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Synthesis of Aminoisoquinolines and Related Compounds. II.[1] Syntheses of 6-Amino-1-benzylisoquinolines by the Bischler-Napieralski Reaction[2]

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The Bischler–Napieralski reaction of the phenethylamides (VIa and VIb) was accelerated by the presence of an ethoxycarbamido group in the 3-position of the benzene ring and the ring-closure occured selectively at the position *para* to the ethoxycarbamido group to give the corresponding 3,4-dihydroisoquinolines (VIIa and VIIb) in good yields.

The preceding paper of this series[1] has shown that the presence of an ethoxycarbamido group in the 3-position of the benzene ring accelerates the Bischler–Napieralski reaction of β-phenethylbenzamides as well as an alkoxyl, and that the cyclization to the corresponding 3,4-dihydroisoquinolines are found to take place selectively at the position *para* to the ethoxycarbamido group.

The present paper shows that the Bischler–Napieralski cyclization of β-phenethylphenylacetamides (VIa and VIb) is accelerated by the presence of the ethoxycarbamido group in the 3-position of the benzene ring as mentioned in the previous paper.

With regard to poor yield of the aldehydes (IIIa, 44% and IIIb, 45%) in the preceding experiments, a modified synthesis was attempted. Ethoxycarbonylation of the aminoacetals (Ia and Ib) with ethyl chloroformate in pyridine instead of 10% sodium hydroxide solution

