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Phenolic Cyclization. II.[1] Syntheses of 6-Hydroxy- and 8-Hydroxy-1,2,3,4-tetrahydroisoquinoline Derivatives (Studies on the Syntheses of Heterocyclic Compounds. CCXXXII[2])

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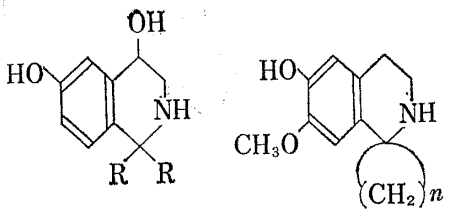
In the previous paper[1] novel syntheses of 1-substituted (I) and 1-spirocycloalkano-isoquinoline derivatives (II) were achieved by condensation of 3-hydroxyphenethylamine derivatives with carbonyl compounds. Furthermore, application of this method led to the total synthesis of (±)-coreximine, but the reaction of the above amine with homoaldehydes has not yet been examined in order to synthesize 1-benzylisoquinoline derivatives. Furthermore, an attempt to obtain 7,8-disubstituted-isoquinoline derivatives by the reaction of 2-bromo-5-hydroxy-4-methoxyphenethylamine with carbonyl compounds was investigated. Therefore, we wish to report these results.



I II

Chart 1

In 1934 Schöpf achieved a Pictet-Spengler type of reaction under conditions of temperature, concentration, and acidity comparable to these which exist in plants. For example, the reaction of tryptamine and acetaldehyde to yield a tetrahydroharman may be carried out at pH 5—6 and 25° for 3 days. This type of reactions involved in the biogenesis of alkaloids are nonenzymatic and therefore depend upon the use of extremely reactive intermediates. Frequently the reaction is slow, and the yields are very poor. Thus, the theoretical elegance of the method is offset considerably by the difficulty of its practical application, and at the present time it offers no threat to the popularity of the Pictet-Spengler reaction for preparative syntheses with the possible exception of the 2-carbolines.[4]

At first, the condensation of 3-hydroxy-4-methoxyphenethylamine (III) with 3,4-methylenedioxyphenylacetaldehyde (IV) was examined without acids as catalyst, in order to obtain the compound (VI), by the result of which the Schiff base (V) was not formed, but our expected 1,2,3,4-tetrahydroisoquinoline (VI) was obtained. In this case one step synthesis of VI, 6-hydroxyisoquinoline derivative as isococlaurine type, was found to be carried out very easily.

Secondly, the synthesis of the 7,8-disubstituted-1,2,3,4-tetrahydroisoquinoline derivatives (XVI—XXII), which could not be obtained by Bischler-Napieralski reaction and Pictet-Spengler reaction, was investigated by application of our phenolic cyclization without acids as catalyst. Various attempts[5a,b] to obtain 7-alkoxy-8-hydroxyisoquinoline derivatives have been hitherto reported, but only a few successful results[6] were reported.

1) Part I; *J. Chem. Soc.* (C), **1968**, 112.
2) Part CCXXXI: *Chem. Pharm. Bull.* (Tokyo), **16**, 909 (1968).
3) Location: *No. 85, Kita-4-bancho, Sendai.*,
4) C. Schöpf and H. Bayerle, *Ann.*, **513**, 190 (1934); G. Hahn and A. Hansel, *Ber.*, **71**, 2163 (1938).
5) *a*) R.D. Haworth and W.H. Perkin, *J. Chem. Soc.*, **127**, 1448 (1925); *b*) A.R. Battersby, R. Southgate, and J. Staunton, *J. Chem. Soc.* (C), **1966**, 1052.
6) T. Kametani, M. Satoh, and S. Shibuya, *Yakugaku Zasshi*, **87**, 1063 (1967).

