Studies on Tetrahydroisoquinolines. XI.¹⁾ A Facile Synthesis of (±)-Aporphines via *p*-Quinol Acetates

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By the treatment of the *p*-quinol acetate (IIa-c) with trifluoroacetic acid, (±)-domesticine (VIa), (±)-thaliporphine (VIb), and (±)-1-hydroxy-2,9,10,11-tetramethoxyaporphine (VIc) were given in good yields, respectively.

In our laboratory, (±)-domesticine³⁾ (VIa) and (±)-thaliporphine⁴⁾ (VIb) have been synthesized by a unique route involving lead tetraacetate [Pb(OAc)₄] oxidation of (±)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinolines (Ia and Ib) and subsequent acid treatment (Ac₂O-conc. H₂SO₄) of their corresponding *p*-quinol acetates (IIa and IIb).

In spite of the fact that formation of *p*-quinol acetates was almost quantitative, the overall yield was not satisfactory. In addition, the method apparently had a drawback in two points. First, hydrolytic process was always necessary to obtain natural products, since the product of acid treatment was (±)-O-acetylporphine (IIIa or IIIb). Second, (±)-4α- (IVa or IVb) and (±)-4β-acetoxy-O-acetylporphines (Va or Vb) were always formed as by-

Chart 1

1) Part X: O. Hoshino, H. Hara, M. Ogawa, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 2578 (1975).

2) Location: 12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.

3) O. Hoshino, H. Hara, N. Serizawa, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 2048 (1975).

4) O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Commun.*, **1971**, 1533; *idem*, *Chem. Pharm. Bull.* (Tokyo), **22**, 1302 (1974).

products. The first problem would be solved if a protonic acid in the absence of Ac_2O could be used for a cyclizing reagent. Among others, trifluoroacetic acid (CF_3COOH) was found most suitable for the purpose and we now report an effective synthesis of ($\pm$)-aporphines (VI).

The crude *p*-quinol acetate (IIa), derived from $\text{Pb}(\text{OAc})_4$ oxidation of the phenolic base (Ia) in acetic acid (AcOH), was treated with CF_3COOH in methylene chloride (CH_2Cl_2) at room temperature for 2 hr. Usual work-up of the reaction mixture gave ($\pm$)-domesticine (VIa), mp 189—191°, in 83.6% yield.

In order to check the probable existence of 4-oxygenated product (VIIa) as a by-product in the reaction, the reaction mixture was treated with acetic anhydride and pyridine yielding no trace of IVa or Va. Therefore, superiority of the present method was further substantiated. Similar treatment with CF_3COOH of the *p*-quinol acetate (IIb) derived from ($\pm$)-codamine (Ib) afforded ($\pm$)-thaliporphine (VIb), mp 189—190° (decomp.) in 96% yield. No trace of VIIb was also formed in this case.

To examine further utility of the method, similar treatment of the *p*-quinol acetate (IIc) from ($\pm$)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-1-(3',4',5'-trimethoxybenzyl)-2-methylisoquinoline (Ic) was undertaken.

The starting material (Ic) was synthesized as follows. Namely, heating of the phenethylamine and methyl 3,4,5-trimethoxyphenylacetate⁵⁾ gave *N*- β -(4-benzyloxy-3-methoxyphenyl)-ethyl-3',4',5'-trimethoxyphenylacetamide (VIII), mp 93—94°, Bishler-Napieralski reaction of which with phosphoryl chloride in CH_2Cl_2 led to 3,4-dihydroisoquinoline hydrochloride (IX·HCl) mp 203—204°. The free base resulted from IX·HCl was converted to a methiodide (X), mp 221—224°, whose reduction with sodium borohydride gave oily ($\pm$)-tetrahydroisoquinoline (XI) (picrate: mp 146—147°). Debenzylation of XI by catalytic reduction gave Ic.

Chart 2

$\text{Pb}(\text{OAc})_4$ oxidation of Ic in AcOH led readily to a *p*-quinol acetate (IIc). The crude *p*-quinol acetate (IIc) in CH_2Cl_2 was treated with CF_3COOH at room temperature for 2 hr. The reaction mixture was purified on preparative thin-layer chromatography (TLC) giving in 48% yield ($\pm$)-1-hydroxy-2,9,10,11-tetramethoxyaporphine (VIc), mp 175—176°, whose nuclear magnetic resonance (NMR) and infrared (IR) spectrum showed signals (δ 6.63 and 7.73, each 1H, singlet) due to two aromatic protons and a band (3180 cm^{-1}) due to a hydroxyl group hydrogen-bonded with the oxygen of 11-methoxy. Spectral data indicated above and elemental analysis strongly supported the structure of VIc.