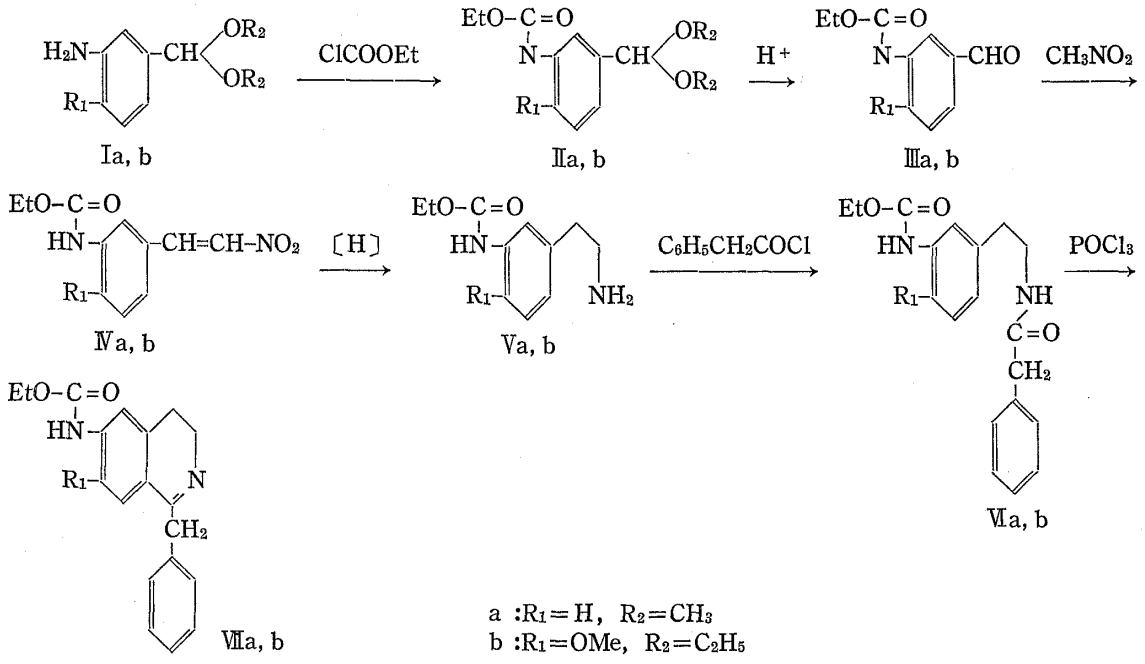

Chart 1

1) Part I: S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), **16**, 778 (1968).
2) This work was presented at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968.
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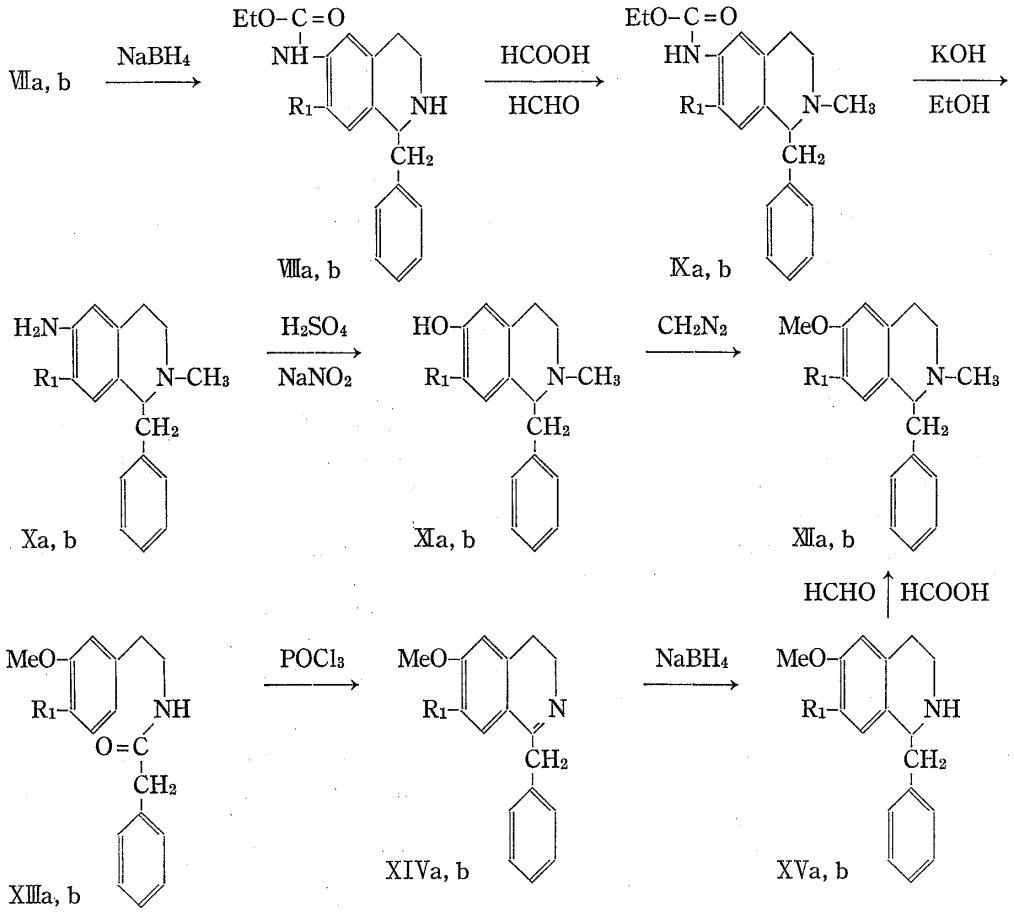
gave ethoxycarbamidoacetals (IIa and IIb), which were hydrolyzed successively without isolation to IIIa and IIIb with 15% hydrochloric acid solution in yield of 61% and 71%, respectively.

The Schotten–Baumann condensation of the phenethylamines (Va and Vb) prepared by electrolytic reduction of the nitrostyrenes (IVa and IVb) with phenylacetyl chloride afforded the amides (VIa and VIb). These amides were submitted to the Bischler–Napieralski reaction under the same conditions as those in the previous work to give the corresponding 3,4-dihydroisoquinolines (VIIa and VIIb) in good yields.

In the cyclization of these amides, the spot of VIa on thin-layer chromatography disappeared after refluxing for 20 min, but that of VIb did after 30 min as in the case of the cyclization of N-(3-ethoxycarbamido-4-methoxyphenethyl)benzamide.[1]

The cyclization of these amides was proved by the following facts (Chart 2). The 3,4-dihydroisoquinolines were reduced with sodium borohydride in methanol to the 1,2,3,4-tetrahydroisoquinolines (VIIIa and VIIIb), which were methylated to the N-methyl derivatives (IXa and IXb) by the Eschweiler–Clark reaction.

