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Syntheses of Aminoisoquinolines and Related Compounds. VI.[1] A Modified Synthesis of *dl*-Pronuciferine

Saburo Ishiwata, Keiichi Itakura and Kazuo Misawa

Tokyo College of Pharmacy[2]

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Decomposition of the diazonium salts of the amino compounds (Ia and Ib) under alkaline conditions gave respectively two kinds of products, which were intranuclear coupling products, proaporphine type compound (II) and aporphine type compounds (IIIa and IIIb).

The previous communication[3] reported that deamination of 8-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (Ia) by hypophosphorous acid combined with diazotization step gave three compounds, one of which was an intramolecular cyclization product, *dl*-pronuciferine (II), in addition to a deamination product and the other cyclization product, *dl*-1,2,10-trimethoxyaporphine (IIIa).

There is much evidence to suggest that deamination of aromatic primary amino group by hypophosphorous acid combined with diazotization step is a free radical chain process[4] and therefore, II should be formed *via* route A as illustrated in Chart 1.

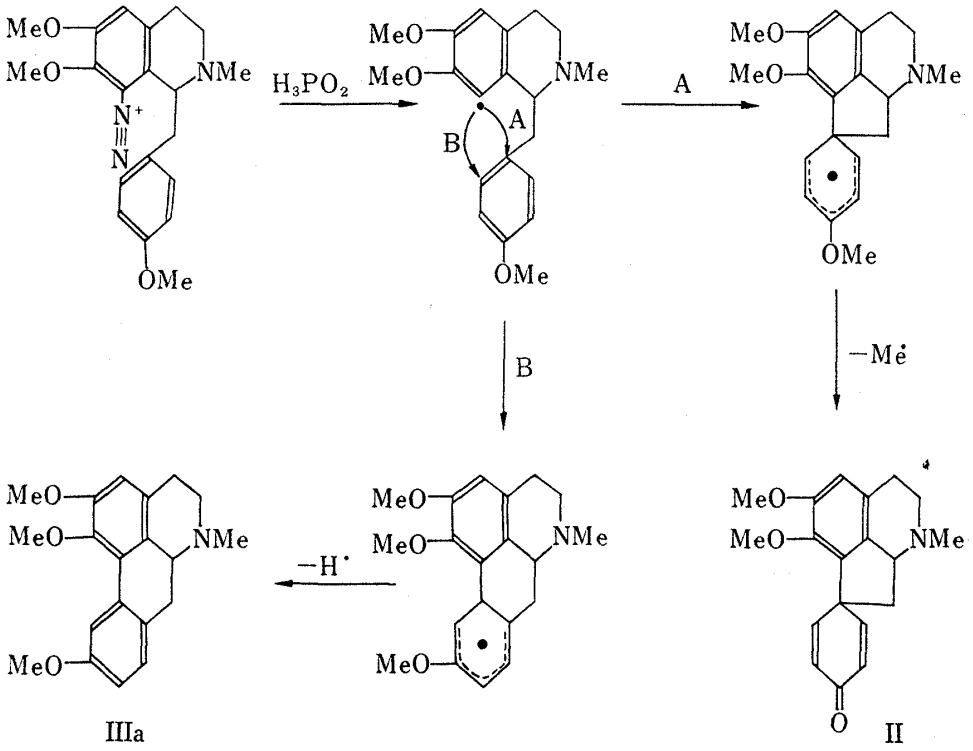

Chart 1

1) Part V: S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), **18**, 896 (1970).
2) Location: *No. 600, Kashiwagi, Shinjuku-ku, Tokyo.*
3) S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), **17**, 1298 (1969).
4) a) E.R. Alexander and R.E. Burge, Jr., *J. Am. Chem. Soc.*, **72**, 3100 (1950); *b*) N. Kornblum, G.D. Cooper, and J.E. Taylor, *J. Am. Chem. Soc.*, **72**, 3013 (1950); *c*) N. Kornblum, A.E. Kelley, and G.D. Cooper, *J. Am. Chem. Soc.*, **74**, 3407 (1952).

