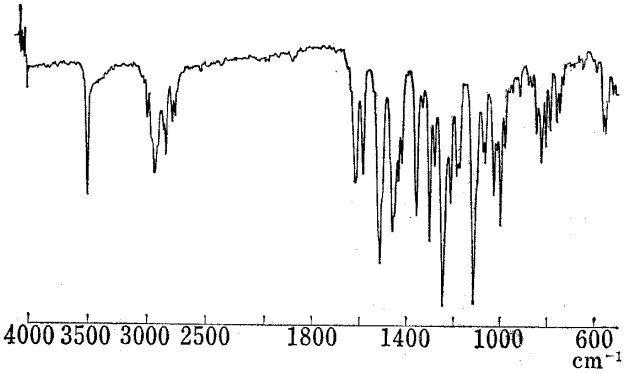
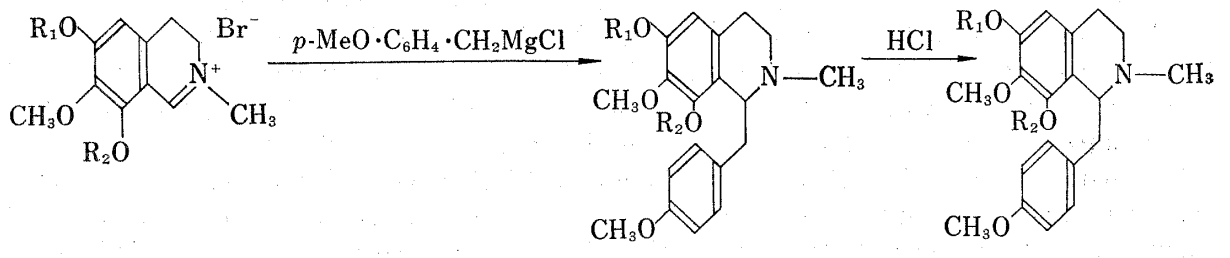


Fig. 4. The Infrared Spectrum (in KBr) of Brossi's Sample

15) T. Kametani, N. Wagatsuma, and F. Sasaki, *Yakugaku Zasshi*, **86**, 913 (1966).
16) R. C. Elderfield, and V.B. Meyer, *J. Am. Chem. Soc.*, **76**, 1883 (1954).
17) M.G. Campen, D.F. Meisner, and S.M. Parmerter, *J. Am. Chem. Soc.*, **70**, 2296 (1948).
18) We thank Dr. Brossi and Dr. Teitel for confirming the identity and suggesting polymorphism. These comparisons were held in the Hoffmann LaRoche Company, Ltd., Nutley, New Jersy.

Finally, the synthesis of 6-hydroxy-derivative (IV) was investigated as follows. Bromomethylation of the compound (VIII) with methyl bromide afforded the methobromide (XIV), mp 170—172°, whose Grignard reaction with 4-methoxybenzylmagnesium chloride afforded 6-benzyloxy-derivative (XVI) as colorless prisms, mp 99—100.5°. The NMR spectrum of XVI shows four aromatic protons at 2.82 and 3.20 τ as a quartet of AB type, one aromatic proton of C_5-position at 3.55 τ as singlet, three methoxyl groups at 6.04, 6.13 and 6.22 τ, and N-methyl group of 7.67 τ. Further debenzylation of XIV with ethanol-36% hydrochloric acid (1:1) afforded a phenolic base (IV) as colorless cubes, mp 121—122°, which were also characterized as its oxalate, mp 181—182°.[19]



XIII : $R_1=CH_3$, $R_2=C_6H_5CH_2$
XIV : $R_1=C_6H_5CH_2$, $R_2=CH_3$
XV : $R_1=CH_3$, $R_2=C_6H_5CH_2$
XVI : $R_1=C_6H_5CH_2$, $R_2=CH_3$
I : $R_1=CH_3$, $R_2=H$
IV : $R_1=H$, $R_2=CH_3$

Chart 3

Experimental[20]

8-Benzyloxy-6,7-dimethoxy-(VII) and 6-Benzyloxy-7,8-dimethoxy-3,4-dihydroisoquinoline (VIII)——A mixture of 7.9 g of N-formylamide[10,13] (VI), 50 ml of dry toluene and 15 ml of $POCl_3$ was heated under reflux in an oil-bath for 2.5 hr. According to the literature,[13] the reaction mixture was treated as usual to give 4.9 g of a mixture of VII and VIII as a reddish-brown oil.

To a solution of 3.2 g of the above mixture in 50 ml of ether was added 60% $HClO_4$ aq. solution until a white precipitate had not been recognized. At first a reddish-brown oil was separated, but it solidified for a short time. Recrystallization from MeOH-ether afforded 1.6 g of the perchlorate of VII as yellow prisms, mp 167—169° and 1.5 g of the perchlorate of VIII as yellow needles, mp 142—144°.