These N-methylisoquinolines were hydrolyzed with 10% ethanolic potassium hydroxide solution to the 6-amino compounds (Xa and Xb), which were successively diazotized to the 6-isoquinolinols (XIa and XIb). Methylation of the 6-isoquinolinols with diazomethane gave the 6-methoxy compounds (XIIa and XIIb), which were identified with the corresponding authentic samples[4] prepared from the usual Bischler–Napieralski cyclization of N-(3-methoxy-



a : R_1=H b : R_1=OMe

Chart 2

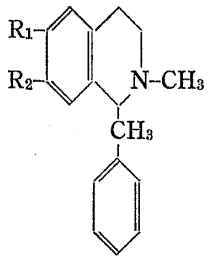
4) *a*) J. Niimi, *Yakugaku Zasshi*, **80**, 1005 (1960); *b*) T. Kametani, K. Wakisaka, and K. Fukumoto, *Yakugaku Zasshi*, **85**, 956 (1965).

phenethyl)- and N-(3,4-dimethoxyphenethyl)phenylacetamides (XIIIa and XIIIb) by mixed melting point determination and infrared (IR) spectral comparison.

In the nuclear magnetic resonance (NMR) spectrum (Table I)[5] of the amino compound (Xa), the proton signal of N-methyl appeared at 7.54 τ as a singlet peak and that of C (5), C (7), and C (8) did about at 3.59 τ as a group. On the other hand, the proton signal of N-methyl and O-methyl of the amino compound (Xb) appeared at 7.50 τ and 6.52 τ as a singlet peak, respectively and that of C (5) and C (8) did also 3.59 τ and 4.10 τ as a singlet peak, respectively.

These spectral data also supported the structure of the amino compounds.

Table I. Chemical Shifts (τ) in $CDCl_3$ at 60 Mc



R_1	R_2		Aromatic-H C(5)-H	C(7)-H	C(8)-H	O-CH_3 R_1	R_2	N-CH_3
NH_2	H	Xa		3.59 (3H)		—	—	7.54
O-CH_3	H	XIIa		3.38 (3H)		6.25	—	7.51
NH_2	O-CH_3	Xb	3.59	—	4.10	—	6.52	7.50
O-CH_3	O-CH_3	XIIb	3.39	—	4.00	6.13	6.46	7.42

On the base of these facts, it revealed that the cyclization of the phenethylamides (VIa and VIb) having an ethoxycarbamido group in the 3-position of the benzene ring was found to take place at the position *para* to the ethoxycarbamido group.

Experimental[6]

3-Ethoxycarbamidobenzaldehyde (IIIa)——To a stirred solution of 20 g of the aminoacetal (Ia)[7] dissolved in 40 ml of pyridine cooled in an ice bath, 15 g of ethyl chloroformate was added dropwise.

After addition, the reaction mixture was heated on a water bath for 30 min and the mixture was added to 200 ml of 15% aq. HCl with stirring. After 1 hr stirring, a precpitated crystalline solid was collected by filtration. The product was recrystallized from benzene to give 12 g of white needles, mp 89—91°.

3-Ethoxycarbamido-4-methoxybenzaldehyde (IIIb)——Prepared from the aminoacetal (Ib)[1] (20 g) in pyridine (40 ml) and ethyl chloroformate (14 g) by the same method described for the above aldehyde. Recrystallization from benzene–ligloin gave 14 g of IIIb as white plates, mp 81—82°.

N-(3-Ethoxycarbamidophenethyl)phenylacetamide (VIa)——A mixture of 1 g of phenylacetic acid, 3 ml of $SOCl_2$ and 10 ml of benzene was refluxed for 1 hr. The solvent and $SOCl_2$ were removed under reduced pressure and the residue dissolved in dry ether was added dropwise to a stirred mixture of Va (liberated from 1.5 g of the hydrochloride) in 200 ml of ether and 100 ml of 3% aq. NaOH cooled in an ice bath. The reaction mixture was stirred for 1 hr and the ethereal solution was washed with 5% aq. HCl and H_2O, dried over K_2CO_3 and evaporated. The residue was recrystallized from benzene–ligloin to yield 1.2 g of colorless needles, mp 101—102°. *Anal.* Calcd. for $C_{19}H_{22}O_3N_2$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.90; H, 6.84; N, 8.71. IR cm^{-1} (KBr): $\nu_{C=O}$ 1700 (urethane), 1646 (amide).

