

Syntheses of Aminoisoquinolines and Related Compounds. VII.¹⁾ Syntheses of O-Methylorientalinone and O-Methyliso-orientalinone

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The Pschorr reaction of 8-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-2-methylisoquinoline (Ia) under alkaline conditions gave three compounds, which were separated by chromatography on silica gel into two components, *dl*-glaucine and a mixture of two isomeric 2,5-dienones, the latter of which were separated by fractional recrystallization of their picrolonate into each dienone (Va and VIa).

The preceding paper¹⁾ reported that the Pschorr reaction of 8-amino compound (Ib) under alkaline conditions gave two compounds, which were 1,2,10-trimethoxyaporphine (IIIb) and a 2,5-dienone, *dl*-pronuciferine (II).

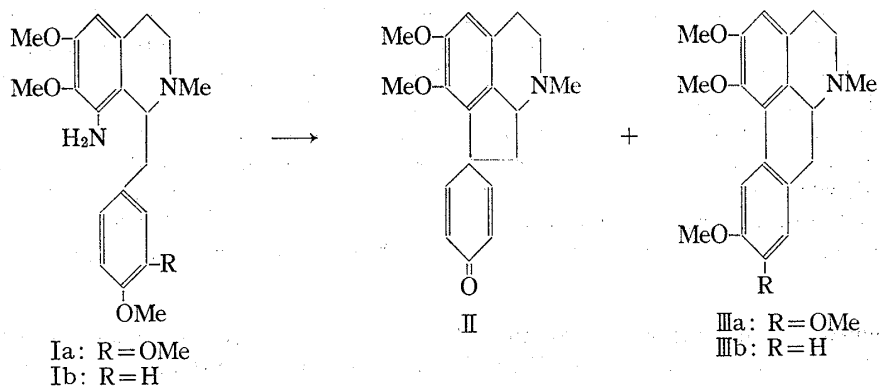


Chart 1

Recently, Shamma and Slusarchyk³⁾ reported that phenolic oxidation of dihydroxyisoquinoline (VII) gave a 2,4-dienone (VIIIb) in 52% yield and that O-methylorientalinone (Va or VIa) was obtained in 10% yield from 2,5-dienols (IX), prepared from the 2,4-dienone (VIIIa). Battersby and his co-workers⁴⁾ also reported that oxidation of orientaline afforded orientalinone and isoorientalinone; the later was obtained as a mixture with orientalinone.

In this paper, we wish to report the Pschorr reaction of another 8-amino compound (Ia) under the same conditions as described in the preceding paper.¹⁾

Ia was prepared as follows: The Bischler-Napieralski reaction of the amide (XII), prepared from the phenethylamine (X)⁵⁾ and 3,4-dimethoxyphenylacetyl chloride (XI) under the Schotten-Baumann conditions, gave two kinds of 3,4-dihydroisoquinolines (XIIIa and XIIIb). Methylation of the 3,4-dihydroisoquinolines with methyl iodide afforded a mixture of methiodides, whose reduction with sodium borohydride gave a mixture of N-methyltetrahydroisoquinolines (XVa and XVb). This mixture showed two spots on thin-layer chromatogram on silica gel. Accordingly, the mixture was chromatographed on silica gel to be separated

