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Syntheses of 6-Amino-1-phenylisoquinolines by Bischler-Napieralski Reaction

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Ethoxycarbamido group was shown to be a good substituent for accelerating Bischler–Napieralski reaction of β–phenethylbenzamides as well as alkoxy group and ring–closure occurred selectively at the *para* position to the ethoxycarbamido group. And an improved synthesis of aminoisoquinoline was achieved by Bischler–Napieralski reaction.

It is known that Bischler–Napieralski reaction of β–phenethylamide begins with an electrophylic attack on the benzenoid ring and ring–closure is dependent upon increased electron density at that position.[2] As an electron–releasing group, alkoxy has been used for synthesis of natural product, but very little is known on the effect of other groups.[3,4]

The experiments described below were initiated in order to examine the ring–closure of β–phenethylamide, in which there was a *meta* acylamide group and to investigate pharmaceutical effect of the corresponding aminoisoquinoline derivatives.

First, N–(3–benzamidophenethyl)benzamide was synthesized and subjected to cyclodehydration under identical conditions following that of Fries and Bestian,[3] but basic product was not isolated.[5]

Caldwell and Walls described the preparation of 6– and 8–ethoxycarbamido–9–methylphenanthridines by cyclodehydration of 2–acetamido–3′–ethoxycarbamidobiphenyl.[6] Accord-

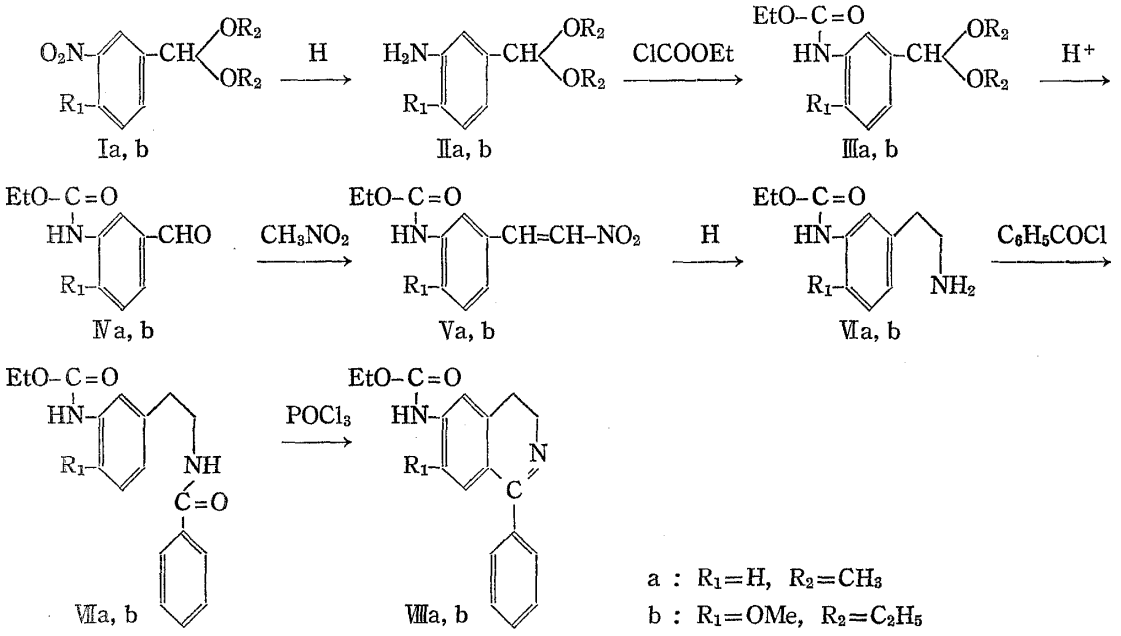


Chart 1

1) Location: *No. 600, Kashiwagi–4–chome, Shinjuku, Tokyo.*
2) W.M. Whaley and T.R. Govindachari, *Org. Reactions*, **6**, 74 (1955).
3) K. Fries and H. Bestian, *Ann.*, **533**, 72 (1937).
4) J.C. Belsten and S.F. Dyke, *J. Chem. Soc.*, **1964**, 22.
5) A. McCoobrey and D.W. Matheson, *J. Chem. Soc.*, **1949**, 696.
6) A.G. Caldwell and L.P. Walls, *J. Chem. Soc.*, **1948**, 188.