1-Benzyl-6-ethoxycarbamido-3,4-dihydroisoquinoline (VIIa)——A mixture of 1.5 g of the above amide and 4.5 ml of $POCl_3$ was refluxed in 20 ml of dry toluene for 20 min. The solvent and $POCl_3$ were removed

5) NMR spectra were measured by HITACHI H-6013 spectrophotometer at 60 Mc in $CDCl_3$ and tetramethylsilane was used as internal standard.
6) All melting points were not corrected.
7) "Org. Syntheses," Coll. Vol. III, 59.

under reduced pressure, and the resultant solid was washed with *n*-hexane and recrystallized from EtOH–ether to give 1.2 g of pale yellow rhombic plates, mp 227—229° (decomp.). *Anal.* Calcd. for $C_{19}H_{20}O_2N_2 \cdot HCl$: C, 66.16; H, 6.14; N, 8.12. Found: C, 66.04; H, 6.15; N, 7.95. IR cm^{-1} (KBr): $\nu_{C=N}$ 1658.

The hydrochloride was taken up in $CHCl_3$ and the extract was washed with H_2O saturated with $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated. The resultant free base was recrystallized from MeOH to give colorless prisms, mp 131—133°. *Anal.* Calcd. for $C_{19}H_{20}O_2N_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 73.73; H, 6.15; N, 9.05.

1-Benzyl-6-ethoxycarbamido-1,2,3,4-tetrahydroisoquinoline (VIIIa)——To a stirred solution of 0.5 g of the above crude hydrochloride in 20 ml of MeOH, 0.5 g of $NaBH_4$ was added portionwise and the mixture was stirred for 1 hr at room temperature. After acidification of the mixture with AcOH, the solvent was removed under reduced pressure, and the residue was basified with conc. NH_4OH and extracted with ether. The extract was washed with H_2O, dried over K_2CO_3 and distilled to give a colorless solid, which was recrystallized from *n*-hexane to give 0.3 g of colorless needles, mp 101—102°. *Anal.* Calcd. for $C_{19}H_{22}O_2N_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.52; H, 7.23; N, 8.97.

1-Benzyl-6-ethoxycarbamido-1,2,3,4-tetrahydro-2-methylisoquinoline (IXa)——A mixture of 0.2 g of VIIIa, 2 ml of HCOOH and 2 ml of 36% HCHO was heated for 3 hr in a boiling water bath and then evaporated. The residue was basified with 10% NH_4OH and extracted with ether. The extract was washed with H_2O, dried over K_2CO_3 and evaporated to give a yellow syrup (0.18 g), which was characterized as hydrochloride. Recrystallization of the hydrochloride from EtOH–ether gave colorless powder, mp 204—206° (decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_2N_2 \cdot HCl$: C, 66.56; H, 6.98; N, 7.76. Found: C, 66.62: H, 7.00; N, 7.93.

6-Amino-1-benzyl-1,2,3,4-tetrahydro-2-methylisoquinoline (Xa)——A mixture of 0.25 g of IXa and 15 ml of 10% KOH–EtOH solution was refluxed for 2 hr in the presence of N_2. The solvent was distilled and the resultant residue was acidified with cnc. HCl and the acidic solution was basified again with conc. NH_4OH. The product was taken up in ether and the extract was dried over K_2CO_3 and evaporated to give a brown product (0.14 g), which was characterized as picrate. Recrystallazation of the picrate from EtOH gave yellow needles, mp 186—188° (decomp.). *Anal.* Calcd. for $C_{17}H_{20}N_2 \cdot C_6H_3O_7N_3$: C, 57.37; H, 4.82; N, 14.55. Found: C, 57.47; H, 4.94; N, 14.72.

1-Benzyl-1,2,3,4-tetrahydro-2-methyl-6-isoquinolinol (XIa)——To a stirred solution of 0.1 g of Xa dissolved in 5 ml of 15% aq. H_2SO_4, a solution of 30 mg of $NaNO_2$ in 1 ml of H_2O was added at 5° and the reaction mixture was stirred for 0.5 hr. After decomposition of excess HNO_2 with urea, the mixture was refluxed for 5 min and the phenolic base was taken up in ether by usual manner and the extract was dried over Na_2SO_4 and evaporated. Recrystallization of the resultant solid from benzene gave 45 mg of colorless plates, mp 166—168°.[8] *Anal.* Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.33. Found: C, 80.87; H, 7.65; N, 5.81. IR cm^{-1} ($CHCl_3$): ν_{OH} 3600.