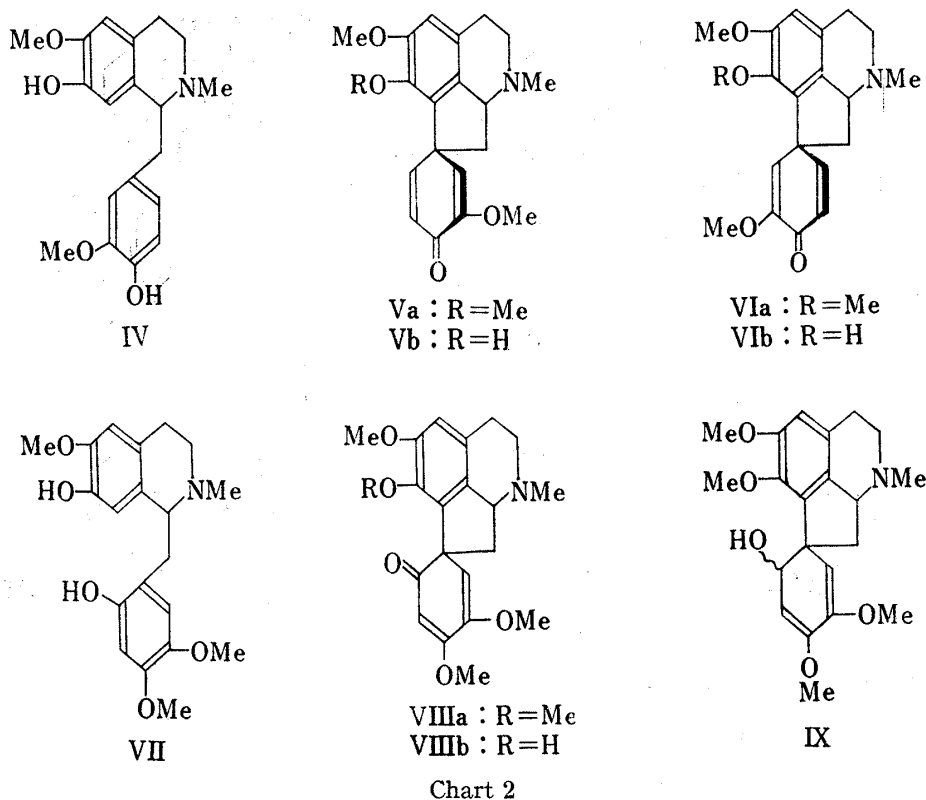
1) Part VI: S. Ishiwata, K. Itakura, and K. Misawa, *Chem. Pharm. Bull.* (Tokyo), **18**, 1219 (1970).

2) Lokation: No. 600 Kashiwagi, Shinjuku-ku, Tokyo.

3) M. Shamma and W.A. Slusarchyk, *Chem. Commun.*, **1965**, 528.

4) a) A.R. Battersby, T.H. Brown, and J.H. Clements, *J. Chem. Soc.*, **1965**, 4550; b) A.R. Battersby, T.J. Brockson, and R. Ramage, *Chem. Commun.*, **1969**, 464.

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



into two components with a ratio of 1:3 (XVb:XVa). Hydrolysis of XVa with 10% ethanolic potassium hydroxide solution gave the 8-amino compound (Ia), which was diazotized with a slight excess of sodium nitrite in 5% sulfuric acid solution and the resulting diazonium salt was decomposed with an excess of sodium acetate at room temperature over period of three hours, resulting in the formation of *dl*-glucine (IIIa) and 2,5-dienone.

In spite of showing one spot on thin-layer chromatogram under various conditions, this dienone was a mixture of two isomers, which were separated by fractional recrystallization of their picrolonate with a ratio of 3:2. Both dienone were characterized as their picrolonate and showed the typical dienone absorption at 1660, 1635, and 1610 cm^{-1} .

In the nuclear magnetic resonance (NMR) spectra⁶⁾ the two dienone showed a difference: one isomer (2 parts) exhibited Ha at 4.00 τ as a doublet, Hb at 3.05 τ as a quartet, and Hx at 3.52 τ as a doublet and the other isomer did Ha as 4.11 τ as a doublet, Hb at 2.92 τ as a quartet, and Hx at 3.65 τ as a doublet. Shamma and Slusarchyk³⁾ had reported NMR data for *O*-methylorientalinone.

These was significant difference between their and our assignment of the chemical shift in the dienone system: Shamma assigned absorption at 3.98 τ to Ha, at 3.05 τ to Hx as a doublet, respectively, and at 3.40 τ to Hb as a quartet. On the other hand, Battersby^{4a)} reported NMR data for orientalinone: at 4.08 τ to Ha as a doublet, at 3.21 τ to Hb as a quartet, and at 3.67 τ to Hx as a doublet.

Kametani and his co-workers⁷⁾ had already reported that the NMR data of the homo-proorphine (Vc or VIc) were compatible with Battersby's assignment.

On the base of these facts, it may be concluded that the Pschorr reaction of 8-amino compound (Ia) under alkaline conditions affords three compounds, *dl*-glucine and two isomeric 2,5-dienones.

6) NMR spectra were measured by JNM-4H 100 spectrophotometer at 100 Mc in deuteriochloroform and tetramethylsilane was used as internal standard.

7) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **33**, 690 (1968).

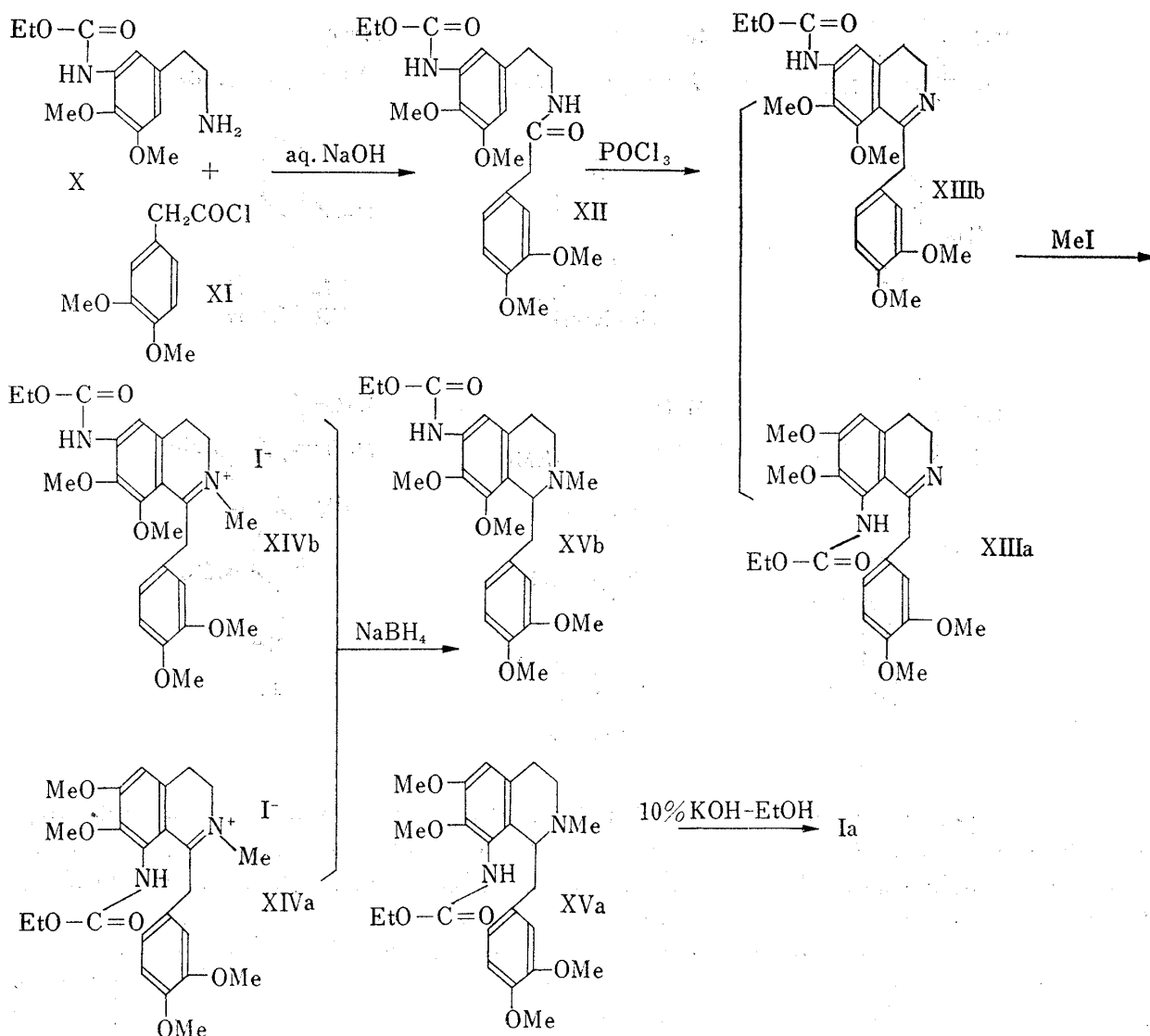
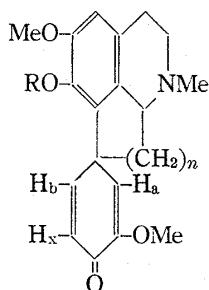