ingly, N-(3-ethoxycarbamidophenethyl)benzamides (VIIa,b) were synthesized and 3,4-dihydroisoquinolines (VIIIa,b) were obtained in good yield by Bischler-Napieralski cyclization of the above amides with phosphoryl chloride in toluene by refluxing for a short time. These cyclization was obvious by infrared and ultraviolet spectra.

For the syntheses of phenethylamides (VIIa,b) which were key intermediates for this procedure, nitroacetals (Ia,b) were used as starting materials.

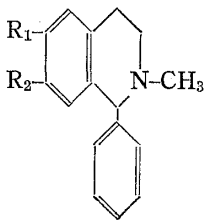
In the course of the cyclization of amides (VIIa,b), the spot of the amide (VIIa) on thin-layer chromatogram disappeared after refluxing for 20 min, but that of the amide (VIIb) did not disappear in the same time. It took 30 min to disappear the spot of the amide (VIIb). This deactivation effect might be due to either steric hindrance or electronic effect of the adjacent methoxy to the ethoxycarbamido group[4] (infrared spectra of two amides showed that stretching vibration of carbonyl group of ethoxycarbamido in the amide (VIIa) was 1710 cm^{-1} (in Potassium Bromide tablet) and 1736 cm^{-1} (in Chloroform solution), but that in the amide (VIIb) was 1734 cm^{-1} (in KBr tab. and in $CHCl_3$ sol.) respectively).

The ring-closure of N-(3-ethoxycarbamidophenethyl)benzamide could yield either 6- or 8-ethoxycarbamido-3,4-dihydro-1-phenylisoquinolines, however the former was exclusively obtained as expected.[2,3] This result was proved by the following facts.

The methiodide (IXa) of VIIIa was reduced with sodium borohydride in methanol to 1,2,3,4-tetrahydro-2-methylisoquinoline derivative (Xa).

This compound was hydrolyzed with 20% hydrochloric acid solution to 6-amino derivative, which was succesively diazotized to 6-hydroxy compound. Methylation of this isoquinolinol with diazomethane gave 1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-phenylisoquinoline, which was identified with 6-methoxy sample prepared from usual Bischler-Napieralski cyclization of N-(3-methoxyphenethyl)benzamide by mixed melting point determination and infrared spectrum comparison. Moreover, the NMR spectra of XIa and XIIIa (prepared from XIVa) in Table I supported the direction of the cyclization.