Recently one of the authors has reported the synthesis of various 6-hydroxyisoquinolines without using acids as catalyst. In this case cyclization has occurred at the position *para* to the phenolic hydroxyl group. Therefore, if the 2-bromo-5-hydroxy-4-methoxyphenethyl-

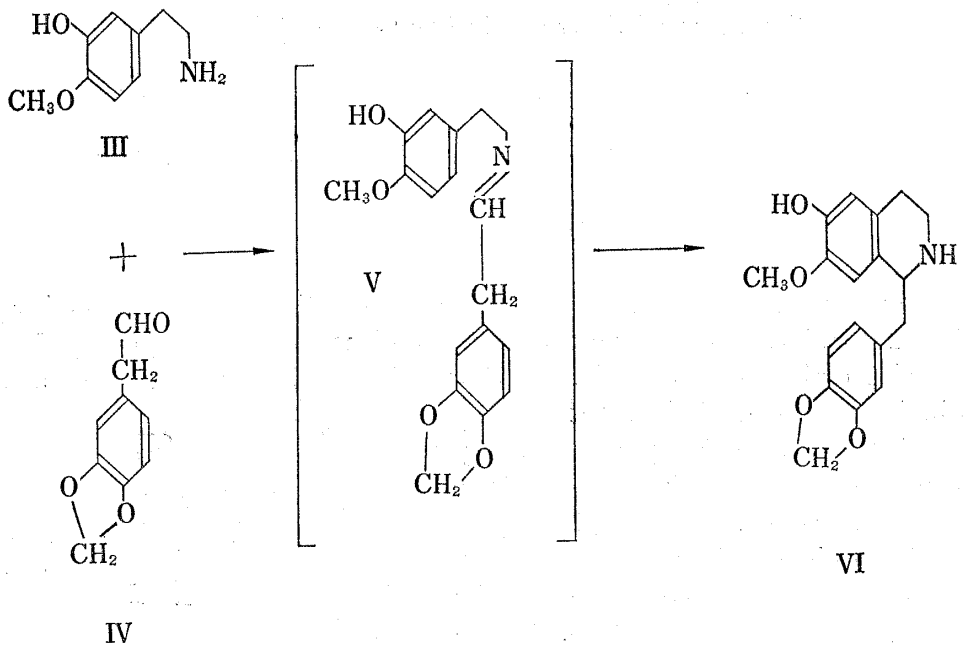


Chart 2

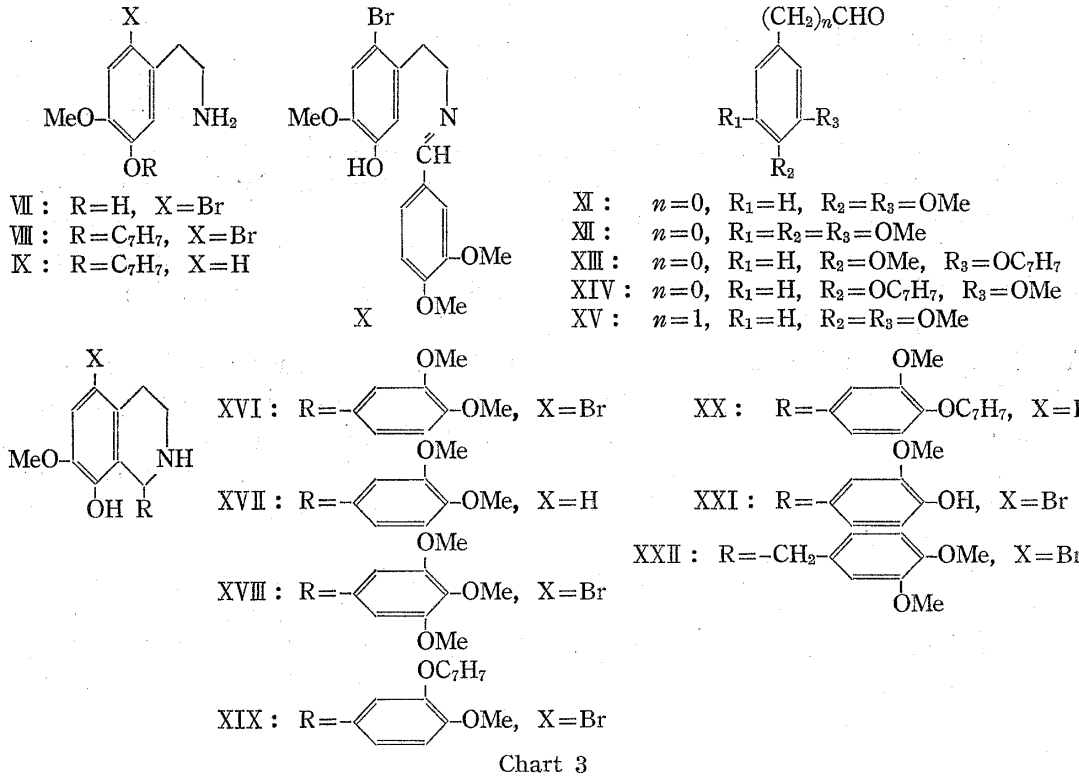


Chart 3

amine (VII) is used in the phenolic cyclization, the cyclized product at the position *ortho* to the hydroxy group will be obtained as in the case of the total syntheses of (±)-scoulerine and tetrahydropalmatine.[7]

7) T. Kametani and M. Ihara, *J. Chem. Soc.* (C), **1967**, 530.

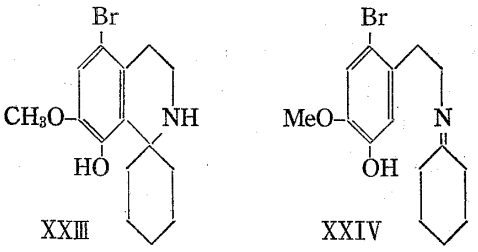


Chart 4

Debenzylation of O-benzyl derivative[5b] (VIII), which was obtained by bromination of the amine (IX), afforded the starting amine (VII). A mixture of the above amine (VII) and veratraldehyde (XI) in ethanol was refluxed for 7 hr, whose treatment as usual gave colorless needles, mp 167—168°. The lack of absorption band of C=N group in its IR spectrum (KBr) shows that the condensation product is not a Schiff base (X) but our expected 1,2,3,4-tetrahydroisoquinoline (XVI). Furthermore, UV spectrum (in MeOH) showed the characteristic maximum of 1,2,3,4-tetrahydroisoquinoline deriva-