In this case, a presumed steric repulsion between 1-hydroxy and 11-methoxy group did not seriously cause an inhibitory effect on the cyclization yielding the desired ($\pm$)-aporphine (VIc) in a fair yield. Apart from the fact that the above cyclization was evidently facilitated by the presence of three methoxy groups at 3', 4', and 5'-position, the success undoubtedly pointed out the usefulness of the reagent.

5) F.W. Semmler, *Ber.*, **41**, 1919 (1908).

Previously,⁴⁾ in the mechanistic pathway leading to ($\pm$)-O-acetylthaliporphine (IIIb), the role of acetylum ion as a reaction initiator was postulated. Recent observation⁶⁾ on the reaction with hydrochloric acid of *p*-quinol acetates, however, suggested another possibility. Accordingly, the mechanistic pathway visualized in Chart 3 seemed operative in the present reaction. Namely, $S_N 2'$ reaction initiated by proton occurred at 8-position and C-C linkage at 8- and 6'-position was directly formed giving an intermediate such as A, whose enolization led to ($\pm$)-aporphine.

Chart 3

In conclusion, the present method would constitute one of widely applicable aporphine syntheses.

Experimental⁷⁾

($\pm$)-Domesticine (VIa)—To a stirred solution of the phenolic isoquinoline (Ia) (2.75 g, 8.41 mmole) in AcOH (55 ml) was added Pb(OAc)₄ (4.43 g, 0.01 mmole) in one portion and stirring was continued at room temp. for 30 min. The reaction mixture was poured onto crashed ice and carefully basified with NaHCO₃ (powder). The product was taken up in CHCl₃. The CHCl₃ extract was washed with brine and dried over K₂CO₃. Removal of the solvent under reduced pressure gave an amorphous mass of a *p*-quinol acetate (IIa) (3.70 g). To a stirred solution of the crude IIa in CH₂Cl₂ (275 ml) was added CF₃COOH (13.8 ml) in one portion and the whole was stirred at room temp. for 2 hr. The reaction mixture was washed with sat. NaHCO₃ solution and brine, and dried over K₂CO₃. Removal of the solvent under reduced pressure furnished pale brown crystals (VIa) (2.3 g, 83.6%), mp 175–182°. Recrystallization from ether–acetone gave pale yellow prisms (1.14 g, 41.5%), mp 189–191° (lit.³⁾ mp 185–186°), which was consistent with an authentic sample in all respects by comparisons of IR spectrum and TLC.

Acetylation of the Acid treated Product from IIa—To a stirred solution of the phenolic isoquinoline (Ia) (100 mg, 0.305 mmole) in AcOH (2 ml) was added Pb(OAc)₄ (163 mg, 0.368 mmole) in one portion and stirring was continued at room temp. for 30 min. Usual work-up gave an amorphous mass of a *p*-quinol acetate (IIa) (139 mg), which was dissolved in CH₂Cl₂ (10 ml) and the solution was treated with CF₃COOH (0.5 ml) under stirring. Stirring was continued at room temp. for 2 hr. Work-up as usual gave a brown amorphous mass (118 mg), to which were added pyridine (0.5 ml) and Ac₂O (0.5 ml). The whole was stood overnight at room temp. and the reaction mixture was poured into water. The product was taken up in CHCl₃. The CHCl₃ layer was washed with sat. NaHCO₃ solution, 2% CuSO₄ solution, and brine, successively. Usual work-up gave brown crystals (125 mg), mp 129–140°. Recrystallization from benzene–*n*-hexane gave pale brown prisms (IIIa) (55 mg, 49%), mp 149–153° (lit.³⁾ mp 157–158°), which was consistent with an authentic sample in all respects by comparisons of IR spectrum and TLC.