Table I. Chemical Shifts (τ) in $CDCl_3$



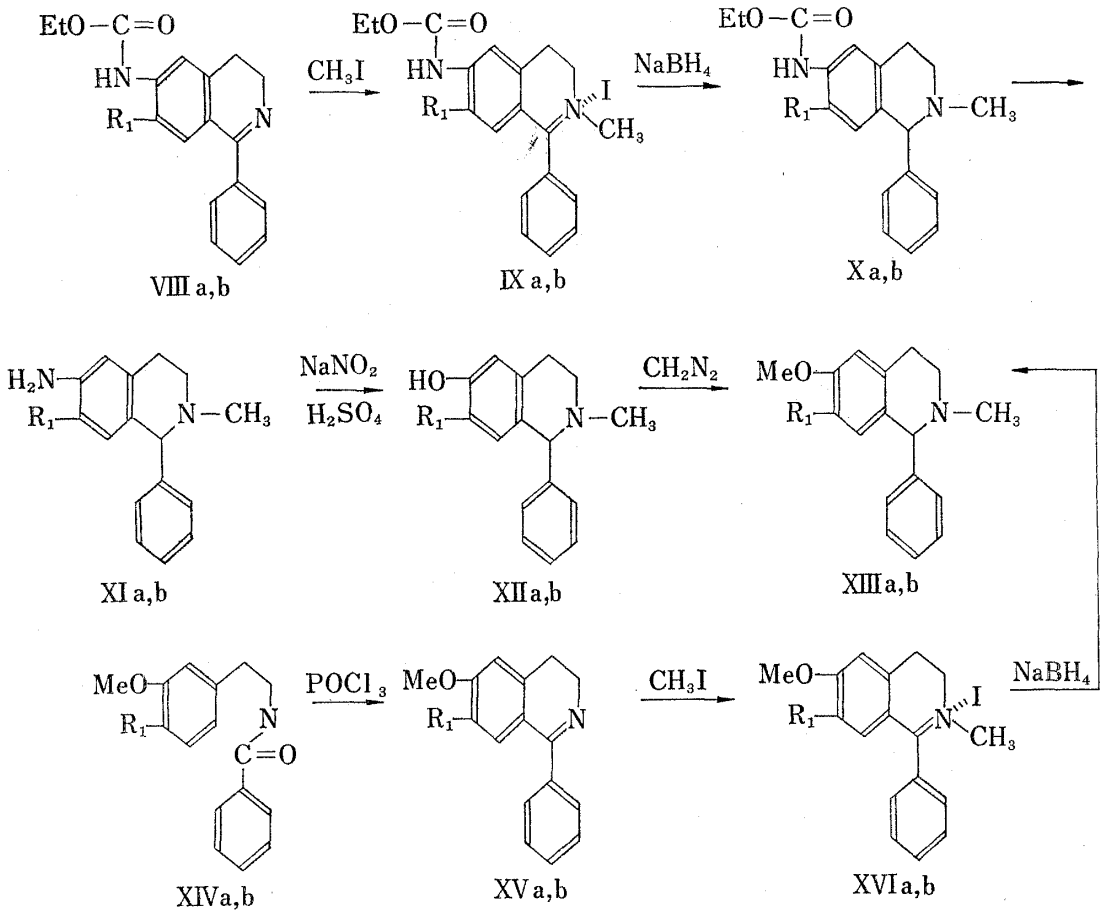
R_1	R_2		Aromatic-H			O-CH_3		N-CH_3
			C(5)-H	C(7)-H	C(8)-H	R_1	R_2	
NH_2	H	XIa		3.65(3H)		—	—	7.80
O-CH_3	H	XIIIa		3.45(3H)		6.26	—	7.79
NH_2	O-CH_3	XIb	3.54	—	4.00	—	6.49	7.79
O-CH_3	O-CH_3	XIIIb	3.39	—	3.88	6.17	6.46	7.77

In the similar way, 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-phenylisoquinoline prepared from N-(3-ethoxycarbamido-4-methoxyphenethyl)benzamide was identified with an authentic sample.[7]

10% Ethanolic potassium hydroxide solution was used for hydrolysis of Xb, since the usual method of hydrolysis with 20% hydrochloric acid solution gave a small amount of demethylated compound. The yield of the present hydrolysis was satisfactory (71%). The NMR spectra of this amino compound (XIb) and XIIIb (prepared from XIVb) in Table I supported also the direction of the cyclization.

7) T. Kametani, M. Shio, and K. Fukumoto, *Yakugaku Zasshi*, **85**, 960 (1965).

Diazotization of the amino compound (XIb) in the same condition as the case of XIa did not give any hydroxy compound, but addition of copper sulfate as a catalyst improved the reaction. The yield of the hydroxy product by improved method, however, was rather poor (30%).[8-10]



a : R_1=H b : R_1=OMe

Chart 2

As shown in the literature on the synthetic method of aminoisoquinolines,[11,12] it is not easy to synthesize 6-aminoisoquinolines having other substituents. But in our manner, these isoquinolines could be synthesized by Bischler-Napieralski reaction of the appropriate amides without difficulty.