1-Benzyl-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (XIIa)——A mixture of 50 mg of XIa and 150 ml of ethereal solution of diazomethane (liberated from 10 g of N-methyl-N-nitroso-*p*-toluenesulfonamide) was kept in an ice box for 4 days.

Evaporation of the solvent gave 40 mg of a pale yellow syrup, which was converted to the picrate. Recrystallization of the picrate from EtOH gave yellow needles, mp 155—157° (decomp.) (lit.,[8] 153°). *Anal.* Calcd. for $C_{18}H_{21}ON \cdot C_6H_3O_7N_3$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.13; H, 5.01; N, 11.02.

N-(3-Methoxyphenethyl)phenylacetamide (XIIIa)——Prepared from 3-methoxyphenethylamine (liberated from 1 g of the oxalate) and phenylacetic acid (1 g) in the same method as described for VIa.

Recrystallization of the product from ether gave 1 g of colorless needles, mp 61—62°, *Anal.* Calcd. for $C_{17}H_{17}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.03; H, 7.19; N, 4.90. IR cm^{-1} (KBr): $\nu_{C=O}$ 1643, ν_{NH} 3250.

1-Benzyl-3,4-dihydro-6-methoxyisoquinoline (XIVa)——A mixture of 1 g of the amide and 3 ml of $POCl_3$ was refluxed in 15 ml of toluene for 1 hr. The solvent and excess $POCl_3$ were removed under reduced pressure to give a reddish brown viscous syrup, which was taken up in $CHCl_3$. The extract was washed with H_2O saturated with $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to give 0.85 g of yellow oil. Picrate: Recrystallization from EtOH gave yellow plates, mp 166—168° (decomp.). *Anal.* Calcd. for $C_{17}H_{15}ON \cdot C_6H_3O_7N_3$: C, 57.50; H, 4.20; N, 11.61. Found: C, 57.55; H, 4.19; N, 11.72.

1-Benzyl-1,2,3,4-tetrahydro-6-methoxyisoquinoline (XVa)——To a stirred solution of 0.8 g of XIVa in 20 ml of MeOH, 1 g of $NaBH_4$ was added in small portions and the reaction mixture was refluxed for 1 hr. After removal of the solvent, the resultant residue was extracted with ether. The extract was dried over K_2CO_3 and evaporated to give 0.7 g of colorless oil. Recrystallization of the picrate from EtOH gave yellow needles, mp 153—155° (decomp.). *Anal.* Calcd. for $C_{17}H_{19}ON \cdot C_6H_3O_7N_3$: C, 57.26; H, 4.60; N, 11.61. Found: C, 57.27; H, 4.19; N, 11.61.

1-Benzyl-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (XIIa)——Prepared from the above amide (0.2 g), 2 ml of HCOOH and 2 ml of 36% HCHO in the same way as described for IXa, yielding 0.18 g of a pale yellow syrup, which was characterized as picrate. Recrystallization of the picrate form EtOH gave yellow

8) H. Furukawa, *Yakugaku Zasshi*, **85**, 850 (1965). This product was reported as an oily product.

needles, mp 155—157° (decomp.). *Anal.* Calcd. for $C_{18}H_{21}ON \cdot C_6H_3O_7N_3$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.96; H, 4.93; N, 11.42.

N-(3-Ethoxycarbamido-4-methoxyphenethyl)phenylacetamide (VIb)——Prepared from 3-ethoxycarbamido-4-methoxyphenethylamine (liberated from 1.5 g of the oxalate) and phenylacetic acid (0.8 g) in the same method as described for VIa. Recrystallization from benzene–ligloin gave 1.1 g of colorless needles, mp 110—112°. *Anal.* Calcd. for $C_{20}H_{24}O_4N_2$: C, 67.39; H, 6.79; N, 7.86. Found: C, 67.39; H, 6.87; N, 8.06. IR cm^{-1} (KBr): $\nu_{C=O}$ 1739 (urethane), 1649 (amide), ν_{NH} 3250 (amide), 3440 (urethane).