In this paper, we wish to report a modified synthesis of II by the Pschorr reaction, whose reaction mechanism was considered to be a homolytic reaction under alkaline conditions.[5]

The Bischler–Napieralski reaction of the amide (VIa), prepared from the amine (IV) and the acid chloride (Va) by the usual method,[6] gave two kinds of 3,4-dihydroisoquinolines (VIIa and Xa). Sodium borohydride reduction of this mixture of VIIa and Xa in methanol gave a mixture of tetrahydroisoquinolines (VIIIa and XIa), which was treated with 36% formaldehyde solution, then reduced with sodium borohydride in methanol afforded a mixture of N-methyltetrahydroisoquinolines (IXa and XIIa). This mixture was chromatographed on silica gel eluted with benzene–methanol to be separated into two components with a ratio of 1(XIIa):4(IXa) and the latter was hydrolyzed to the 8-amino compound (Ia) with ethanolic potassium hydroxide solution in the presence of nitrogen gas.

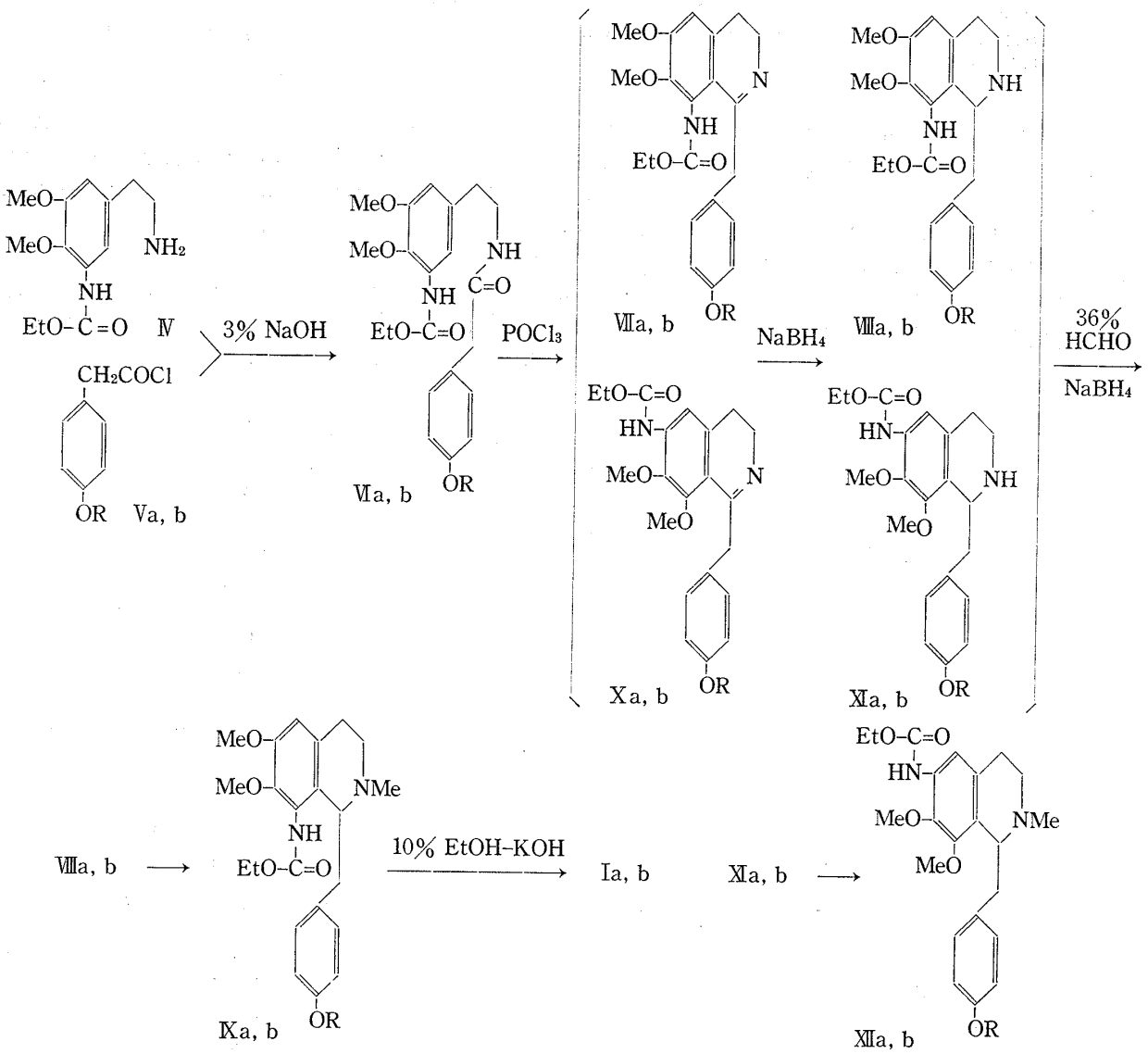

Chart 2

5) *a*) D.F. Detar, *Org. Reaction*, **9**, 411 (1957); *b*) E.L. Eliel and J.G. Saha, *J. Am. Chem. Soc.*, **87**, 2451 (1965); *c*) C. Rüchardt and E. Merz, *Tetrahedron Letters*, **1964**, 2431; *d*) G. Binsch, E. Merz, and C. Rüchardt, *Ber.*, **100**, 247 (1967).

6) S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), **17**, 2261 (1969).

Ia was diazotized with a slight excess of sodium nitrite in 5% sulfuric acid solution at 0—5° and decomposition of the resulting diazonium salt with an excess of sodium acetate at room temperature gave a product, which showed two spots on thin-layer chromatogram of silica gel. Separation of the mixture by chromatography on silica gel eluted with chloroform–methanol gave II in 15% yield in addition to a small amount of IIIa.

In a similar way, decomposition of the diazonium salt of Ib prepared by the same method as described for Ia, with 10% sodium hydroxide solution gave II in 20% yield and a small amount of 10-hydroxy-1,2-dimethoxyaporphine (IIIb). The latter was identified by the infrared (IR) spectral comparison with the product of the dienone-phenol rearrangement of II by treatment with hydrochloric acid in acetic acid solution and moreover, methylation of IIIb with diazomethane afforded a trimethoxyaporphine, whose infrared spectrum was superimposable with that of IIIa.