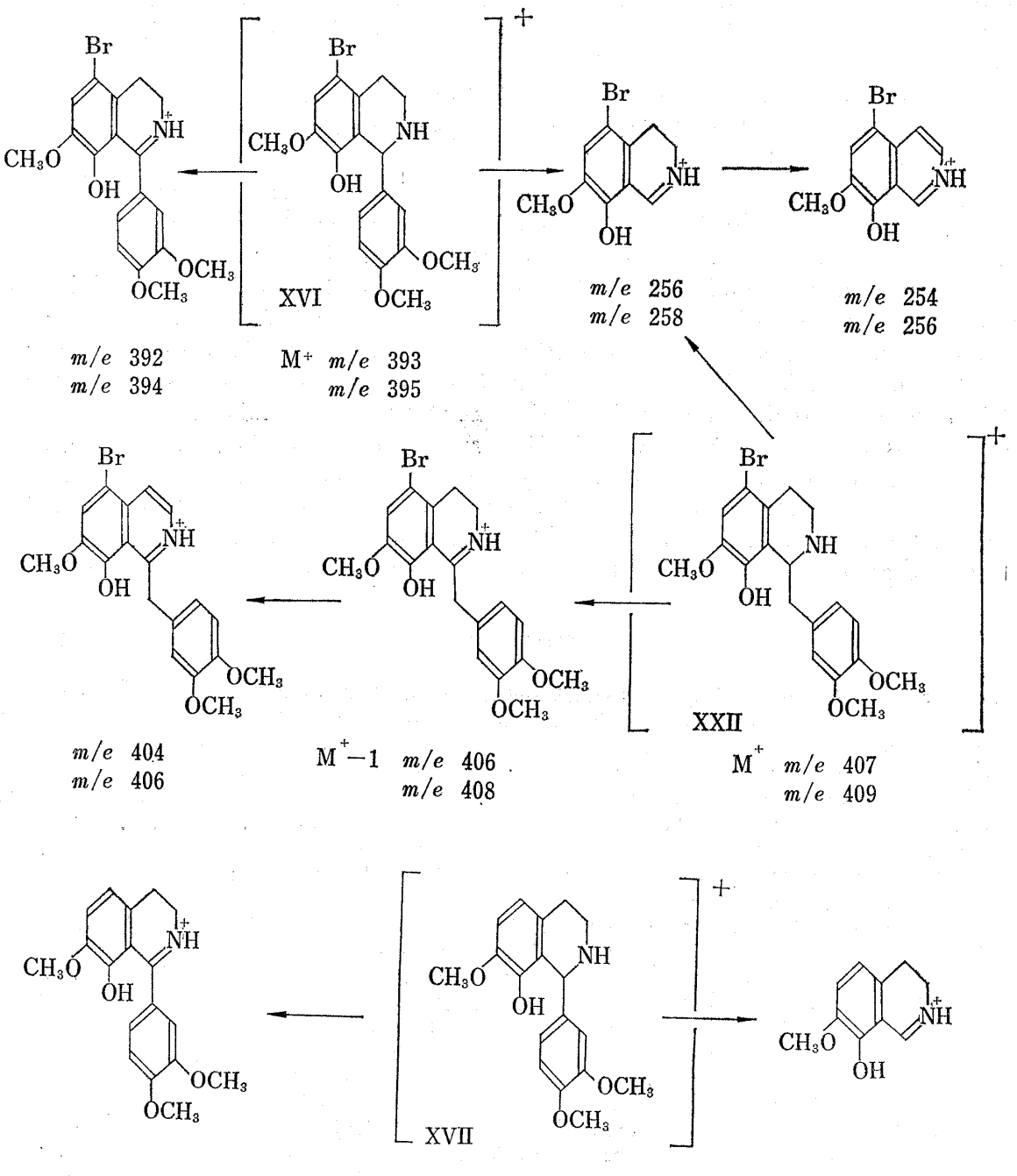


Chart 5

tives at 282 mμ, and its NMR spectrum (in CF_3CO_2H) also showed one proton of the C_1–methine at 6.15 ppm and four aromatic protons at 6.80—7.35 ppm. Debromination of (XVI) by catalytic hydrogenation in the presence of ethanol and 5% palladium charcoal afforded the compound (XVII), in the NMR spectrum of which the signal due to one aromatic proton of C_6–position at 7.35 ppm (XVI) has shifted to the high field because of the loss of the deshielding effect of the bromine atom and that of five aromatic protons has appeared at 7.15—6.87 ppm as multiplet. These facts prove the structures of XVI and XVII to be correct.

The same condensation of the amine (VII) with various aldehydes (XII, XIII, XIV) also afforded the corresponding isoquinolines (XVIII, XIX, XX), respectively. In the latter case, since the compound (XX) could not be purified, debenzylation of XX was carried out to give the compound (XXI), which was characterized as its hydrochloride. Furthermore, the NMR spectra (in CF_3CO_2H) also support the structure of these isoquinolines to be reasonable.

In the case of homoaldehyde (XV), the yield of our expected product (XXII) was very poor because of the formation of a large amount of resinous substance, and it was characterized only as its hydrochloride.