Experimental[13]

3-Ethoxycarbamidobenzaldehyde (IVa)——To a stirred mixture of 150 ml of 5% aq. NaOH and 200 ml of ethereal solution of 20 g of the aminoacetal (IIa),[14] 14 g of ClCOOEt was added dropwise. After stirring for 1 hr, the ether solution was washed with H_2O, and added to excess 15% aq. HCl and the mixture was stirred for 1 hr. The separated ether solution was washed with H_2O, dried over K_2CO_3 and evaporated. The residue was recrystallized from benzene, yielding 10 g (44%) of IVa as colorless needles, mp 89—91.

8) L. Limpack, *Ber.*, **24**, 4136 (1891).
9) J.C. Cain, *J. Chem. Soc.*, **80**, 19 (1906).
10) K.N. Campbell, P.F. Hopper, and B.K. Campbell, *J. Org. Chem.*, **16**, 1736 (1951).
11) R.C. Elderfield, "Heterocylic Compound," **4**, 344.
12) E. Ochiai and T. Nakagome, *Chem. Pharm. Bull.* (Tokyo), **6**, 495 (1958).
13) All melting points were uncorrected.
14) Org. Syntheses, Coll. Vol. III, 59.

Anal. Calcd. for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74. Found: C, 62.39; H, 5.66; IR cm^{-1} (KBr): $\nu_{C=O}$ 1735 (ethoxycarbamido), 1690 (aldehyde).

3-Ethoxycarbamido-β-nitrostyrene (Va)——A solution of 5g of KOH in each 10 ml of H_2O and EtOH was added dropwise to a mixture of 10g of IVa and 5g of CH_3NO_2 in 50ml of EtOH with vigorous stirring at −5—0°. After 1 hr, the reaction mixture was added to 300 ml of 15% aq. HCl with stirring to form yellow crystalline precipitates. Recrystallization from EtOH gave 7 g (58%) of Va as yellow needles, mp 112—114°. *Anal.* Calcd. for $C_{11}H_{12}O_4N_2$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.29; H, 5.37; N, 11.54. IR cm^{-1} (KBr): $\nu_{C=O}$ 1738, $\nu_{C=C}$ 1635.

3-Ethoxycarbamidophenethylamine (VIa)——Electrolytic reduction of 10 g of Va (Anode solution: 20% aq. H_2SO_4. Cathode: Lead plate 200 cm^2. Cathode solution: A solution of each 100 ml of EtOH, THF, AcOH and 40 ml of conc. HCl. Current: 12A, 4 hr, 15—20°) gave an oily base, which was converted to the hydrochloride and recrystallized from EtOH–ether to yield 4 g of hydrochloride as colorless plates, mp 183—185° (decomp.). *Anal.* Calcd. for $C_{11}H_{16}O_2N_4 \cdot HCl$: C, 53.89; H, 7.00; N, 11.45. Found: C, 53.64; H, 6.75; N, 11.85. IR cm^{-1} (KBr): $\nu_{C=O}$ 1700, $\nu_{NH_3^+}$ 2700—3170.

N-(3-Ethoxycarbamidophenethyl)benzamide (VIIa)——To a stirred mixture of VIa (liberated from 1.5 g of the hydrochloride) in 200 ml of ether and 100 ml of 5% aq. NaOH, 0.8 g of benzoyl chloride dissolved in 10 ml of ether was added drop by drop. The reaction mixture was stood overnight and ether layer was washed with 5% HCl, H_2O, dried over K_2CO_3 and distilled to give colorless needles, mp 110—112° (57%). *Anal.* Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.84; H, 6.36; N, 8.96. IR cm^{-1} (KBr): $\nu_{C=O}$ 1710 (ethoxycarbamido), 1640 (amide).

6-Ethoxycarbamido-3,4-dihydro-1-phenylisoquinoline (VIIIa)——A mixture of 1.5 g of the above amide, 4.5 ml of $POCl_3$ and 20 ml of dry toluene was refluxed for 20 min. The solvent and $POCl_3$ were removed under reduced pressure. After addition of 10% NH_4OH, the product was taken up in AcOEt and the extract was washed with H_2O, dried over K_2CO_3 and evaporated. Recrystallization of the crude product from ether gave 1.2 g (85%) of colorless prisms, mp 148—150°. *Anal.* Calcd. for $C_{18}H_{18}O_2N_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.66; H, 6.28; N, 9.56.