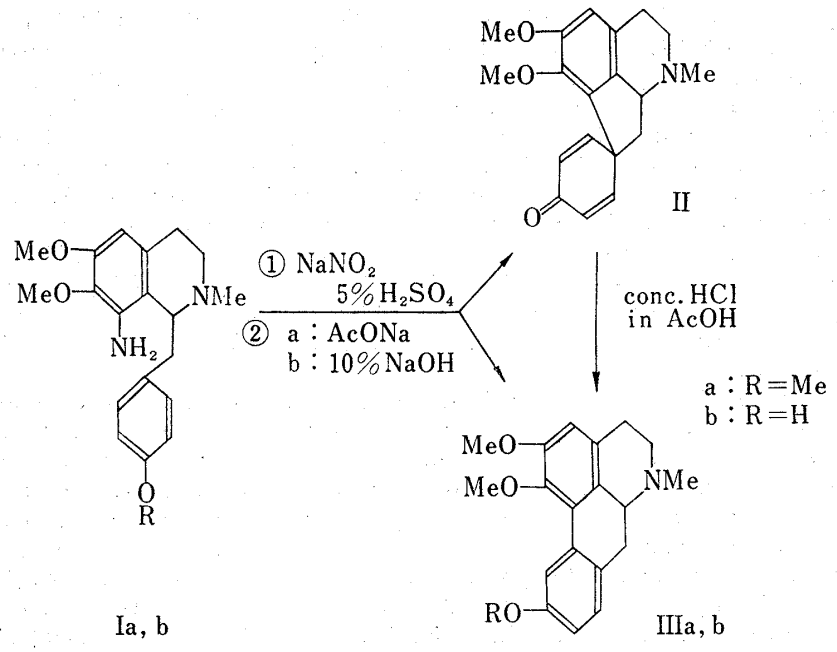

Chart 3

On the base of these facts, it may be concluded that the Pschorr reaction of the 8-amino compound under alkaline conditions was a useful method for synthesizing the spiro-dienone system, the proaporphine type compound.

Experimental[7]

N-(3-Ethoxycarbamido-4,5-dimethoxyphenethyl)-2-(4-methoxyphenyl)acetamide (VIa)——To a stirred mixture of the amine (IV)[6] (liberated from 1.5 g of the hydrochloride) in 100 ml of benzene and 50 ml of 3% aq. NaOH cooled in an ice bath was added dropwise Va (prepared from 1 g of acid and 3 ml of $SOCl_2$ by the usual manner). After addition, the reaction mixture was further stirred for 1 hr and the benzene solution was washed with successively with water, 5% aq. HCl, and water, and dried over K_2CO_3. Evaporation of the solvent gave a colorless solid, which was recrystallized from benzene–*n*-hexane to yield 2.1 g of the amide as colorless needles, mp 129—131°. IR cm^{-1} (KBr): ν_{NH} 3400, 3250. $\nu_{C=O}$ 1744 (urethane), 1647 (amide). *Anal.* Calcd. for $C_{22}H_{28}O_6N_2$: C, 63.44; H, 6.78; N, 6.73. Found: C, 63.12; H, 7.02; N, 6.67.

The Bischler-Napieralski Reaction of the Amide (VIa)——A mixture of 1.5 g of the amide, 3 ml of $POCl_3$, and 20 ml of benzene was refluxed for 1.5 hr on a water bath and the solvent and the reagent were evaporated under reduced pressure; the residue was immediately dissolved in 60 ml of MeOH and treated with 1.5 g of $NaBH_4$ for 1 hr with stirring. The reaction mixture was poured into 200 ml of ether and the basic product

7) All melting points were not corrected. Nuclear magnetic resonance (NMR) spectra were measured by JNM-4H 100 spectrophotometer at 100 Mc and tetramethylsilane was used as internal standard and chemical shift was reported as τ value.

was extracted with 3% aq. HCl. The aqueous extract was made alkaline with conc.NH_4OH and the product was extracted with ether, and the extract was washed with water, dried over K_2CO_3 and evaporated to give 0.9 g of glassy mass.

The foregoing product was treated with 2 ml of 36% HCHO in 60 ml of MeOH for 30 min with stirring, then reduced for 1 hr by 3 g of $NaBH_4$ added. After acidification of the mixture with AcOH, the solvent was evaporated to give a pale yellow residue, which was treated with conc.NH_4OH and the basic material was extracted with ether. Removal of the solvent by distillation afforded a mixture of N-methyltetrahydroisoquinolines as a pale yellow glassy mass. Yield: 0.8 g. The product was chromatographed on silica gel (20 g) eluted with benzene–MeOH (50:1) to be separated into two components. The former component (XIa): Yield: 130 mg. IR cm^{-1} ($CHCl_3$): ν_{NH} 3400, $\nu_{C=O}$ 1730. NMR ($CDCl_3$): 8.70 (3H, triplet, $J=7$ cps, O–$CH_2C\underline{H}_3$), 7.76 (3H, singlet, N–$C\underline{H}_3$), 6.25, 6.19, and 6.18 (9H, $3\times$O–$C\underline{H}_3$), 5.75 (2H, quartet, $J=7$ cps, O–$C\underline{H}_2CH_3$), 3.20 and 2.85 (4H, A_2B_2 type quartet, $J=8$ cps, aromatic $\underline{H}$), 2.41 (1H, singlet, C_5–$\underline{H}$). Hydrobromide: Recrystallized from EtOH–ether, as colorless needles, mp 198—200° (decomp.). *Anal.* Calcd. for $C_{23}H_{30}O_5N_2\cdot HBr\cdot \frac{1}{4}H_2O$: C, 55.26; H, 6.35. Found: C, 55.39; H, 6.28.