Finally, the same condensation as above of the amine (VII) with acetone according to our procedure[1] was tried, but the starting material was recovered. Furthermore, cyclohexanone was also used as one of the starting materials. In this case, although the condensation product was obtained as colorless crystals, mp 155—157°, but its NMR spectrum (in CF_3CO_2H) showed two aromatic protons at 7.00 and 7.25 ppm as singlet, respectively, and the signal due to the methylene group of $-C=N-C\underline{H}_2-$ was also shown at 4.2—3.9 ppm as triplet. Therefore, no formation of our expected 1–spiro–isoquinoline (XXIII) was recognized, but only the Schiff base (XXIV) was obtained.

The mass spectrum of XVI showed M^+, M^+-1 and M^+-137 at *m/e* 393, 392 and 256, respectively, which were characteristic of the 1,2,3,4–tetrahydroisoquinolines. Furthermore, the mass spectrum of XXII showed M^+,M^+-1 and M^+-151 at *m/e* 407, 406 and 256, respectively, in which an increase of 2 mass units due to Br^{81} was observed. The compound (XVII) also gives the expected fragments at M^+,M^+-1 and M^+-137 at *m/e* 315, 314 and 178, respectively.

Experimental[8]

7-Methoxy-1-(3,4-methylendioxybenzyl)-1,2,3,4-tetrahydroisoquinolin-6-ol (VI)——A mixture of 300 mg of 3–hydroxy–4–methoxyphenethylamine, 400 mg of homopiperonal (IV) and 5 ml of EtOH was refluxed on a water–bath for 3 hr in a current of N_2, and the solvent was then removed by distillation to give 700 mg of a yellowish orange syrup, which was washed with 5 ml of $CHCl_3$ in order to remove a resinous substance. Recrystallization of the resultant solid from EtOAc afforded 120 mg (21%) of colorless prisms, mp 171—172°. IR cm^{-1}: ν_{NH}^{KBr} 3260. UV mμ: λ_{max}^{MeOH} 288. *Anal.* Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.68; H, 6.37; N, 4.35. Recrystallization of the HCl salt from MeOH gave yellow prisms, mp 236—238°. UV mμ: λ_{max}^{MeOH} (log ε) 288 (3.97). *Anal.* Calcd. for $C_{18}H_{19}NO_4HCl\cdot\frac{3}{4}H_2O$: C, 59.62; H, 5.98; N, 3.80. Found: C, 59.65; H, 5.91; N, 3.89.

4-Benzyloxy-2-bromo-3-methoxyphenethylamine (VIII)——Bromine (3.5 g) in 30 ml of $CHCl_3$ was added dropwise to a solution of 5 g of 3–benzyloxy–4–methoxyphenethylamine in 30 ml of $CHCl_3$ at room temperature. After the mixture had been stirred at room temperature for 30 min, the solvent was removed by distillation to give a dark brown solid which was basified with 10% NaOH aq. solution and extracted with benzene. The extract was dried on Na_2SO_4 and evaporation of the solvent left 5 g of a brown gum, whose solution in a small amount of MeOH was added to a dry ethereal solution saturated with HCl gas to give 5 g of the hydrochloride. Recrystallization from MeOH–ether to give 4 g of amine–HCl as colorless needles, mp 181—182°, which were identical with an authentic sample[5] on mixed melting point test and IR spectrum (KBr).

5-Bromo-7-methoxy-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (XVI)——An aqueous solution of the free base, which was obtained by basification of 200 mg of hydrochloride of VII with 10% Na_2CO_3 aq. solution, was extracted with BuOH. The extract was dried on Na_2SO_4 and evaporated to afford

8) All melting points were not corrected.

the free base of VII as colorless needles. To an ethanolic solution of the above free base (VII) was added 200 mg of veratraldehyde, and the mixture was refluxed for 7 hr. After the reaction, removal of the solvent gave pale brown crystals, which were recrystallized from EtOH–ether to afford 150 mg of the tetrahydroisoquinoline derivative as colorless prisms, mp 167—168°. *Anal.* Calcd. for $C_{18}H_{20}O_4NBr$: C, 54.83; H, 5.11; N, 3.25. Found: C, 54.97; H, 5.37; N, 3.43. NMR (CF_3COOH) (ppm): 3.2—3.8 (4H, multiplet, $C_3\underline{H}_2$–$C_4\underline{H}_2$), 3.97 (9H, $3OC\underline{H}_3$), 6.15 (1H, singlet, C_1–$\underline{H}$), 6.8—7.35 (4H, aromatic H).