8-Benzyloxy-6,7-dimethoxy-3,4-dihydroisoquinoline (VII)——To a solution of 1.4 g of the above perchlorate of VII in 6 ml of MeOH was added 4 ml of conc. NH_4OH aq. solution on cooling, an oil being separated as a free base (VII), which was extracted with ether. The extract was dried on K_2CO_3 and distilled to give 1.04 g of a pale yellow oil. NMR (τ) ($CDCl_3$): 1.49 (1H, triplet, $J=2.5$ cps, $C_1\underline{H}$), 2.60 (5H, multiplet, $-CH_2C_6\underline{H}_5$), 3.52 (1H, singlet, $C_5-\underline{H}$), 4.87 (2H, singlet, $-OC\underline{H}_2C_6H_5$), 6.10, 6.13 (6H, two singlets, $2OC\underline{H}_3$), 6.34—7.42 (4H, multiplet, $-C_3\underline{H}_3-C_4\underline{H}_2-$).

Perchlorate of VII: mp 167—169°. *Anal.* Calcd. for $C_{18}H_{19}O_3N\cdot HClO_4$: C, 54.35; H, 5.07; N, 3.52. Found: C, 54.72; H, 5.54; N, 3.68.

Hydrochloride of VII: Colorless needles (EtOH-ether), mp 140—142° (lit.,[14] mp 152—153°[21]). *Anal.* Calcd. for $C_{18}H_{19}O_3N\cdot HCl\cdot 2H_2O$: C, 58.45; H, 6.54; N, 3.79. Found: C, 58.61; H, 6.73; N, 4.28.

6-Benzyloxy-7,8-dimethoxy-3,4-dihydroisoquinoline (VIII)——To a solution of 1.6 g of the above perchlorate of VIII in 6 ml of MeOH was added 4 ml of conc. NH_4OH aq. solution on cooling, a free base being separated as an oil, which was extracted with ether. The extract was dried on K_2CO_3 and distilled to give 1.41 g of a pale yellow oil. NMR (τ) ($CDCl_3$): 1.42 (1H, triplet, $J=2.5$ cps, $C_1-\underline{H}$), 2.59 (5H, multiplet, $-CH_2-C_6\underline{H}_5$), 3.49 (1H, singlet, $C_5-\underline{H}$), 4.85 (2H, singlet, $-C\underline{H}_2C_6H_5$), 6.02, 6.13 (6H, two singlets, 2 $OC\underline{H}_3$), 6.30—7.40 (4H, multiplet, $-C_3\underline{H}_2-C_4\underline{H}_2-$).

Perchlorate: mp 142—144°. *Anal.* Calcd. for $C_{18}H_{19}O_3N\cdot HClO_4$: C, 54.35; H, 5.07; N, 3.52. Found: C, 53.97; H, 4.91; N, 3.81.

Hydrochloride : Colorless needles (MeOH-ether), mp 148—150°.

6-Benzyloxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (X)——To a solution of 3.47 mg of VIII in 50 ml of MeOH was added gradually 0.3 g of $NaBH_4$ at room temperature, and the reaction mixture was allowed

19) In a previous paper[11] we reported it as a hemi-hydrate, mp 173—175°.
20) All melting points were not corrected and measured on a microscopic hot stage, and all the NMR spectra were taken on Varian A-60 in deuteriochloroform containing tetramethylsilane as an internal standard.
21) According to the literature,[14] this was also recrystallized from EtOH-ether.

to stand for 2 hr. After removal of the solvent, the residue was mixed with water and extracted with ether. The extract was dried on K_2CO_3 and distilled to give 231 mg (76.5%) of a colorless syrup, which could not be crystallized. Therefore, it was characterized as the hydrochloride, whose recrystallization from MeOH–ether afforded the HCl salt of X as colorless needles, mp 204—207°. *Anal.* Calcd. for $C_{18}H_{21}O_3N \cdot HCl$: C, 64.38; H, 6.60; N, 4.17. Found: C, 64.82; H, 6.82; N, 3.79.

7,8-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-6-ol (XII)——A mixture of 172 mg of X, 151 ml of EtOH, and 15 ml of conc. HCl aq. solution was refluxed on a water-bath for 45 min. After the removal of EtOH from the reaction mixture, the resultant reddish-brown solution was washed with benzene. The aqueous solution was made basic with conc. NH_4OH aq. solution and extracted with $CHCl_3$. The extract was dried on K_2CO_3 and distilled to give 112 mg (93.2%) of XII as pale yellow crystals, which were recrystallized from MeOH to give pale yellow cubes, mp 173—175° (lit.,[13] mp 172—174°). The IR and NMR spectra of the above compound (XII) was identical with those of an anthentic sample.[13]

6,7-Dimethoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-8-ol (I)——A mixture of 233 mg of XV, 15 ml of EtOH, and 15 ml of conc. HCl aq. solution was refluxed on a water-bath for 1 hr. An aqueous layer, which was obtained by removal of EtOH from the reaction mixture, was washed with benzene. The resulting aq. layer was made basic with conc. NH_4OH aq. solution and extracted with ether. The extract was dried on K_2CO_3 and distilled to give 145 mg (78.4%) of a pale yellow oil, whose recrystallization from $CHCl_3$–*n*-hexane afforded the compound (I) as colorless prisms, mp 84—86°. Recrystallization from *n*-hexane gave needles, mp 84—86°, whose IR and NMR spectra were identical with those of an authentic sample[4,11] *Anal.* Calcd. for $C_{20}H_{25}O_4N$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.86; H, 7.03; N, 4.28.