The latter component (IXa): Yield: 500 mg. IR cm^{-1} ($CHCl_3$): ν_{NH} 3400, $\nu_{C=O}$ 1730. NMR ($CDCl_3$): 8.76 (3H, triplet, $J=7$ cps, O–$CH_2C\underline{H}_3$), 7.60 (3H, singlet, N–$C\underline{H}_3$), 6.26, 6.23, and 6.17 (9H, $3\times$O–$C\underline{H}_3$), 5.85 (2H, quartet, $J=7$ cps, O–$C\underline{H}_2CH_3$), 3.21 and 2.98 (4H, A_2B_2 type quartet, $J=8$ cps, aromatic $\underline{H}$), 3.38 (1H, singlet, C_5–$\underline{H}$). Picrolonate: Recrystallized from EtOH, as yellow plates, mp 212—215° (decomp.). *Anal.* Calcd. for $C_{23}H_{30}O_5N_2\cdot C_{10}H_8O_5N_4$: C, 58.40; H, 5.64; N, 12.38. Found: C, 58.46; H, 5.89; N, 12.47.

8-Amino-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (Ia)——A mixture of 350 mg of IXa and 30 ml of 10% EtOH–KOH solution was refluxed for 2 hr in the presence of N_2. Evaporation of the solvent gave a reddish brown residue, which was acidified with conc. HCl and this acidic solution was basified again with conc. NH_4OH, and the product was extracted with benzene. The extract was dried over K_2CO_3 and evaporated to give 200 mg of a yellow syrup. IR cm^{-1} ($CHCl_3$): ν_{NH_2} 3350, 3420. NMR ($CDCl_3$): 7.60 (3H, singlet, N–$C\underline{H}_3$), 6.27—6.23 (9H, $3\times$O–$C\underline{H}_3$), 3.91 (1H, singlet, C_5–$\underline{H}$), 3.22 and 2.89 (4H, A_2B_2 type quartet, $J=8$ cps, aromatic $\underline{H}$). Picrolonate: Recrystallized from EtOH, as yellow needles, mp 182—184° (decomp.). *Anal.* Calcd. for $C_{20}H_{26}O_3N_2\cdot C_{10}H_8O_5N_4$: C, 59.39; H, 5.65; N, 13.86. Found: C, 59.26; H, 5.68; N, 13.52.

The Pschorr Reaction of Ia——To a stirred mixture of 200 mg of Ia and 6 ml of 5% aq. H_2SO_4 was added 45 mg of $NaNO_2$ dissolved in 0.5 ml of water at 0° and the mixture was stirred further for 30 min at 0—5°. To this mixture was added 2 g of AcONa dissolved in 5 ml of water over period of 5 min and the mixture was stirred for 3 hr. After basification of the mixture with conc. NH_4OH, the product was extracted with $CHCl_3$ and the extract was dried over K_2CO_3 and evaporated to give a reddish brown glassy mass (120 mg), which was chromatographed on silica gel (5 g) eluted with $CHCl_3$–MeOH (100:1) to be separated into two components. The first eluted product was *dl*-1,2,10-trimethoxyaporphine (IIIa): Yield 15 mg. NMR ($CDCl_3$): 7.47 (3H, singlet, N–$C\underline{H}_3$), 6.35, 6.20, and 6.16 (9H, $3\times$O–$C\underline{H}_3$), 3.39 (1H, singlet, C_3–$\underline{H}$), 3.25 (1H, quartet, $J=9$ cps, 2.5 cps, C_9–$\underline{H}$), 2.88 (1H, doublet, $J=9$ cps, C_8–$\underline{H}$), 2.00 (1H, doublet, $J=2.5$ cps, C_{11}–$\underline{H}$). Picrate: Recrystallized from THF–EtOH, as yellow needles, mp 183—185° (decomp.). *Anal.* Calcd. for $C_{20}H_{23}O_3N\cdot C_6H_3O_7N_3$: C, 56.31; H, 4.73. Found: C, 56.42; H, 5.23.

