Syntheses of Aminoisoquinolines and Related Compounds. VIII.\textsuperscript{1)}

Total Synthesis of \textit{dl}-Homolinearisine

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8-Amino-1,2,3,4-tetrahydro-7-methoxy-1-(4-methoxybenzyl)-2-methyl-6-isoquinolinol (IIa) was synthesized and the Pschorr reaction of this compound under alkaline conditions gave \textit{dl}-homolinearisine, which could not be synthesized by the phenolic oxidative coupling method. Infrared and nuclear magnetic resonance spectra of the synthesized sample were superimposable with those of the natural product.

Homolinearisine, \textit{C}_{14}\textit{H}_{19}\textit{O}_{2}\textit{N}, melted at 220°, was isolated from \textit{Croton linearis} Jacq.\textsuperscript{4)} and chemical and spectral investigation led to the proposed structure (Ia) by Haynes and his co-workers.\textsuperscript{5)}

\textit{RO-}  
\textit{MeO-}  
\textit{NM}\textsubscript{e}-  
\textit{O-}

\textit{Ia : R = H}  
\textit{Ib : R = Me}

\textit{RO-}  
\textit{MeO-}  
\textit{NM}\textsubscript{e}-  
\textit{O-}

\textit{IIa : R = H}  
\textit{IIb : R = Me}

Chart 1

\textit{HO-}  
\textit{MeO-.}  
\textit{NM}\textsubscript{e}-  
\textit{OH-}

\textit{III}

The phenolic oxidation is a useful method for synthesizing proaporphine type compound,\textsuperscript{6)} but coupling occurs only at the position \textit{para} or \textit{ortho} to the hydroxyl group. However, homolinearisine has a hydroxyl group at the position meta to the site of carbon–carbon coupling, and therefore, homolinearisine can not be synthesized by the phenolic oxidation of 1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-7-methoxy-2-methyl-6-isoquinolinol (III).\textsuperscript{6)}

In a previous paper,\textsuperscript{7)} the authors reported that the Pschorr reaction of 8-amino-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (IIb) under alkaline conditions gave two compounds, one of which was a proaporphine type compound, \textit{dl}-pronuciferone (Ib).

This paper reports the synthesis of \textit{dl}-homolinearisine by the Pschorr reaction of 8-amino-1,2,3,4-tetrahydro-7-methoxy-1-(4-methoxybenzyl)-2-methyl-6-isoquinolinol (IIa) under the same conditions as described in the previous paper.

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8-Amino compound was prepared as follows: The aldehyde (VI) prepared from O-acetyl-5-nitroisovaniline (IV) by the usual method, was condensed with nitromethane in the presence of ammonium acetate in acetic acid gave the deacetylated nitrostyrene (VII), which was reduced to the phenethylamine (VIII) by the electrolytic reduction. Condensation of the phenethylamine and 4-methoxyphenylacetic acid with the aid of dicyclohexylcarbodiimide (DCC)\(^8\) furnished the hydroxymide (IX), which was further converted to the benzoxylated amide (X). The Bischler–Napieralski reaction of X with phosphoryl chloride in benzene solution gave two kinds of 3,4-dihydroisoquinolines (XIa and XIb), which were methylated with methyl iodide afforded a mixture of methiodides (XIIa and XIIb).

Reduction of the methiodides with sodium borohydride in methanol solution gave a mixture of N-methyltetrahydroisoquinolines (XIIIa and XIIIb), which was chromatographed on silica gel separated into two components with a ratio of 1:4 (XIIIa:XIIIb).

Hydrolysis of XIIIa with 10% ethanolic potassium hydroxide solution gave XIVa, which was successively hydrolyzed to the 8-amino compound (IIa) with ethanolic hydrochloric acid solution.