7-Methoxy-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (XVII)——A solution of 150 mg of the foregoing isoquinoline derivative (XVI) in 50 ml of EtOH was hydrogenated at atmospheric pressure in the presence of 50 mg of 5% Pd–C for 48 hr. Filtration and removal of the solvent *in vacuo* gave the HBr salt of XVII as colorless prisms, mp 245—247°, which were recrystallized from EtOH–ether to give colorless prisms, mp 246—247°. *Anal.* Calcd. for $C_{18}H_{22}O_4NBr$: C, 54.55; H, 5.60; N, 3.37. Found: C, 54.49; H, 6.03; N, 3.24. NMR (CF_3COOH) (ppm): 3.25—3.7 (4H, multiplet, $C_3\underline{H}_2$–$C_4\underline{H}_2$), 3.97 (9H, $3OC\underline{H}_3$), 6.2 (1H, singlet, C_1–$\underline{H}$), 6.87—7.15 (5H, aromatic $\underline{H}$).

5-Bromo-7-methoxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (XVIII)——3,4,5-Trimethoxybenzaldehyde (210 mg) was added to a solution of 170 mg of the free base (VII) in 45 ml of EtOH, which was prepared by the same method as above, and the mixture was refluxed for 8 hr. Removal of the solvent afforded 250 mg of a colorless powder. To a solution of the free base of XVIII in a small amount of MeOH was added 0.5 ml of an ethereal solution saturated with dry HCl gas, and the mixture was allowed to stand for a short time to precipitate the HCl salt of XVIII. Separation of the crystals and recrystallization from EtOH–ether afforded 220 mg of colorless needles, mp 248—249°. *Anal.* Calcd. for $C_{19}H_{22}O_5NBr\cdot HCl$: C, 49.52; H, 5.03; N, 3,04. Found: C, 49.84; H, 5.37; N, 2.84. NMR (CF_3COOH) (ppm): 3.2—3.8 (4H, multiplet, $C_3\underline{H}_2$–$C_4\underline{H}_2$), 3.88, 3.95, 3.99 (12H, $4OC\underline{H}_3$), 6.15 (1H, singlet, C_1–$\underline{H}$), 6.71 (2H, singlet, C_2'–$\underline{H}$ and C_6–$\underline{H}$), 7.35 (C_6–$\underline{H}$).

1-(3-Benzyloxy-4-methoxyphenyl)-5-bromo-7-methoxy-1,2,3,4-tetrahydroisoquinolin-8-ol (XIX)——To a solution of 170 mg of the free base (VII) in 50 ml of EtOH was added 250 mg of O-benzylisovanillin, and the mixture was refluxed for 10 hr. Evaporation of the solvent left a gum, which was dissolved in a small amount of MeOH. An ethereal solution (0.1 ml) saturated with dry HCl gas was added to the above solution, and the mixture was allowed to stand for a short time to precipitate a colorless powder. Separation and recrystallization from EtOH–ether afforded 100 mg of the HCl salt of 1,2,3,4-tetrahydroisoquinoline derivative (XIX) as colorless needles, mp 172—173°. *Anal.* Calcd. for $C_{24}H_{24}O_4NBr\cdot HCl\cdot \frac{1}{2}H_2O$: C, 55.88; H, 5.08; N, 2.71. Found: C, 56.12; 55.89; H, 5.39, 5.06, N, 2.79. NMR (CF_3COOH) (ppm): 2.9—3.6 (4H, multiplet, $C_3\underline{H}_2$–$C_4\underline{H}_2$), 3.91 (6H, $2OC\underline{H}_3$), 5.07 (2H, singlet, $C_6H_5C\underline{H}_2O$–), 6.0 (1H, singlet, C_1–$\underline{H}$).