The second eluted product was *dl*-pronuciferine as a brown solid: Yield 27 mg. IR cm^{-1} ($CHCl_3$): 1656, 1618 (dienone). NMR ($CDCl_3$): 7.57 (3H, singlet, N–$C\underline{H}_3$), 6.41, 6.20 (6H, singlet, $2\times$O–$C\underline{H}_3$), 3.80—3.55 and 3.20—2.90 (4H, two AB type quartets, dienone). IR and NMR spectra were superimposable with those of authentic sample prepared by the same method as described in the literature.[8] Picrolonate: Recrystallized from THF–EtOH, as yellow plates, mp 230—233° (decomp.). *Anal.* Calcd. for $C_{19}H_{21}O_3N\cdot C_{10}H_8O_5N_4$: C, 60.51; H, 5.08; N, 12.17. Found: C, 60.05; H, 4.90; N, 12.12.

Dienone-phenol Rearrangement of II——A mixture of 40 mg of II and 1 ml of conc. HCl in 20 ml of AcOH was stirred for 4 day and the reaction mixture was evaporated under reduced pressure to give a yellow residue, which was basified with 10% NH_4OH. The product was taken up in $CHCl_3$ and the extract was dried over K_2CO_3, and evaporated to give a reddish brown solid. The crude product was purified by chromatography on alumina (1 g) eluted with $CHCl_3$–MeOH (50:1). Recrystallization of the product from benzene gave 10 mg of *dl*-10-hydroxy-1,2-dimethoxyaporphine, as colorless plates, mp 211—213°. IR cm^{-1} ($CHCl_3$): 3600 (free OH), 3300 (associated OH). NMR (CF_3COOH): 6.68 (3H, doublet, N–$C\underline{H}_3$), 6.19, 6.03 (6H, singlet, $2\times$O–$C\underline{H}_3$), 3.11 (1H, singlet, C_3–$\underline{H}$), 2.97 (1H, quartet, $J=9$ cps, 2.5 cps, C_9-$\underline{H}$), 2.66 (1H, doublet, $J=9$ cps, C_8-$\underline{H}$), 1.95 (1H, doublet, $J=2.5$ cps, C_{11}–$\underline{H}$). *Anal.* Calcd. for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80. Found: C, 73.56; H, 6.83.

N-(3-Ethoxycarbamido-4,5-dimethoxyphenethyl)-2-(4-ethoxycarbonyloxyphenyl)acetamide (VIb)——Prepared from IV (liberated from 1.5 g of the hydrochloride) and Vb (prepared from 1 g of the acid) by the same method as described for VIa. Recrystallization of the amide from benzene gave 2 g of colorless needles, mp 115—117°. IR cm^{-1} ($CHCl_3$): ν_{NH} 3400, $\nu_{C=O}$ 1760, 1730, and 1660. *Anal.* Calcd. for $C_{24}H_{32}O_8N_2$: C, 60.49; H, 6.77; N, 5.88. Found: C, 60.56; H, 6.43; N, 5.64.

8) T. Kametani and H. Yagi, *J. Chem. Soc.* (*C*), **1967**, 2182.

