Studies on the Syntheses of Heterocyclic Compounds. CDLXXXIII.1) Synthesis of Homoaoporphine and Attempts to Synthesize C-Noraoporphine by Pchorr Reaction

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Photolysis of the diazonium salt derived from 1-(2-amino-4-hydroxy-5-methoxyphenethyl)-7-hydroxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (V) gave, 1,11-dihydroxy-2,10-dimethoxyhomoaporphine (IX), which was identical with the rearranged product of kroyksigine (VII) by acid. The same reaction of 1-(2-amino phenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XXI) gave an abnormal product, 3,4-dihydro-6,7-dimethoxy-1-phenylisoquinoline (XXV), in addition to the deamination product (XXII) and the phenolic isoquinoline (XXIII).

Previously, we reported that phenol oxidation of the diphenolic isoquinoline (I) gave kroyksigine (VII) and its spiro isomer (VIII), which on acidic treatment afforded the 1, 11-dihydroxy-2,10-dimethoxy (IX) and 1,10-dihydroxy-2,11-dimethoxyhomoaporphine (X), respectively.3,4) Since the structures (IX and X) of both homoaoporphines were assigned tentatively by the spectroscopic method using mainly nuclear magnetic resonance (NMR) spectra, the reinvestigation of the structures was carried out by the synthesis of the homoaoporphines by a photo-Pchorr reaction developed in our laboratory.5) Herein we wish to report the suggested structures (IX and X) to be correct, and, moreover, examined a synthetic approach of C-noraoporphine (XIII) by a similar reaction.

![Chemical Structures]

**Chart 1**

2) Location: a) Aoba yama, Sendai; b) Madras, India.
We have not obtained fruitful result for synthesizing the homoaporphine by a C. Pschorr reaction,\(^6\) and only one example of the homoaporphine synthesis without a cation of the rearrangement was carried out by Battersby,\(^7\) phenol oxidation of autumn (II) gave 1,12-dihydroxy-2,10,11-trimethoxyhomoaporphine (XI). However, the expe homoaporphine (X) could not be obtained from homoorientaline (III) by this method.

Recently, we reported a new way of synthesizing kreyssigine\(^8\) (XII), and homoaoporph alkaloid from Kreysigia multiflora,\(^9\) from the diastereom phenethylisoquinoline (IV) by pl lytic cyclization.\(^5\) This method was applied to the synthesis of the homoaporphines and X) from the aminoisouquinoline (V), which was prepared as follows.

Nitration of the phenylpropionic acid derivative (XIV) gave the 2-nitrophenylpropionic acid (XV), which was fused with 4-benzyloxy-3-methoxyphenethylamine to afford the corresponding amide (XVI). A Bischler–Napieralski reaction of the above amide furnished 3,4-dihydroisoquinoline (XVII), the methiodide (XVIII) of which was reduced with and hydrochloric acid to give the aminoisouquinoline (VI). Debenzylation of VI by ethan hydrochloric acid afforded the starting phenolic aminoisouquinoline (V).

\[ \text{Chart 2} \]

The diazotization of V, followed by the irradiation of the resulting diazonium salts with a Hanovia 650 W mercury lamp enclosed in a pyrex filter, afforded the homoaporphine which was identical perfectly with the product (IX) derived from kreyssigine (VII) in spectroscopic methods. Thus, we confirmed that kreyssigine (VII) rearranged to 1,2-dihydroxy-2,10,11-dimethoxyhomoaporphine (IX) and that the structures (IX and X) tentatively assigned by NMR spectroscopy to the homoaporphines were correct.\(^6\)

Secondly, the synthesis of C-noraporphine (XIII) was examined by Phschorr and phoschorr reaction as follows. The aminoisouquinoline (XXI), which was synthesized by methylation of 2'-nitroisoquinoline\(^6\) (XIX) with methyl iodide, followed by reduction of XX with zinc dust and sulfuric acid, was diazotized and the resulting diazonium salt was decomposed at 70\(^\circ\)C without metallic catalyst to give the deamination product (XXII), the phenolic ba

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(XXIII) and the abnormal product which was characterized as oxalate. In the latter compound the microanalysis and mass spectrometry revealed the molecular formula \( C_{13}H_{17}O_2N \), and ultraviolet (UV) spectrum showed the presence of 3,4-dihydropseudoquinoline system. In the NMR (\( \delta \)) spectrum, two O-methyl resonances were shown but not N-methyl resonance. Moreover, two methylene groups resonated at 2.78 and 3.88 ppm as distorted triplets, and the methine proton could not be observed. The aromatic protons were observed at 6.78 corresponding to two protons as a singlet and at 7.5 equivalent to five protons as a broad signal. These data revealed the product to the 3,4-dihydropseudoquinoline (XXV), which was proved by direct comparison with the authentic sample\(^{11} \) by spectroscopic method and melting point determination.