Chart 3



Va or Vb: $n=1$, $\text{R}=\text{Me}$
 Vb or Vc: $n=1$, $\text{R}=\text{H}$
 Vc or Vd: $n=2$, $\text{R}=\text{H}$

Chart 4

Experimental⁸⁾

N-(3-Ethoxycarbamido-4,5-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide (XII)—To a stirred mixture of the amine (X)⁶⁾ (liberated from 3 g of the hydrochloride) in 200 ml of benzene and 100 ml of 3% aq. NaOH, was added drop by drop the acid chloride (XI) (prepared from 3 g of the acid and 6 ml of SOCl_2 by the usual method) in 20 ml of dry benzene and the mixture was stirred further for 1 hr. 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 5 g of the amide as a colorless oily product. IR cm^{-1} (CHCl_3): ν_{NH} 3400, $\nu_{\text{C=O}}$ 1730 (urethane), 1660 (amide). NMR (τ): 8.70 (3H, triplet, $J=7$ cps, $\text{O}-\text{CH}_2\text{CH}_3$), 6.16–6.22 (12H, 4XO- CH_3), 5.80 (2H, quartet, $J=7$ cps, $\text{O}-\text{CH}_2\text{CH}_3$), 3.64 (1H, doublet, $J=2$ cps, aromatic H), 3.26 (3H, multiplet, aromatic H), 2.47 (1H, doublet, $J=2$ cps, aromatic H).

The Bischler-Napieralski Reaction of the Amide (XII)—A mixture of 4 g of the amide, 8 ml of POCl_3 , and 60 ml of dry benzene was refluxed for 1.5 hr and the solvent and excess reagent were evaporated under reduced pressure. The residue was dissolved in CHCl_3 and the extract was washed with water saturated with NaHCO_3 and water and evaporated to give a yellow oil, which was treated with 10 ml of MeI over

8) All melting points were not corrected.

period of 10 hr. Evaporation of the reagent afforded a yellow glassy mass, which was dissolved in 40 ml of MeOH.

To this solution, was added portionwise 3 g of NaBH₄ with stirring in an ice bath and the reaction mixture was stirred further for 1 hr at room temperature, and was poured into 300 ml of ether.

The ethereal solution was extracted with 3% aq. HCl and this acidic solution was basified with conc. NH₄OH, and the basic product was extracted with benzene. The extract was washed with water, dried over K₂CO₃, and evaporated to give a yellow syrup (2.5 g), which was chromatographed on silica gel (50 g) eluted with benzene-MeOH (50:1) to be separated into two components.

The first eluted component was XVb (1 part, 0.5 g): IR cm⁻¹ (CHCl₃): ν_{NH} 3400, ν_{C=O} 1728. NMR (τ): 8.70 (3H, triplet, *J*=7 cps, O-CH₂CH₃), 7.62 (3H, singlet, N-CH₃), 6.15-6.19 (12H, 4XO-CH₃), 5.77 (2H, quartet, *J*=7 cps, O-CH₂CH₃), 3.22 (3H, multiplet, aromatic H), 2.37 (1H, singlet, C₅-H).

The second was XVa (3 part, 1.5 g): IR cm⁻¹ (CHCl₃): ν_{NH} 3400, ν_{C=O} 1730. NMR (τ): 8.78 (3H, triplet, *J*=7 cps, O-CH₂CH₃), 7.56 (3H, singlet, N-CH₃), 6.25-6.15 (12H, 4XO-CH₃), 5.82 (2H, quartet, *J*=7 cps, O-CH₂CH₃), 3.35-3.25 (4H, aromatic H). Picrate: Recrystallized from EtOH, as yellow plates, mp 178-181° (decomp.). Anal. Calcd. for C₂₄H₃₂O₆N₂·C₁₀H₈O₅N₄: C, 57.62; H, 5.69; N, 11.86. Found: C, 57.24; H, 5.54; N, 11.54.