The hydrochloride was recrystallized from EtOH–ether to give a pale yellow powder, mp 258—260° (decomp.). *Anal.* Calcd. for $C_{18}H_{18}O_2N_2 \cdot HCl$: C, 65.35; H, 5.70; N, 8.34. Found: C, 65.58; H, 5.79; N, 8.47. IR cm^{-1} (KBr): $\nu_{C=N}$ 1635, $\nu_{C=O}$ 1734.

6-Ethoxycarbamido-3,4-dihydro-1-phenylisoquinoline Methiodide (IXa)——A mixture of 1 g of VIIIa, 5 ml of MeI and 20 ml of MeOH was refluxed for 2 hr. Removal of the solvent and MeI gave a pale yellow solid, which was recrystallized from MeOH–ether yielding 0.9 g (61%) of pale yellow prisms, mp 192—194°. *Anal.* Calcd. for $C_{19}H_{21}O_2N_2I$: C, 52.30; H, 4.85; N, 6.42. Found: C, 52.21; H, 4.85; N, 6.22. IR cm^{-1} (KBr): $\nu_{C=N}$ 1630.

6-Ethoxycarbamido-1,2,3,4-tetrahydro-2-methyl-1-phenylisoquinoline (Xa)——To a stirred solution of 0.5 g of IXa in 20 ml of MeOH contained 0.5 ml of H_2O, 0.5 g of $NaBH_4$ was added in small portions, and the reaction mixture was stirred for 1 hr at room temperature. After the reaction mixture had been acidified with AcOH, the solvent was removed under reduced pressure, and 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 distilled to give a colorless solid. Recrystallization from aq. EtOH gave 0.3 g (84%) of Xa as colorless plates, mp 108—109°. *Anal.* Calcd. for $C_{19}H_{22}O_2N_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.80; H, 7.22; N, 9.03.

6-Amino-1,2,3,4-tetrahydro-2-methyl-1-phenylisoquinoline (XIa)——A mixture of 0.5 g of Xa and 15 ml of 20% aq. HCl was refluxed for 20 hr in the presence of N_2. The reaction mixture was basified with conc. NH_4OH and the product was taken up in ether. The ether solution was dried over K_2CO_3 and evaporated to give a pale yellow solid, which was recrystallized from hexane to yield 0.25 g (65%) of XIa as colorless needles, mp 110—112°. *Anal.* Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.64; H, 7.64; N, 11.61. IR cm^{-1} (KBr): ν_{NH} 3360, 3230, δ_{NH} 1645. NMR (τ): 7.80 (3H, N–CH_3), 5.88 (1H, C(1)–H), 3.65 (3H, C(5,7,8)–H).

1,2,3,4-Tetrahydro-2-methyl-1-phenyl-6-isoquinolinol (XIIa)——To a stirred solution of 0.1 g of XIa in 5 ml of 15% aq. H_2SO_4, 30 mg of $NaNO_2$ was added at 5° and the reaction mixture was allowed to stand for 0.5 hr at 5—10°. After decomposition of HNO_2 with urea, the reaction mixture was refluxed for 5 min. On treating the mixture with conc. NH_4OH, the phenolic base was taken up in ether, and the extract was dried over Na_2SO_4 and evaporated. Recrystallization of the resulting solid from benzene gave 50 mg (50%) of a colorless powder, mp 180—182°. *Anal.* Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.04; H, 7.03; N, 5.85.