The elimination of N-methyl group in this reaction was shown in Chart 3. The photolysis of the diazonium salt of the aminopseudoquinoline (XXI) after decomposition of an excess of nitrous acid by urea gave the 3,4-dihydropseudoquinoline (XXV) in low yield after purification by column chromatography.

\[
\text{XXI} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \\
\quad \text{XXI} : X = \text{NH}_2  \\
\quad \text{XXII} : \text{X} = \text{H}  \\
\quad \text{XXIII} : \text{X} = \text{OH}  \\
\quad \text{XXIV} : \text{X} = \text{OAc}
\]

Thus, the homosaporphine was synthesized by the Pschorr reaction which has been applied to a synthesis of the saporphine and an abnormal reaction was observed in case of the Pschorr reaction of 2'-amino-1-phenylpseudoquinoline.

\(^{11}\) S. Sugaiawa, Yakugaku Zasshi, 55, 224 (1935).
Experimental

4-Benzoxyl-5-methoxy-2-nitrophenylpropionic Acid (XV)—To a solution of 30 g of 4-benzoxyl methoxyphenylpropionic acid (XIV) in 200 ml of AcOH was added dropwise 40 ml of conc. HNO₃, 1.42 at 0.5 hr with stirring under cooling, and the mixture was stirred at room temperature for 1 hr a poured into an excess of ice-H₂O. The separated crystals were collected and recrystallized from MeC₆H₄OH to give 20 g of the nitrophenylpropionic acid (XV) as pale yellow prisms, mp 130—140°C. IR 5111 cm⁻¹ 1705 (C=O), 1328 (NO₂). Anal. Calcd. for C₂₅H₂₄O₃N: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.41; H, 5.13; N, 4.42.

N-(4-Benzoxyl-3-methoxyphenyl)-4-benzoxyl-5-methoxy-2-nitrophenylamidine (XVI)—A mixture of 6.4 g of 4-benzoxyl-3-methoxyphenylamine and 7.1 g of 2-nitrophenylpropionic acid (X) was heated at 175—180°C for 1.5 hr and the cooled mixture was recrystallized from MeOH to give 8.7 g of the amide (XVI) as colorless needles, mp 165—167°C. IR 5111 cm⁻¹ 3400 (NH), 1660 (C=O), 1325 (NC). Anal. Calcd. for C₂₅H₂₄O₃N: C, 69.46; H, 6.01; N, 4.91. Found: C, 69.17; H, 5.52; N, 4.84.

7-Benzoxyl-1-(4-benzoxyl-3-methoxy-2-nitrophenyl)-3,4-dihydro-6-methoxyisoquinoline (XVII)—A mixture of 614 mg of the amide (XVI), 1 ml of POCl₃ and 20 ml of anhyd. CHCl₃ was refluxed for 1 hr, the solvent and reagent were distilled off in vacuo to give 510 mg of the 3,4-dihydroisoquinoline (XVII) hydrochloride as pale yellow needles (from MeOH), mp 205—207°C. IR νmax cm⁻¹: 1648 (C=C=N). Anal. Calcd. for C₂₆H₂₃O₂N₂Cl: C, 67.28; H, 5.65; N, 4.39. Found: C, 67.43; H, 5.77; N, 4.40. The free base (XVII) gave the methiodide (XVIII) as pale yellow needles (from MeOH), mp 195—195.5°C. IR νmax cm⁻¹ 1625 (C=N). Anal. Calcd. for C₂₆H₂₃O₂N₂I: C, 58.79; H, 5.08; N, 4.39. Found: C, 58.43; H, 5.19; N, 4.39.