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IIa was diazotized and decomposition of the resulting diazonium salt with sodium acetate by a usual manner described in the previous work\(^9\) afforded two compounds. The mixture of these two compounds was chromatographed on silica gel eluted with chloroform–methanol (30:1) to give a small amount of 2-hydroxy-1,11-dimethoxyaporphine (XV) and \(dl\)-homolinearisine in 10% yield. The latter was identified with the natural product by the infrared (IR) and nuclear magnetic resonance (NMR) spectral comparison and moreover, the mass spectrum was also supported the structure as illustrated in Chart 4.\(^9\)

Methylation of XV with diazomethane gave a trimethoxyaporphine, whose IR spectrum was superimposable with that of authentic sample.\(^7\)

These facts revealed that the Pschorr reaction of the 8-amino compound (IIa) was a useful method for synthesizing the proaporphine alkaloid, which could not be synthesized by the phenolic oxidative coupling method.

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Experimental

O-Acetyl-5-nitrosovaniline Diethylacetal (V)—A mixture of 30 g of IV, 1 g of NH₂Cl, and 30 ml of (EtO)₂CH was refluxed in 60 ml of EtOH for 3 hr. After evaporation of the solvent and excess of the reagent, the residue was extracted with ether and the ethereal solution was washed with water, dried over K₂CO₃, and evaporated to afford a yellow viscous oily product. The product was purified by distillation under 0.005 mmHg, bp 135—140°C. Yield: 35 g. IR cm⁻¹ (NaCl plate): ν₂O 1775.

3-Acetoxy-5-ethoxy carbamido-4-methoxy benzaldehyde (VI)—The nitroacetate (30 g) was reduced catalytically over Raney-Ni (5 g) in ethanol (60 ml) to an aminocetal, which was used for the next step without purification. IR cm⁻¹ (CHCl₃): νOH 3350, 3430, νC=O 1770.

To a stirred mixture of the amino compound (from 30 g of V) in 40 ml of pyridine, was added 15 ml of ethyl chloroformate drop by drop and the reaction mixture was stirred further for 3 hr. The mixture was diluted with 40 ml of water and poured into a mixture of 500 g of ice and 150 ml of conc. HCl to yield pale yellow precipitates, which were taken up in CHCl₃. The extract was washed with water, dried over K₂CO₃, and filtered. The filtrate was evaporated to afford a yellow solid, which was recrystallized from benzene, yielding 14 g of colorless needles, mp 129—131°C. IR cm⁻¹ (CHCl₃): νCH 3400, νC=O 1780 (acetoxy), 1735 (urethane), 1695 (aldehyde). NMR (CDCl₃): δ 7.29 (3H, t, J=7.5 cps, O-CH₃CH₂), 7.68 (3H, s, CO-CH₃), 6.19 (3H, s, O-CH₃), 5.75 (2H, q, J=7.5 cps, O-CH₂CH₃), 2.66 and 1.44 (2H, d, J=2 cps, aromatic H), 0.10 (1H, s, CHO). Anal. Calcd. for C₁₉H₂₀O₂N: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.88; H, 5.37; N, 4.91.

3-Ethoxycarbamido-5-hydroxy-4-methoxy-β-nitrostyrene (VII)—A mixture of 15 g of VI, 15 ml of CH₃NO₂, 7 g of ammonium acetate, and 50 ml of AcOH was refluxed for 2 hr. The reaction mixture was poured into 100 ml of water and the resultant precipitates were filtered. The product was recrystallized from aq. EtOH to give 7 g of yellow rhombic plates, mp 125—127°C. IR cm⁻¹ (CHCl₃): νOH 3570, νCH 3400, νC=O 1730, νC=O 1630. Anal. Calcd. for C₁₉H₁₈O₄N: C, 48.00; H, 5.37; N, 8.33. Found: C, 48.38; H, 5.26; N, 8.29.

N-[3-Ethoxycarbamido-5-hydroxy-4-methoxyphenyl]-2-(4-methoxyphenyl)acetamide (IX)—A mixture of 1.1 g of 4-methoxyphenylacetic acid, 1.5 g of the amide (VIII), and 1.4 g of DCC was stirred in 40 ml of CH₂Cl₂ for 5 hr. After filtration of the mixture, the CH₂Cl₂ solution was washed with successively 3%aq. HCl, 5%aq. NaHCO₃, and water and dried over K₂CO₃. Evaporation of the solvent gave a colorless oily product, which was purified by chromatography on silica gel to give 1.7 g of the amide as a viscous oil. IR cm⁻¹ (CHCl₃): νOH 3500, νCH 3400, νC=O 1730 (urethane), 1650 (amide). NMR (CDCl₃): δ 7.60 (3H, t, J=7.5 cps, O-CH₂CH₃), 6.26 and 6.20 (6H, s, 2×O-CH₃), 5.58 (2H, q, J=7.5 cps, O-CH₂CH₃), 3.60 (1H, d, J=2 cps), 3.16 (1H, d, J=8 cps), 2.90 (1H, d, J=8 cps), 2.61 (1H, d, J=2 cps): Aromatic H.