1,2,3,4-Tetrahydro-6-methoxy-2-methyl-1-phenylisoquinoline (XIIIa)——A solution of 50 mg of XIIa and 150 ml of an ethereal solution of diazomethane (liberated from 10 g of N-methyl-N-nitroso-*p*-toluenesulfonamide) was kept in an ice box for 4 days. The solvent and CH_2N_2 were evaporated and the residue was recrystallized from hexane, giving 30 mg (57%) of colorless plates, mp 76—77°. *Anal.* Calcd. for $C_{17}H_{19}ON$: C, 80.57: H, 7.65; N, 5.53. Found: C, 80.40; H, 7.58; N, 5.24.

N-(3-Methoxyphenethyl)benzamide (XIVa)——Prepared from 3-methoxyphenethylamine (liberated from 1.5 g of the oxalate) and benzoyl chloride (0.8 g) by Schotten–Baumann condensation and recrystallized from aq. EtOH, giving 1.2 g (76%) of colorless needles, mp 65—66°. *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27;

H, 6.71; N, 5.49. Found: C, 74.98; H, 6.89; H, 5.18. IR cm^{-1} (KBr): $\nu_{C=O}$ 1634.

3,4-Dihydro-6-methoxy-1-phenylisoquinoline (XVa)——A mixture of 1 g of XIVa, 3 ml of $POCl_3$ and 15 ml of dry toluene was refluxed for 1 hr. After removal of the solvent and $POCl_3$, the free base liberated with conc. NH_4OH was taken up in ether. The base was characterized as oxalate. Recrystallization of the oxalate from EtOH–ether gave a colorless plates, mp 160—162° (decomp.). *Anal.* Calcd. for $C_{15}H_{15}ON \cdot (COOH)_2$: C, 66.05; H, 5.24; N, 4.28. Found: C, 66.01; H, 5.24; N, 4.08.

Methiodide (XVIa)——Prepared from the above amine (0.6 g) and MeI (4 ml) in the usual manner. Recrystallized from MeOH–ether gave 0.66 g of yellow prisms, mp 193—195° (decomp.). *Anal.* Calcd. for $C_{17}H_{18}ONI$: C, 53.84; H, 4.87. Found: C, 54.08; H, 4.86. IR cm^{-1} (KBr): $\nu_{C=N}$ 1639.

1,2,3,4-Tetrahydro-6-methoxy-2-methyl-1-phenylisoquinoline (XIIIa)——The methiodide (0.5 g) was reduced with $NaBH_4$ (0.5 g) in the usual way. Recrystallization from hexane gave 0.27 g of colorless plates, mp 76—77°. NMR (τ): 7.79 (3H, N–CH_3), 6.62 (3H, O–CH_3), 5.84 (1H, C(1)–H), 3.45 (3H, C(5,7,8)–H).

3-Nitroanisaldehyde Diethylacetal (Ib)——A mixture of 30 g of 3-nitroanisaldehyde,[15] 30 g of $(EtO)_3CH$ and 1 g of NH_4Cl was refluxed in 60 ml of EtOH for 3 hr. The mixture was evaporated and the resultant oil was extracted with ether. The extract was washed with H_2O, dried over K_2CO_3 and distilled. The product was purified by distillation under 3 mmHg pressure, bp 165—167°, as a yellow oil. Yield: 35 g (84%).

3-Aminoanisaldehyde Diethylacetal (IIb)——The nitroacetal (25 g) dissolved in 50 ml of EtOH was hydrogenated in the presence of PtO_2 (0.15 g) catalyst. Removal of the solvent and the catalyst gave 20 g of IIb as a reddish brown viscous oil, which was used for the next step without purification.

3-Ethoxycarbamido-4-methoxybenzaldehyde (IVb)——Prepared from in the same way as IV. Recrystallization from benzene–ligroin gave colorless plates, mp 81—82° (45%). *Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.18; H, 5.91; N, 6.62. IR cm^{-1} (KBr): $\nu_{C=O}$ 1747 (ethoxycarbamido), 1691 (aldehyde).