1-(2-Amino-4-benzoxyl-5-methoxyphenethyl)-7-benzoxyl-1,2,3,4-tetrahydro-6-methoxy-2-methylquinoline (VI)—Zinc powder (57 g) was added in portions to 250 ml of 50% of the acid of the methiodide (XVII) 125 ml of AcOH, 125 ml of conc. HCl, and 31 ml of H₂O with stirring at 0—2°C, and the mixture was stirr for 5 hr at 0—2°C. An excess of zinc was filtered off, and the filtrate was basified with 10% NH₄OH and extracted with CHCl₃. The extract was washed with H₂O, dried over K₂CO₃, and evaporated in vacuo giving 5.4 g of a brown viscous syrup, which was purified on 100 g of silica gel by elution with CHCl₃-MeOH (v/v 99:1) to give 4.2 g of the 1,2,3,4-tetrahydroisoquinoline (VI) as a pale brown viscous syrup. IR νmax cm⁻¹: 3400, 3300 (NH). NMR (in CDCl₃ ppm): 2.40 (3H, s, N-CH₃), 3.76 (3H, s, OCH₃), 8.02 (3H, s, OCH₃ 5.67 (4H, s, 2 × OCH₂CH₃), 6.04 (1H, s, 3'-H), 6.56 (3H, s, Ar-H), 7.35 (10H, s, 2 × OCH₂CH₃).

Debenzylation of VI—A mixture of 2 g of the aminoisooquinoline (VI), 20 ml of conc. HCl, and 20 ml of EtOH was refluxed for 3 hr, and the excess of reagent and solvent were distilled off in vacuo to give 1.3 g of the phenolic aminoisooquinoline (VII), which was immediately purified without precipitation.

1,2,3,4-Tetrahydro-1,11-dihydroxy-2,10-dimethoxy-6-methylhomocoumarin (IX)—To a stirred solut of 1.28 g of the aminoisooquinoline (V) in 35 ml of 5% H₂SO₄, was added dropwise 3 ml of 10% NaNO₃, 0°C, and the stirring was continued for 1 hr at 0°C. This solution was diluted to 1 liter with H₂O and irradiated with a Hanovia 450 W mercury lamp in the presence of a pyrex filter for 4.5 hr at 5—10°C with stirring. The reaction mixture was basified with 10% NH₄OH and extracted with CHCl₃. The extract was washed with H₂O, dried over K₂CO₃, and distilled to leave 0.05 ml of a brown gum, which was chromatographed on 10 g silica gel. The CHCl₃-MeOH (96:4 v/v) eluate gave 45.8 mg of the homocoumarin (IX) as colorless needles, mp 185—187°C. The IR (5111 cm⁻¹: 3505 (OH), UV (νmax nm: 264, 291) and NMR (in CDCl₃ ppm): 6.05 (1H, s, C-H), 6.78 (1H, s, C-H), 6.88 (1H, s, C-OH) spectra of which were identical with those of the authentic sample as prepared from kresignoinine (VIII).

3,4-Dihydro-6,7-dimethoxy-1-(2-nitrophenyl)isoquinoline Methiodide (XX)—A mixture of 0.5 g 3,4-dihydroisoquinoline (XX), 5.4 ml of CHCl₃, and an excess of MeI was left overnight at room temperature. Evaporation of the solvent yielded 0.7 g of a yellow solid, which was recrystallized from MeOH to give yellow needles, mp 194°C. Anal. Calcd. for C₂₂H₁₆O₂N₃S: C, 47.59; H, 4.22. Found: C, 47.90; H, 4.41.

1-(2-Aminophenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XXI)—To a solution 1 g of the methiodide (XX) in a mixture of 40 ml of 4% H₂SO₄ and 2 ml of MeOH was added in portions 25 g of zinc dust under stirring for 1 hr. Further 10 ml of H₂SO₄ was added towards the end. The resulting solution was filtered from the excess zinc and the residue was washed with H₂O. The combined solution was basified with 28% NH₄OH and extracted with ether. The extract was washed with saturated NaCl solution and dried over Na₂SO₄. Evaporation of the solvent afforded 0.6 g of the 2'-aminooisoquinoline (XXI), mp 145—146°C (from EtOH). Anal. Calcd. for C₂₅H₂₄O₂N₃S: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.48; H, 7.54; N, 9.47.