N-[3-Benzylxoy-5-ethoxycarbamido-4-methoxyphenyl]-2-(4-methoxyphenyl)acetamide (X)—A mixture of IX (0.95 g), benzyl chloride (0.35 g), K₂CO₃ (0.4 g), and DMF (15 ml) was warmed at 95—100°C for 3 hr with stirring and the reaction mixture was diluted with water (50 ml). The product was extracted with CHCl₃ and the extract was washed with 3%aq. NaOH and water, dried over K₂CO₃, and evaporated to give a pale yellow solid. Recrystallization of the product from benzene gave 0.9 g of colorless needles, mp 153—154°C. IR cm⁻¹ (CHCl₃): νOH 3400, νC=O 1730 (urethane), 1655 (amide). Anal. Calcd. for C₁₉H₂O₄N₂: C, 68.27; H, 6.55; N, 5.69. Found: C, 68.69; H, 6.74; N, 5.70.

The Bischler-Napieralski Reaction of the Amide (XI)—The amide (2 g) was suspended on anhyd. benzene (30 ml), and the mixture was refluxed with POCl₃ (4 ml) for 2 hr. The solvent and reagent were evaporated under reduced pressure and the yellowish brown residue was washed with n-hexane for several times and dissolved in CHCl₃. The CHCl₃ solution was shaked with 10% NH₄OH and washed with water, dried over K₂CO₃, and evaporated to give a yellow oil, which was treated with 10 ml of Me₃ for 10 hr. Evaporation of the reagent afforded a yellow glassy mass, which was treated with NaBH₄ (2 g) on an ice bath in 30 ml of MeOH for 1 hr. The mixture was poured into ether (200 ml) and extracted with 3%aq. HCl. The extract was basified with conc. NH₄OH and the basic product was extracted with benzene and benzene solution was washed with water and dried over K₂CO₃. Evaporation of the solvent gave 1.5 g of oily substance, which was chromatographed on silica gel (30 g) eluted with benzene-MeOH (70:1) and separated into XIIa (1 g) and XIIb (0.25 g). XIIa: IR cm⁻¹ (CHCl₃): νOH 3400, νC=O 1730. NMR (CDCl₃): δ 8.75 (3H, t, J=7.5 cps, O-CH₂CH₃), 7.60 (3H, s, N-CH₃), 5.55 (2H, q, J=7.5 cps, O-CH₂CH₃), 6.23 and 6.26 (6H, s, 2×O-CH₃), 4.92 (2H, s, O-CH₂CO₂H), 3.30 (1H, s, C₂H), 3.15—2.90 (4H, q, aromatic H), 2.58 (5H, m, O-CH₂C₆H₅). Picrolonate: Recrystallized from EtOH as yellow plates, mp 142—144°C (decomp.). Anal. 10

10 All melting points were not corrected. 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 δ value. Mass spectrum was measured by Hitachi RMU-6 mass spectrometer.

Calcd. for $C_{29}H_{34}O_2N_2\cdot C_{12}H_6O_2N_2 \cdot \frac{1}{2}H_2O$: C, 61.35; H, 5.67; N, 11.00. Found: C, 61.32; H, 5.57; N, 10.98.

NMR (CDCl$_3$): 6.86 (3H, t, $J=7.5$ cps, O-CH$_2$CH$_3$), 6.15 and 6.25 (6H, s, 2×O-CH$_3$), 7.85 (3H, s, N-CH$_3$), 5.74 (2H, q, $J=7.5$ cps, O-CH$_2$CH$_3$), 5.06 and 4.86 (2H, AB type, q, $J=10$ cps, O-CH$_2$CH$_3$), 3.28–3.10 (4H, q, aromatic H), 2.62 (5H, m, O-CH$_2$CH$_3$), 2.35 (1H, s, CH$_3$). Picrolonate: Recrystallized from EtOH as yellow prisms, mp 165–167$^\circ$ (decomp.). Anal. Calcd. for $C_{29}H_{34}O_2N_2\cdot C_{12}H_6O_2N_2$: C, 62.02; H, 5.61. Found: C, 62.20; H, 5.85.