The Bischler-Napieralski Reaction of the Amide (VIb)——The amide (VIb, 2 g) was suspended in anhyd. benzene (20 ml); and the mixture was refluxed for 1.5 hr with $POCl_3$ (4 ml). The residue left after evaporation of the solvent and the reagent was treated with $NaBH_4$ (2 g) in MeOH (30 ml) for 1 hr at room temperature. The reaction mixture was poured into ether (250 ml) and basic product was extracted with 3% aq. HCl. The extract was basified with conc. NH_4OH and the basic product was extracted with ether. Evaporation of the solvent gave an oily product (1.1 g). The foregoing product was dissolved in MeOH (60 ml) and treated with formalin (2 ml), then with $NaBH_4$ (3 g) at room temperature. The product isolated by the same method as described for VIa was a reddish brown viscous syrup (0.9 g). The product was chromatographed on silica gel (30 g) eluted with benzene (saturated with NH_4OH)–MeOH (50:1) to be separated into two components. The former component (XIIb): Yield: 0.18 g. IR cm^{-1} ($CHCl_3$): ν_{OH} 3580, ν_{NH} 3400, $\nu_{C=O}$ 1730. NMR ($CDCl_3$): 8.70 (3H, triplet, $J=7$ cps, O–$CH_2\underline{CH_3}$), 7.63 (3H, singlet, N–$\underline{CH_3}$), 6.17 and 6.12 (6H, singlet, $2\times$O–$\underline{CH_3}$), 5.75 (2H, quartet, $J=7$ cps, O–$\underline{CH_2}CH_3$), 3.50 and 2.95 (4H, A_2B_2 type quartet, aromatic H), 2.35 (1H, singlet, C_5–$\underline{H}$). Recrystallization from benzene gave colorless needles, mp 162—164°. *Anal.* Calcd. for $C_{22}H_{28}O_5N_2$: C, 65.98; H, 7.25; N, 7.00. Found: C, 65.84; H, 6.92; N. 6.72.

The latter component (IXb): Yield: 0.65 g. IR cm^{-1} ($CHCl_3$): ν_{OH} 3600, ν_{NH} 3400, $\nu_{C=O}$ 1730. Picrolonate: Recrystallized from EtOH, yellow needles, mp 195—197° (decomp.). *Anal.* Calcd. for $C_{22}H_{28}O_5N_2\cdot C_{10}H_8O_5N_4$: C, 57.82; H, 5.46. Found: C, 58.01; H, 5.74.

8-Amino-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-6,7-dimethoxy-2-methylisoquinoline (Ib)——Prepared from IXb (0.5 g) by the same method as described for IXa. Recrystallization of the amino compound gave colorless plates (0.25 g), mp 175—177°. IR cm^{-1} ($CHCl_3$): ν_{OH} 3590, ν_{NH_2} 3350, 3420. *Anal.* Calcd. for $C_{19}H_{24}O_3N_2$: C, 69.49; H, 7.37. Found: C, 69.29; H, 7.50.

The Pschorr Reaction of Ib——To a stirred mixture of Ib (220 mg) in 5% aq. H_2SO_4 (6 ml), was added $NaNO_2$ (50 mg) dissolved in 1 ml of water at 0° and the reaction mixture was stirred further for 30 min at 0—5°. Then 10% aq. NaOH (10 ml) was added over period of 10 min and the reaction mixture was stirred for 3 hr. The mixture was diluted with water (10 ml) and the product was extracted with $CHCl_3$ and the extract was washed with water, dried over K_2CO_3, and evaporated to give 40 mg of II. The IR spectrum of this compound was superimposable with that of the product from Ia.

Addition of excess of NH_4Cl to the alkaline solution from which II was extracted, gave a phenolic base. The product was extracted with $CHCl_3$ and the extract was dried over K_2CO_3, and evaporated to give 20 mg of a colorless solid, which was identified by the IR spectral comparison with the product of the dienone–phenol rearrangement of II. Methylation of this phenolic base (20 mg) in 20 ml of MeOH with diazomethane (in 100 ml of ether) gave a trimethoxyaporphine (10 mg), whose IR spectrum was superimposable with that of IIIa.

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