12) IR and UV spectra were taken with a type EPI-3 and EPS-3 Hitachi recording spectrometers, respectively. Mass spectra were measured with a Hitachi RMU-7 mass spectrometer, and NMR spectra were taken with a Hitachi A-20 with tetramethylsilane as internal standard.

Pschorr Reaction of 1-(2-Aminophenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XXI)

(a) Thermal Decomposition of the Diazonium Salt of XXI: A solution of 2.0 g of the aminoisouquinoline (XXI) in 180 ml of 5% H$_2$SO$_4$ was diazotized with 25 ml of 10% NaNO$_2$ at 0° with stirring and the stirring was continued for 1 hr at 0°. The resulting mixture was gradually warmed to 10° C and stirred for a further 1 hr at the same temperature. After being cooled to room temperature, this was washed with benzene, basified with 10% NH$_4$OH, and extracted with CHCl$_3$. The extract was washed with H$_2$O, dried over Na$_2$SO$_4$, and distilled to leave 2.5 g of a brown gum, which was chromatographed on 30 g of silica gel using CHCl$_3$ (fractions F$_5$ 1—37 (each 25 ml), monitored by IR and UV spectra, CHCl$_3$—MeOH (99.5: 0.5 v/v; fractions F$_5$ 38—50), CHCl$_3$—MeOH (99:1 v/v; fractions F$_5$ 56—65), and CHCl$_3$—MeOH (97.3: 2.7 v/v; fractions F$_5$ 66—69) as eluants.

Fractions F$_5$ 9—26 were combined and evaporated to leave 360 mg of a reddish viscous oil, which was recrystallized from EtOH to give 155 mg of 1,2,3,4-tetrahydro-1-(2-acetoxypyphenyl)-6,7-dimethoxy-2-methylisoquinoline (XXII) as pale brown plates, mp 146—147°. NMR (in CDCl$_3$) ppm: 2.38 (3H, s, NCH$_3$), 3.65, 3.76 (6H, each s, OCH$_3$), 4.30 (1H, t, J = 9 Hz), 5.02 (1H, s, 8-H), 6.50 (1H, s, 5-H), 6.60—7.20 (4H, m, ArH). Anal. Calcd. for C$_{20}$H$_{22}$O$_3$: C, 72.4; H, 7.02; N, 4.69. Found: C, 72.29; H, 7.07; N, 4.69. A mixture of 40 mg of the hydroxy derivative (XXIII), 0.1 ml of Ac$_2$O, and 3 drops of pyridine was stirred at room temperature and then poured into 10 ml of H$_2$O. The resulting mixture was stirred for a further 10 hr at the same temperature. After an addition of 20 ml of H$_2$SO$_4$, the mixture was extracted with 50 ml of CHCl$_3$. The extract was washed with 5% NaHCO$_3$ and H$_2$O, dried over Na$_2$SO$_4$, and evaporated to afford 30 mg of 1-[(2-acetoxypyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XXIV) as a yellow gum. IR $\nu_{max}$ cm$^{-1}$: 1750 (C-O). NMR (in CDCl$_3$) ppm: 2.37 (3H, s, NCH$_3$), 3.53, 3.78 (6H, each s, OCH$_3$), 4.33 (1H, t, J = 9 Hz), 5.13 (1H, d, J = 5 Hz), 5.70 (1H, s, 8-H), 6.58—7.20 (4H, m, ArH), which was recrystallized from EtOH—hexane to give pale yellow prisms, mp 142.5—143.5°. Mass Spectrum $m/e$: 341 (M$^+$), 259 (M$^+$—82). Anal. Calcd. for C$_{20}$H$_{22}$O$_3$: C, 70.36; H, 7.06. Found: C, 70.60; H, 7.06.