8-Amino-6-benzylxoxy-1,2,3,4-tetrahydro-7-methoxy-1-(4-methoxybenzyl)-2-methyliisoquinoline (XIVA)—A mixture of XIIa (0.5 g), KOH (3 g), and 90% EtOH (30 ml) was refluxed for 2 hr in the presence of N$_2$. Evaporation of the solvent gave a reddish brown oil, which was acidified with conc. HCl and the acidic solution was basified again with conc. NH$_4$OH. The amino compound was extracted with CHCl$_3$ and the extract was washed with water, dried over K$_2$CO$_3$, and evaporated to give 0.3 g of yellow oil. IR cm$^{-1}$ (CHCl$_3$): pH 3360, 3440. NMR (CDCl$_3$): 6.22 (6H, s, 2×O-CH$_3$), 4.92 (2H, s, O-CH$_2$CH$_3$), 3.76 (1H, s, CH$_3$), 3.15–2.80 (4H, q, aromatic H), 2.58 (5H, m, O-CH$_2$CH$_3$). Picrolonate: Recrystallized from EtOH as yellow needles, mp 152–154$^\circ$ (decomp.). Anal. Calcd. for $C_{29}H_{34}O_2N_2\cdot C_{12}H_6O_2N_2$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.51; H, 5.70; N, 12.17.

8-Amino-1,2,3,4-tetrahydro-4-methoxy-1-(4-methoxybenzyl)-2-methyl-6-isouquinolinol (IIa)—A mixture of 300 mg of XIVA, 10 ml of EtOH, and 10 ml of conc. HCl was refluxed for 2 hr. After evaporation of the solvent and the reagent, the residue was basified with conc. NH$_4$OH and the product was extracted with CHCl$_3$. The CHCl$_3$ solution was dried over K$_2$CO$_3$ and evaporated to yield 150 mg of yellow oil, which could not be crystallized. IR cm$^{-1}$ (CHCl$_3$): pH 3380, 3440. NMR (CDCl$_3$): 7.59 (3H, s, N-CH$_3$), 6.25 and 6.30 (6H, s, 2×O-CH$_3$), 3.85 (1H, s, CH$_3$), 3.15–2.90 (4H, q, aromatic H).

The Preparation of IIa—To a stirred mixture of IIa (100 mg) and 5%aq, H$_2$SO$_4$ (4 ml), was added slight excess of NaNO$_2$ (in 0.5 ml of water) at 0–5$^\circ$ and the reaction mixture was stirred further for 0.5 hr at 5$^\circ$. A solution of 1.5 g of AcONa in 4 ml of water was added to this mixture and the reaction mixture was stirred for 3 hr at room temperature. After basification of the mixture with conc. NH$_4$OH, the product was taken up in CHCl$_3$ and the extract was dried over K$_2$CO$_3$ and evaporated to give a reddish brown viscous oil (50 mg), which showed two spots on thin-layer chromatogram of silica gel. The mixture was chromatographed on silica gel (2.5 g) eluted with CHCl$_3$:MeOH (30:1) to give 5 mg of XV and 10 mg of Ia.

XV: IR cm$^{-1}$ (CHCl$_3$): pH 3580, NMR (CDCl$_3$): 7.32 (3H, s, N-CH$_3$), 6.36 and 6.15 (6H, s, 2×O-CH$_3$). Methylation of XV with diazomethane gave a trimethoxyaporphine, whose IR spectrum was superimposable with that of authentic sample.

Ia: IR cm$^{-1}$ (CHCl$_3$): pH 3560, pH 1660, pH 1620. NMR ($d_6$-DMSO): 7.75 (3H, s, N-CH$_3$), 6.50 (3H, s, O-CH$_3$), 3.97 (1H, s, aromatic H), 3.97–3.55 and 3.00–2.65 (4H, diene H).

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