($\pm$)-Thaliporphine (VIb)—To a solution of ($\pm$)-codamine (Ib) (2 g, 5.83 mmole) in AcOH (40 ml) was added Pb(OAc)₄ (3.10 g, 6.99 mmole) in one portion and stirring was continued at room temp. for 30 min. Usual work-up gave an oily *p*-quinol acetate (IIb) (2.73 g), which was dissolved in CH₂Cl₂ (200 ml) and the stirred solution was treated with CF₃COOH (10 ml). Stirring was continued at room temp. for 2 hr. The

6) H. Hara, O. Hoshino, and B. Umezawa, *Heterocycles*, **3**, 123 (1975).

7) All melting points were uncorrected and measured on a Büchi melting point measuring apparatus. NMR spectra were taken with a JEOL Model JNR-4H-100 spectrometer (100 MHz) in CDCl₃ solution (5–10%) by using (CH₃)₄Si as internal standard. Following abbreviations were used; s: singlet; d: doublet; t: triplet; bs: broad singlet. IR spectra were run on a Hitachi Model 215 spectrometer, unless otherwise noted. Preparative thin-layer chromatographies were performed over Silicagel GF₂₅₄ (Merck).

same work-up as described above gave a greenish yellow amorphous mass (2.53 g), which was crystallized from *n*-hexane to give greenish yellow crystals (VIb) (1.91 g, 96%), mp 175–179°. Recrystallization from ether gave colorless prisms (1.11 g, 55.8%), mp 189–190° (decomp.) [lit.⁴ mp 193–195° (decomp.)], which was consistent with an authentic sample in all respects by comparisons of IR spectrum and TLC.

N-β-(4-Benzoyloxy-3-methoxyphenyl)ethyl-3',4',5'-trimethoxyphenylacetamide (VIII)—A mixture of the phenethylamine (7.5 g) [freed from its oxalate (9.2 g)] and methyl 3,4,5-trimethoxyphenylacetate⁵ (5.3 g) was heated at 170° (bath tempt.) for 3 hr. Usual work-up of the reaction mixture gave a dark brown amorphous mass (11.9 g), which was crystallized from AcOEt–CH₃OH yielding pale yellow prisms (VIII) (6.084 g, 59.5%), mp 93–94°. Recrystallization from AcOEt gave colorless prisms, mp 93–94°. IR⁸⁾ $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3270 (NH), 1662 (CONH–). NMR δ : 2.67 (2H, t, *J* = 7.5 Hz, ArCH₂CH₂NH), 3.41 (2H, s, COCH₂Ar), 3.76 (6H, s, 2xOCH₃), 3.79, 3.81 (each 3H, s, 2xOCH₃), 5.08 (2H, s, OCH₂C₆H₅), 5.74 (1H, bs, NH), 6.38 (2H, s, 2'- and 6'-H). Anal. Calcd. for C₂₇H₃₁O₆N: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.53; H, 6.62; N, 2.88.

7-Benzoyloxy-3,4-dihydro-6-methoxy-1-(3',4',5'-trimethoxybenzyl)isoquinoline Hydrochloride (IX·HCl)—A mixture of the amide (VIII) (4.65 g) and POCl₃ (20 ml) in anhydrous CH₂Cl₂ (50 ml) was refluxed for 3 hr with stirring. Removal of the solvent under reduced pressure gave a viscous oil, which was washed well with petr. benzene to afford a crystalline mass. Recrystallization from iso-C₃H₇OH furnished pale yellow prisms (IX·HCl) (4.516 g, 93.4%), mp 203–204°, which was further recrystallized from CH₃OH to give colorless prisms, mp 203–204° (hygroscopic). IR⁸⁾ $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1645 (C=N–). Anal. Calcd. for C₂₇H₃₀O₅N·Cl·1/2H₂O: C, 65.78; H, 6.34; N, 2.84. Found: C, 65.70; H, 6.37; N, 2.86.

7-Benzoyloxy-3,4-dihydro-6-methoxy-1-(3',4',5'-trimethoxybenzyl)-2-methylisoquinolinium Iodide (X)—A solution of the 3,4-dihydroisoquinoline (IX) (2.50 g) [freed from its hydrochloride (IX·HCl) (2.42 g)] and CH₃I (10 ml) in CH₃OH (20 ml) was gently refluxed for 2 hr. The reaction mixture was condensed under reduced pressure giving a methiodide (X) (2.54 g, 86%), mp 217–219°, which was recrystallized from CH₃OH to give yellow prisms, mp 221–224°. Anal. Calcd. for C₂₈H₃₂O₅NI: C, 57.05; H, 5.47; N, 2.38. Found: C, 57.07; H, 5.33; N, 2.16.