Fractions F$_5$ 30—37 were combined and evaporated to leave 90 mg of a yellow gum, which was again chromatographed on 5 g of alumina and eluted successively with benzene (fractions each 6 ml) 1—50 and benzene—CHCl$_3$ (0:1 v/v; fractions 51—68), benzene—CHCl$_3$ (1:1 v/v; fractions 69—82), and benzene—CHCl$_3$ (2:1 v/v; fractions 83—88). Fraction 2 was extracted with 20 ml of ether and the extract was evaporated to leave a pale red gum, the crystallization of which from hexane yielded 2 mg of 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-phenylisoquinoline (XXVII) as pale orange granules, mp 79—80° (lit., $\nu_{max}$ 81—82°). Mass Spectrum $m/e$: 263 (M$^+$). Anal. Calcd. for C$_{16}$H$_{14}$O$_2$: C, 78.32; H, 7.24; N, 4.90. Found: C, 78.08; H, 7.66; N, 5.05. Fractions 2—29 were collected and chromatographed on 4 g of silicic acid eluting with CHCl$_3$ (fractions 1—63) and CHCl$_3$—MeOH (99:1 v/v; fractions 64—67). Among the above eluates, fractions 19—63 gave 13 mg of the 3,4-dihydroxyisoquinoline (XXVI) as a pale yellow oil, which was identical with the following sample.

Fractions F$_5$ 38—45 were evaporated to leave 148 mg of a yellow gum, which was purified by preparative TLC on silica gel using ether to give 67.5 mg of the alkaloid (XXVII) as a pale yellow oil, mp 119.5—120° (lit., $\nu_{max}$ 120—121°), which was also characteristic of its exalate, mp 186—187° (from EtOH—ether). NMR (in CDCl$_3$) (free base) ppm: 3.72, 3.94 (3H, s, OCH$_3$), 6.08 (2H, s and 5-H), 7.32—7.70 (5H, m, ArH). UV $\lambda_{max}$ nm $\mu$: (free base) 313, 283 (e 5400, 5200). Mass Spectrum $m/e$: 267 (M$^+$), 286, 252, 236. Anal. Calcd. for C$_{16}$H$_{14}$O$_2$: C, 78.36; H, 7.56; N, 3.92. Found: C, 78.85; H, 7.58; N, 4.04.

(b) Photolysis of the Diazonium Salt of XXI: To a solution of 2.0 g of the aminoisouquinoline (XXI) in 180 ml of 5% H$_2$SO$_4$ was added dropwise a solution of 25 ml of 10% NaNO$_2$ during 20 min at 0—3°, and the stirring was continued for a further 1 hr at the same temperature. After decomposition of the excess of HNO$_2$ with 2.45 g of NH$_4$OH, followed by dilution to 1 liter with H$_2$O, the mixture was irradiated by a Hanovia 450 W mercury lamp with a pyrex filter at 4—4.6° for 4.6 hr. The reaction mixture was basified with conc. NH$_4$OH and extracted with CHCl$_3$. The extract was washed with H$_2$O, dried over Na$_2$SO$_4$, and evaporated to afford 2.1 g of a dark red gum, which was chromatographed on 30 g of silica gel using CHCl$_3$ (fractions each 25 ml) 1—(50), CHCl$_3$—MeOH (99.1 v/v; fractions 56—74), CHCl$_3$—MeOH (97.3: 2.7 v/v; fractions 75—101), and CHCl$_3$—MeOH (95:5 v/v; fractions 102—112) as eluants (monitored by IR and UV spectra). Fractions 18—41 were evaporated to leave 142 mg of a reddish viscous oil, which was recrystallized from EtOH to give 60 mg of 1,2,3,4-tetrahydro-1-(2-hydroxyphynyl)-6,7-dimethoxy-2-methylisoquinoline (XXIII) as pale brown plates, mp 146—147°, which were identical with the above authentic sample.

Fractions 53—72 gave 200 mg of a dark brown gum, which was again chromatographed on 10 g of silicic acid with CHCl$_3$ (fractions each 10 ml) 1—51 and CHCl$_3$—MeOH (90.5: 0.5 v/v; fractions 52—64). Fractions 9—12 were treated as usual and purified by preparative TLC on silica gel in ether to give 10 mg of a pale brown oil, which was recrystallized from hexane to give 2 mg of the isoquinoline (XXIII) as pale orange granules, mp 79—80°, which was identical with the above authentic sample. Fractions 19—38 left 32.5 mg of a pale yellow oil, which was extracted with ether. The extract was evaporated to leave 18 mg of a pale yellow oil, which was purified by preparative TLC on silica gel using ether to afford 15 mg of a pale yellow

oil, which was again chromatographed on 1 g of alumina with benzene. The fractions (each 5 ml) 4—11
gave 5 mg of the above 3,4-dihydroisoquinoline (XXV) which was identical with the above authentic sample.

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