5-Bromo-1-(4-hydroxy-3-methoxyphenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinolin-8-ol (XXI)——Benzylvanillin (250 mg) was added to a solution of 170 mg of the free base (VII) in 50 ml of EtOH, which was prepared as usual, and the mixture was refluxed for 10 hr. Removal of the solvent gave a gum, which was dissolved in a small amount of MeOH, and an ethereal solution (2—3 ml) saturated with HCl gas was added to the above solution. Since no crystals had been separated, removal of the solvent afforded the solid, mp 245—248°, which was characterized as the HCl salt of debenzylated isoquinoline derivative (XXI). Recrystallization from EtOH–ether gave 30 mg of colorless needles, mp 246—247.5°. *Anal.* Calcd. for $C_{17}H_{18}O_4NBr\cdot HCl$: C, 48.99; H, 4.60. Found: C, 48.70; H, 4.72. NMR (CF_3COOH) (ppm): 3.10—3.80 (4H, multiplet, $C_3\underline{H}_2$–$C_4\underline{H}_2$), 3.95 (6H, $2OC\underline{H}_3$), 6.15 (1H, singlet, C_1–$\underline{H}$).

5-Bromo-7-methoxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (XXII)——To a solution of 400 mg of the free base (VII) in 60 ml of EtOH was added 350 mg of homoveratraldehyde. After the mixture had been refluxed for 8 hr, it was allowed to stand for 24 hr at room temperature, giving a dark brown solution. Removal of the solvent gave a resinous substance which was dissolved in MeOH and treated with an ethereal solution saturated with dry HCl gas, and the mixture was allowed to stand for a short time to precipitate the HCl salt of XXII, mp 226—228°. Separation of 100 mg of crystals, which were recrystallized from EtOH–ether to give colorlesn seedles, mp 230°. *Anal.* Calcd. for $C_{19}H_{22}O_4NBr\cdot HCl\cdot 1\frac{1}{2}H_2O$: C, 48.16; H, 5.32; N, 2.98. Found: C, 48.35; 48.53; H, 5.55, 5.93; N, 3.04. NMR (CF_3COOH) (ppm): 3.0—3.85 (7H, C_1–$\underline{H}$ and $C_3\underline{H}_2$–$C_4\underline{H}_2$, C_1–$C\underline{H}_2$–), 4.0 (9.0, $3OC\underline{H}_3$), 7.04 (3H, C_2'–$\underline{H}$, C_5'–$\underline{H}$, C_6'–$\underline{H}$), 7.30 (1$\underline{H}$,singlet, C_6–$\underline{H}$).

Schiff base (XXIV)——A mixture of 200 mg of free base (VII), 200 mg of cyclohexanone and 60 ml of EtOH was refluxed for 10 hr in a current of N_2. Removal of the solvent afforded 150 mg of a pale brown solid mp 156—158°, which was so labile that it was decomposed gradually on its exposure in the air or in the organic solvents to give the starting material (cyclohexanone). NMR (CF_3COOH) (ppm): 1.6—2.0 (6H, multiplet cyclohexyl $-C\underline{H}_2C\underline{H}_2C\underline{H}_2-$ 2.4—3.0 (4H, multiplet, cyclohexyl $-C\underline{H}_2-\overset{\overset{\|}{N}}{C}-C\underline{H}_2-$) 3.05—3.4 (2H, triplet, $-C\underline{H}_2-CH_2-N=$), 3.90—4.2 (2H, triplet, $-CH_2C\underline{H}_2-N=$), 3.95 (3H, singlet, $OC\underline{H}_3$), 7.00 (1H, singlet C_2–$\underline{H}$), 7.25 (1H, singlet, C_5–$\underline{H}$).

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