(±)-7-Benzoyloxy-1,2,3,4-tetrahydro-6-methoxy-1-(3',4',5'-trimethoxybenzyl)-2-methylisoquinoline (XI)—To a stirred suspension of the methiodide (X) (1.77 g) in CH₃OH (60 ml) was added NaBH₄ (570 mg) in small portions. The reaction mixture gradually became clear as NaBH₄ was added. After 0.5 hr's stirring at room tempt., the solvent was removed under reduced pressure. To the residue was added 10% NaOH solution and the product was taken up in ether. Usual work-up of the ether extract gave a pale yellow oil (XI) (1.35 g, 97%). NMR δ : 2.48 (3H, s, NCH₃), 3.70, 3.76 (each 6H, s, 4 × OCH₃), 4.76, 4.87 (each 1H, d, *J* = 12 Hz, OCH₂C₆H₅), 6.15, 6.37 (each 1H, s, arom. H), 6.26 (2H, s, 2'- and 6'-H), 7.28 (5H, bs, arom. H). Picrate: yellow prisms, mp 146–147° (CH₃OH). Anal. Calcd. for C₃₄H₃₆O₁₂N₄: C, 58.95; H, 5.24; N, 8.09. Found: C, 59.01; H, 5.13; N, 8.17.

(±)-1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-1-(3',4',5'-trimethoxybenzyl)-2-methylisoquinoline (Ic)—A mixture of the benzyloxyisoquinoline (XI) (1.11 g), 2% PdCl₂ (5 ml), and active carbon (250 mg) in CH₃OH (100 ml) was shaken in an atmosphere of H₂ at room tempt., until uptake of H₂ ceased. After filtration of the catalyst, removal of the solvent under reduced pressure afforded an oil, which was dissolved in 10% NaOH solution. The alkaline solution was washed with ether and treated with NH₄Cl (solid). The product was taken up in CHCl₃. Usual work-up of the CHCl₃ extract furnished an oil (Ic) (0.891 g, quantitative). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3530 (OH). NMR δ : 2.45 (3H, s, NCH₃), 3.72, 3.77 (each 6H, s, 4 × OCH₃), 6.32 (2H, s, 2'- and 6'-H), 6.39, 6.52 (each 1H, s, arom. H). Methiodide: colorless prisms, mp 243–245° (CH₃OH). Anal. Calcd. for C₂₂H₃₀O₅NI: C, 51.27; H, 5.87; N, 2.72. Found: C, 51.27; H, 5.85; N, 2.69.

(±)-1-Hydroxy-2,9,10,11-tetramethoxyaporphine (VIc)—To a stirred solution of phenolic isoquinoline (Ic) (151 mg, 0.390 mmole) in AcOH (3 ml) was added Pb(OAc)₄ (208 mg, 0.468 mmole) in one portion and stirring was continued at room tempt. for 30 min. Usual work-up gave an oily *p*-quinol acetate (IIc) (210 mg) [IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1735 (–OCOCH₃), 1670, 1645, 1625 (dienone)], which was dissolved in CH₂Cl₂ (15 ml), followed by addition of CF₃COOH (0.75 ml). The mixture was stirred at room tempt. for 2 hr. Work-up as usual gave a dark brown amorphous mass (160 mg), which was purified on preparative TLC (CHCl₃:CH₃OH = 25:1). Elution with CHCl₃–CH₃OH (5:1) gave pale green crystals (VIc) (72 mg, 48%), mp 167–168°. Recrystallization from ether–*n*-hexane gave pale green needles (36 mg, 24%), mp 171–173°, and an analytical sample had mp 175–176°. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3180 (OH). NMR δ : 2.51 (3H, s, NCH₃), 3.75, 3.85, 3.87, 3.90 (each 3H, s, 4 × OCH₃), 6.63 (1H, s, 3-H), 6.73 (1H, s, 8-H), 8.55 (1H, bs, OH). Anal. Calcd. for C₂₁H₂₅O₅N: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.94; H, 6.74; N, 3.66.

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8) A Hitachi Model 225 spectrometer was used.