Recrystallization of the HCl salt of I from EtOAc afforded colorless prisms, mp 136—137° (lit.,[4] mp 134°; lit.,[9] mp 192—194°). *Anal.* Calcd. for $C_{20}H_{25}O_4N \cdot HCl \cdot \frac{1}{2}H_2O$[22]: C, 61.77; H, 7.00; N, 4.32. Found: C, 61.68; H, 7.37; N, 3.89.

6-Benzyloxy-7,8-dimethoxy-2-methyl-3,4-dihydroisoquinolinium Bromide (XIV)——To a solution of 1.4 g of VIII in 10 ml of dry benzene was added 12 ml of 60% methanolic MeBr solution, and the mixture was allowed to stand at room temperature for 2 days, to which was added an excess of ether to precipitate yellow needles. Collection by filtration gave 1.2 g (73.7%) of XIV, whose recrystallization from MeOH–ether afforded yellow needles, mp 170—172°. *Anal.* Calcd. for $C_{19}H_{22}O_3NBr$: C, 58.17; H, 5.65; N, 3.57. Found: C, 58.39; H, 6.08; N, 3.98.

6-Benzyloxy-7,8-dimethoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (XVI)——A mixture of 10 g of Mg turnings, 0.6 g of 4-methoxybenzyl chloride, 0.1 g of I_2 and 50 ml of ether was allowed to stand for a short time, the color of I_2 being disappeared suddenly. After the reaction mixture had been refluxed on a water-bath for 10 min, an ethereal solution (20 ml) containing 2.9 g of 4-methoxybenzyl chloride was added dropwise to the above mixture under mild refluxing within 35 min. After the addition, the reaction mixture was refluxed for further 40 min. After cooling, the above mixture was filtered in a current of N_2, and 1.2 g of powdered compound (XIV) was added to the resulting filtrate within 30 min. After 1.5 hours' refluxing, the reaction mixture was admixed with 1 ml of MeOH, allowed to stand overnight, and filtered. The precipitate obtained by filtration was washed with ether. The filtrate and washings were combined, dried on K_2CO_3, and distilled to give a syrup, which was converted into the corresponding HCl salt. The preceding HCl salt (0.6 g) was treated as usual to give 0.45 g (34%) of a free base (XVI), whose recrystallization from petroleum ether afforded colorless prisms,[22] mp 99—100.5°. *Anal.* Calcd. for $C_{27}H_{31}O_4N$: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.79; H, 7.18; N, 3.64. NMR (τ) ($CDCl_3$): 2.60 (5H, singlet, $-CH_2C_6\underline{H}_5$), 2.82 (2H, doublet, $J=8.5$ cps, $C_2'\underline{H}$ and $C_6'\underline{H}$), 3.20 (2H, doublet, $J=8.5$ cps, $C_3'\underline{H}$ and $C_5'\underline{H}$), 3.55 (1H, singlet, $C_5-\underline{H}$), 4.93 (2H, singlet, $OC\underline{H}_2Ph$), 6.04, 6.13, 6.22 (12H, three singlets, 3 $OC\underline{H}_3$), 7.67 (3H, singlet, $N-C\underline{H}_3$).

7,8-Dimethoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ol (IV)——A mixture of 222 mg of XVI, 20 ml of EtOH, and 20 ml of conc. HCl aq. solution was refluxed on a water-bath for 1 hr, and the solvent was removed by distillation. The resulting aq. solution was washed with benzene, made basic with conc. NH_4OH aq. solution, and extracted with ether. The extract was dried on K_2CO_3 and distilled to give 147 mg (83.5%) of a pale yellow oil, whose recrystallization from *n*-hexane afforded the compound (IV) as colorless prisms, mp 121—122° (lit.,[11] mp 128—130°). *Anal.* Calcd. for $C_{20}H_{25}O_4N$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.15; H, 7.75; N, 4.38. Recrystallization of its oxalate from MeOH–ether gave colorless cubes, mp 181—182°. *Anal.* Calcd. for $C_{20}H_{25}O_4N \cdot C_2H_2O_4$: C, 60.96; H, 6.28; N, 3.23. Found: C, 60.96; H, 6.49; N, 3.25. The IR (in KBr) spectrum of this oxalate was identical with that of our authentic sample.[11]

Acknowledgement We express our deep gratitude to Dr. A. Brossi and Dr. S. Teitel, Hoffmann-La Roche INC. (Nutley, New Jersey) for the spectral comparison with their sample. We are also grateful to Miss R. Kobayashi, Miss R. Hasebe, and Miss T. Yamaki for microanalyses.

22) This salt was dried on P_2O_5 at 55° for 2 days, and further attempts to remove the water of crystallization were tried, but failed.

22) According to the literature[10] this compound was obtained as an oil, bp 22° (0.0004 mmHg).