1-Benzyl-6-ethoxycarbamido-3,4-dihydro-7-methoxyisoquinoline (VIIb)——A mixture of 1.5 g of the amide, and 4.5 ml of $POCl_3$ was refluxed in 20 ml of toluene for 30 min. The solvent and $POCl_3$ were removed under reduced pressure and the resultant reddish brown residue was dissolved in $CHCl_3$. The extract was washed with H_2O saturated with $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to give 1.35 g of a yellow syrup, which was characterized as following derivatives. Picrate: Recrystallized from EtOH as yellow needles, mp 174—176° (decomp.). *Anal.* Calcd. for $C_{20}H_{22}O_3N_2 \cdot C_6H_3O_7N_3$: C, 55.03; H, 4.44; N, 12.34. Found: C, 55.13; H, 4.57; N, 12.41.

Oxalate: recrystallized from EtOH–ether as colorless needles, mp 168—170° (decomp.). *Anal.* Calcd. for $C_{20}H_{22}O_3N_2 \cdot (COOH)_2$: C, 61.67; H, 5.65; N, 6.54. Found: C, 61.89; H, 5.65; N, 6.59.

1-Benzyl-6-ethoxycarbamido-1,2,3,4-tetrahydro-7-methoxyisoquinoline (VIIIb)——Prepared from the above amine (0.5 g) and $NaBH_4$ (0.5 g) as described for VIIIa, giving 0.45 g of a pale yellow oil.

Recrystallization of the oxalate from EtOH–ether gave colorless plates, mp 182—184° (decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_3N_2 \cdot (COOH)_2$: C, 61.38; H, 6.09; N, 6.51. Found: C, 61.71; H, 6.11; N, 6.61.

1-Bnezyl-6-ethoxycarbamido-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (IXb)——Prepared from the above amine (0.45 g), 5 ml of HCOOH and 5 ml of 36% HCHO in the same method as described for the N-methyl compound (IXa). Recrystallization of IXb from *n*-hexane gave 0.33 g of colorless rhombic plates, mp 113—115°. *Anal.* Calcd. for $C_{21}H_{26}O_3N_2$: C, 71.16; H, 7.49; N, 7.90. Found: C, 71.36; H, 7.47; N, 8.16. IR cm^{-1} (KBr): ν_{N-CH_3} 2800.

6-Amino-1-benzyl-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (Xb)——Prepared from the above amine (0.3 g) and 10% KOH–EtOH solution (20 ml) as described for Xa, yielding 0.21 g of a yellow oil, which was characterized as picrate. Recrystallization of the picrate from EtOH gave yellow needles, mp 153—155° (decomp.). *Anal.* Calcd. for $C_{18}H_{22}ON_2 \cdot C_6H_3O_7N_3$: C, 56.35; H, 4.93; N, 13.69. Found: C, 56.48; H, 4.93; N, 13.73. NMR (τ): 7.50 (3H, N–C<u>H</u>$_3$), 6.52 (3H, O–C<u>H</u>$_3$), 4.10 (1H, C_8–<u>H</u>), 3.59 (1H, C_5–<u>H</u>).

1-Benzyl-1,2,3,4-tetrahydro-7-methoxy-2-methyl-6-isoquinolinol (XIb)——To a stirred solution of 0.2 g of Xb dissolved in 10 ml of 10% aq. H_2SO_4, 60 mg of $NaNO_2$ in 2 ml of H_2O was added at 5° and the reaction mixture was allowed to stand for 0.5 hr at 5—10°.

After decomposition of excess HNO_2 with urea, the mixture was added dropwise to 30 ml of boiling H_2O contained 2 g of $CuSO_4$, and boiling was continued for 2 hr. On cooling, the reaction mixture was basified with conc.NH_4OH and resultant precipitates were extraced with ether, and the phenolic base was taken up in 5% aq.NaOH from the extract. After addition of excess NH_4Cl to this alkaline solution, the product was extracted with ether and the extract was dried over K_2CO_3. Evaporation of the solvent gave 60 mg of a yellow syrup, which was used for the next step without purification. IR cm^{-1} ($CHCl_3$): ν_{OH} 3575.

1-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XIIb)——Prepared from the above phenolic base (60 mg) and ethereal solution of diazomethane (liberated from 10 g of N-methyl-N-nitroso-*p*-toluenesulfonamide) in the usual manner. The dimethoxy compound was converted into the picrate, which was recrystallized from EtOH to give yellow plates, mp 177—179° (decomp.) (lit.,[4a,b] 177—178°).

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