3-Ethoxycarbamido-4-methoxy-β-nitrostyrene (Vb)——Prepared from the above aldehyde (10 g), CH_3NO_2 (4.5 g) and KOH (4.5 g) as described for Va. The nitrostyrene was recrystallized from EtOH to give 7.5 g (63%) of yellow needles, mp 131—133°. *Anal.* Calcd. for $C_{12}H_{14}O_5N$: C, 54.13; H, 5.30; N, 16.53. Found: C, 54.22; H, 5.64; N, 16.71. IR cm^{-1} (KBr): $\nu_{C=O}$ 1735, $\nu_{C=C}$ 1620.

3-Ethoxycarbamido-4-methoxyphenethylamine (VIb)——The nitrostyrene (10 g) was converted into the amine (VIb) by electrolytic reduction as described for the preparation of VIa. The oxalate of the amine was recrystallized from EtOH to give 4 g of colorless rhombic plates, mp 163—165° (decomp.). *Anal.* Calcd. for $C_{12}H_{18}O_3N_2 \cdot (COOH)_2$: C, 51.12; H, 6.14; N, 8.53. Found: C, 51.10; H, 6.23; N, 8.68.

N-(3-Ethoxycarbamido-4-methoxyphenethyl)benzamide (VIIb)——A mixture of 100 ml of 5% aq. NaOH and 200 ml of an ethereal solution of VIb (liberated from 1.5 g of the oxalate) was allowed to react with 0.8 g of benzoyl chloride as described for VIa. Recrystallization from benzene–ligroin gave 1.2 g (76%) of colorless needles, mp 112—113°. *Anal.* Calcd. for $C_{19}H_{22}O_4N_2$: C, 66.65; H, 6.48; N, 8.13; Found: C, 66.79; H, 6.35; N, 8.43. IR cm^{-1} (KBr): $\nu_{C=O}$ 1734 (ethoxycarbamido), 1640 (amide).

6-Ethoxycarbamido-3,4-dihydro-7-methoxy-1-phenylisoquinoline (VIIIb)——A mixture of 1.5 g of the amide, 4.5 ml of $POCl_3$ and 20 ml of dry toluene was refluxed for 30 min. After evaporation of the solvent and $POCl_3$, pale yelllw precipitates obtained from the residue on treatment with 10% NH_4OH was taken up in ether. The extract was washed with H_2O, dried over K_2CO_3 and evaporated. Recrystallization from hexane yielded 1.2 g (85%) of colorless needles, mp 137—139°. *Anal.* Calcd. for $C_{19}H_{20}O_3N_2$: C, 70.35; H, 6.62; N, 8.64. Found: C, 70.30; H, 6.64; N, 8.85. IR cm^{-1} (KBr): $\nu_{C=O}$ 1735.

Oxalate: recrystallized from EtOH–ether as colorless needles, mp 169—171° (decomp.). *Anal.* Calcd. for $C_{19}H_{20}O_3N_2 \cdot (COOH)_2$: C, 60.86; H, 5.35; N, 6.76. Found: C, 61.16; H, 5.45; N, 6.70.

Methiodide (IXb): Prepared from 1 g of VIIIb and 5 ml of MeI in the usual way. The methiodide was recrystallized from MeOH–ether giving 0.9 g (63%) of a yellow powder, mp 113—115° (decomp.). *Anal.* Calcd. for $C_{20}H_{23}O_3N_2I \cdot H_2O$[16]: C, 49.59; H, 5.02; N, 5.87. Found: C, 49.17; H, 4.65; N, 5.97. IR cm^{-1} (KBr): $\nu_{C=N}$ 1630.

6-Ethoxycarbamido-1,2,3,4-tetrahydro-7-methoxy-2-methyl-1-phenylisoquinoline (Xb)——This product was prepared from the methiodide (0.5 g) and $NaBH_4$ (0.5 g) in the same method as descirbed for Xa.

Recrystallization of the product from aq. EtOH gave 0.25 g (68%) of colorless needles, mp 98—99°. *Anal.* Calcd. for $C_{20}H_{24}O_3N_2$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.45; H, 7.10; N, 8.31. IR cm^{-1} (KBr): $\nu_{C=O}$ 1735.