8-Amino-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-2-methylisoquinoline (Ia)—A mixture of 400 mg of XVa and 30 ml of 10% EtOH-KOH solution was refluxed for 1.5 hr in the presence of N₂. Evaporation of the solvent gave a yellow residue, which was acidified with 10% aq. HCl and the aqueous acidic solution was basified with conc. NH₄OH, and the product was extracted with benzene. The extract was dried over K₂CO₃ and evaporated to give a yellow oily product, which on alumina (10 g) chromatography, afforded 0.25 g of a pale yellow oil. IR cm⁻¹ (CHCl₃): ν_{NH} 3350, 3450. NMR (τ): 7.56 (3H, singlet, N-CH₃), 6.17, 6.20, 6.26, 6.28 (12H, 4XO-CH₃), 3.86 (1H, singlet, C₅-H), 3.30, 3.20 (3H, aromatic H). Picrate: Recrystallized from EtOH, as yellow needles, mp 167-169° (decomp.). Anal. Calcd. for C₂₁H₂₈O₄N₂·C₆H₃O₇N₃: C, 53.91; H, 5.19; N, 11.64. Found: C, 54.33; H, 5.47; N, 11.33.

The Pschorr Reaction of Ia under Alkaline Conditions—To a stirred mixture of 0.5 g of Ia and 12 ml of 5% aq. H₂SO₄, was added a slight excess of NaNO₂ in 1.5 ml of water at 5° and the reaction mixture was stirred further at 0-5° for 30 min. After addition of 5 g of AcONa in 10 ml of water, the reaction mixture was stirred for 3 hr at room temperature and basified with conc. NH₄OH. The product was extracted with CHCl₃ and the extract was washed with water, dried over K₂CO₃, and evaporated to give a reddish brown glassy mass (0.3 g). The product was chromatographed on silica gel (15 g) eluted with CHCl₃-MeOH (100:1) to be separated into two components. The first eluted product was *dl*-glaucine (50 mg). The IR and NMR spectra of this compound were superimposable with those of authentic sample.⁹⁾ NMR (τ): 7.38 (3H, singlet, N-CH₃), 6.35, 6.12, and 6.07 (9H, 3XO-CH₃), 3.38, 3.19, and 1.86 (3H, singlet, aromatic H). Picrate: Recrystallized from EtOH-THF, as yellow prisms, mp 191-193° (decomp., lit.^{9b)} 194°). Anal. Calcd. for C₂₁H₂₅O₄N·C₆H₃O₇N₃: C, 55.38; H, 4.82; N, 9.57. Found: C, 55.70; H, 4.83; N, 9.10.

The second eluted product was a mixture of two 2,5-dienones (100 mg), which were separated by fractional recrystallization of their picrolonate from THF gave 40 mg of yellow prisms, mp 215-217° (decomp.). Anal. Calcd. for C₂₁H₂₃O₄N·C₁₀H₈O₅N₄·½H₂O¹⁰⁾: C, 59.42; H, 5.15; N, 11.18. Found: C, 59.40; H, 5.06; N, 10.62. IR cm⁻¹ (CHCl₃): 1658, 1630, and 1608 (dienone). NMR (τ): 7.58 (3H, singlet, N-CH₃), 6.42, 6.31, and 6.29 (9H, singlet, 3XO-CH₃), 4.11 (1H, doublet, *J*=2 cps, Ha), 3.65 (1H, doublet, *J*=10 cps, Hx), 3.32 (1H, singlet, aromatic H), 2.92 (1H, quartet, *J*=2 cps, 10 cps, Hb).

On the other hand, evaporation of the mother liquor from which one dienone was removed, gave the another dienone. Recrystallization from EtOH-THF gave 25 mg of yellow plates, mp 199-201° (decomp.). Anal. Calcd. for C₂₁H₂₃O₄N·C₁₀H₈O₅N₄: C, 60.28; H, 5.06; N, 11.34. Found: C, 60.38; H, 5.47; N, 10.94. IR cm⁻¹ (CHCl₃): 1660, 1635, and 1609 (dienone). NMR (τ): 7.58 (3H, singlet, N-CH₃), 6.40, 6.34, and 6.28 (9H, singlet, 3XO-CH₃), 4.00 (1H, doublet, *J*=2 cps, Ha), 3.52 (1H, doublet, *J*=10 cps, Hx), 3.32 (1H, singlet, aromatic H), 3.05 (1H, quartet, *J*=2 cps, 10 cps, Hb).

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9) a) R. Pschorr, *Ber.*, **37**, 1926 (1904); b) A.H. Jackson and J.A. Martin, *J. Chem. Soc. (C)*, **1966**, 2061.

10) This product was dried over P₂O₅ at 100° (5 mmHg) for 5 hr.