6-Amino-1,2,3,4-tetrahydro-7-methoxy-2-methyl-1-phenylisoquinoline (XIb)——A mixture of 0.5 g of Xb and 30 ml of 10% KOH–EtOH solution was refluxed for 2 hr in the presence of N_2. The solvent was removed under reduced pressure and the resultant residue was acidified with 10% aq. HCl. The acidic solution was basified with conc. NH_4OH and the product was taken up in ether. The extract was dried over K_2CO_3 and evaporated. Recrystallization from hexane gave 0.3 g (71%) of pale yellow needles, mp 114—116°. *Anal.* Calcd. for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.52; N, 10.44. Found: C, 76.11; H, 7.62; N, 10.64.

15) K.H. Slotta and G. Szyszka, *Ber.*, **68**, 184 (1935).
16) This was dried over P_2O_5 at 80—90 (5 mmHg) for 24 hr.

IR cm^{-1} (KBr): ν_{NH_2} 3410, 3330, δ_{NH_2} 1624. NMR (τ): 7.79 (3H, N–CH_3), 6.49 (3H, O–CH_3), 5.87 (1H, C(1)–H), 3.54 (1H, C(5)–H), 4.00 (1H, C(8)–H).

1,2,3,4-Tetrahydro-7-methoxy-2-methyl-1-phenyl-6-isoquinolinol (XIIb)——To a stirred solution of 0.2 g of XIb dissolved in 10 ml of 15% 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 HNO_2 with urea, the mixture was added to 30 ml of boiling H_2O contained 2 g of $CuSO_4$ and boiling was continued for 2 hr. On cooling, the mixture was basified with conc. NH_4OH and precipitate was extracted with ether and the phenolic base was taken up in 5% aq. NaOH from ethereal solution. After addition of excess NH_4Cl to this alkaline solution, the product was extracted again with ether and the extract was dried over K_2CO_3. Evaporation of the solvent gave 60 mg of XIIb as a yellow viscous syrup, which was used for the next step without purification. IR cm^{-1} ($CHCl_3$): ν_{OH} 3570.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-phenylisoquinoline (XIIIb)——Prepared from the above phenolic base (60 mg) and an ethereal solution of diazomethane (liberated from 10 g of N–methyl–N–nitroso–*p*–toluenesulfonamide) in the usual way. The dimethoxy compound was recrystallized from hexane giving 35 mg of colorless needles, mp 82—83° (lit.[7] 82°). *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.31; H, 7.55; N, 4.75.

3,4-Dihydro-6,7-dimethoxy-1-phenylisoquinoline (XVb)——A mixture of 1 g of the amide (XIVb),[7,17] 3 ml of $POCl_3$ and 15 ml of dry toluene was refluxed for 1 hr. The solvent and $POCl_3$ were removed under reduced pressure and the residue was dissolved in warm H_2O.

The H_2O solution was washed with benzene and basified 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 pale yellow solid, which was recrystallized from aq. EtOH yielding 0.65 g of colorless needles, mp 122—123° (lit.[17] 121.5°).

Methiodide (XVIb): Prepared from XVb(0.5 g) and MeI (4 ml) in the usual way. Recrystallization of the methiodide from MeOH–ether gave 0.46 g of pale yellow plates, mp 189—191° (lit.[18] 199°). *Anal.* Calcd. for $C_{18}H_{20}O_2NI$: C, 52.82; H, 4.93; N, 3.42. Found: C, 52.82; H, 4.99; N, 3.44. IR cm^{-1} (KBr): $\nu_{C=N}$ 1634.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-phenylisoquinoline (XIIIb)——The methiodide was reduced with $NaBH_4$ to XIIIb in the usual manner. Recrystallization from hexane afforded colorless needles, mp 82—83°. NMR (τ): 7.73 (3H, N–CH_3), 6.46 (3H, O–C(7)H_3), 6.17 (3H, O–C(6)H_3), 5.82 (1H, C(1)–H), 3.39 (1H, C(5)–H), 3.88 (1H, C(8)–H).

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