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STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—DXXII

PHOTOLYTIC SYNTHESIS OF 1,12-DIHYDROXY-2,10,11-TRIMETHOXYHOMOAPORPHINE

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Abstract—Photolysis of 1-(2-bromo-3-hydroxy-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (8) gave 4,5,6,6a-tetrahydro-1,12-dihydroxy-2,10,11-trimethoxy-6-methylhomoaporphine (7), which is identical with the alkaloid CC-24 isolated from *Cholchicum cornigerum.*

In the last decade, many alkaloids, forming a large new class based upon the 1-phenethylisoquinoline system biogenetically, were isolated from the plants of the sub-family *Wurmbaeoidae (Liliacea).* Thus *Kreysigia multiflora*[2] was found to contain the homoaporphine alkaloids, (−)-floramultine (1), (−)-multifloramine (2), and (±)-kreysigine (3) together with the homoproaporphine alkaloid, kreysiginone (4), and the homomorphinan alkaloid, kreysiginine (5).[3]

The homoaporphine alkaloids are biosynthesized by the direct phenolic oxidation[4] from autumnaline (6),[5] but this conversion *in vitro* could not be achieved successfully.[6] Therefore, we examined the general synthetic methods for this type of compounds with phenolic oxidation and reported previously the synthesis of (±)-kreysignine (3) in low yield by the photo-Pschorr reaction.[7] In this paper, we wish to report the new synthetic method of the homoaporphine (7), which corresponds to the alkaloid CC-24 isolated from *Colchicum cornigerum*,[8,19] by the photolytic cyclization[10,11] of 1-(2-bromo-3-hydroxy-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (8).

Bromination of 3-hydroxy-4,5-dimethoxyphenyl-

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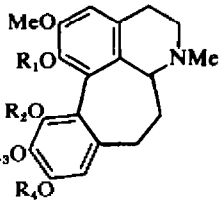
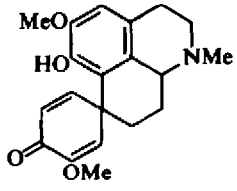


1: $R_1 = R_4 = H, R_2 = R_3 = Me$
2: $R_1 = R_3 = H, R_2 = R_4 = Me$
3: $R_1 = H, R_2 = R_3 = R_4 = Me$
7: $R_1 = R_2 = H, R_3 = R_4 = Me$
17: $R_1 = R_2 = R_3 = R_4 = Me$



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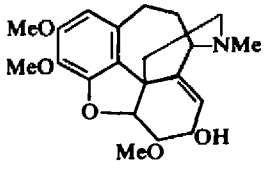

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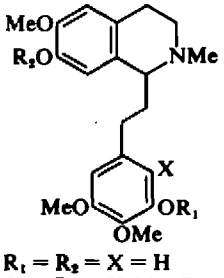

6: $R_1 = R_2 = X = H$
8: $R_1 = R_2 = H, X = Br$
16: $R_1 = R_2 = CH_2Ph, X = Br$

propionic acid (9)[6] in acetic acid gave 2-bromo-derivative (**10a**), and the position of Br atom in this product was determined as follows. An aromatic proton of **10a** resonanced at 6·45 ppm in its NMR spectrum (δ in $CDCl_3$), but that of the acetate (**10b**) of **10a** appeared at 6·76 ppm. Moreover, the corresponding ester (**11a**) of **10a** showed its aromatic proton at 6·46 ppm and the acetate (**11b**) of ester **11a** at 6·77 ppm. Highet and Highet[12] indicated that the chemical shift of the aromatic proton shifted to down-field by conversion of the phenolic OH group into its acetate. Thus, the *para* proton is shifted by about 0·30 ppm, and the *ortho* by about 0·17 ppm. In our case, an aromatic proton shifted to down-field by about 0·31 ppm by conversion of **10a** and **11a** into the corresponding acetates (**10b** and **11b**), respectively. Therefore, **10a** should be formulated as 2-bromo-3-hydroxy-4,5-dimethoxyphenylpropionic acid.

The usual esterification of the above compound (**10a**), followed by benzylation of the ester (**11a**) with benzyl chloride and potassium carbonate in methanol, afforded methyl 3-benzyloxy-2-bromo-4,5-dimethoxyphenylpropionate (**12**), which was fused with 4-benzyloxy-3-methoxyphenethylamine to give the amide (**13**). Bischler-Napieralski reaction of this amide (**13**) gave the 3,4-dihydroisoquinoline (**14**), the methiodide (**15**) of which was reduced with sodium borohydride to afford the 2-methyl-1,2,3,4-tetrahydroisoquinoline (**16**). Debenzylation of **16** with ethanolic hydrochoric acid yielded the starting diphenolic bromoisoquinoline (**8**).

Irradiation of the diphenolic bromoisoquinoline (**8**) with a Riko 400 W mercury lamp (Pyrex filter) was carried out in aqueous alcoholic solution in the presence of sodium hydroxide at room temperature with stirring for 7 hr to give **7** in 5·5% yield. The structure of this compound was confirmed as follows. Microanalysis and mass spectrometry (M^+ *m/e* 371) confirmed the formula $C_{21}H_{25}NO_5$. The UV spectrum showed the typical homoaporphine system,[13] which was supported by mass spectrometry.[9] The NMR spectrum (δ in $CDCl_3$, ppm) showed two aromatic protons at 6·30 and 6·55, and three O-Me resonances at 3·78 (6H) and 3·83, which indicated that positions 1 and 12 carried phenolic OH groups. This fact was proved by conversion of this product into the pentamethoxy-derivative (**17**), in which two high-field O-Me signals were observed in its NMR spectrum.[9,14] Moreover, this (**17**) was identical with the authentic product prepared from kreysigine (**3**) by usual method. It follows that structure (**7**) is a complete representation for photo-coupled product. When the foregoing photolysis was done in the presence of sodium iodide in order to get the homomorphinandienone type compound,[15] it afforded the homoaporphine (**7**) in the same yield.

The UV and mass spectral comparison of synthetic product with natural CC-24, provided by professor F. Šantavý, revealed both compounds to

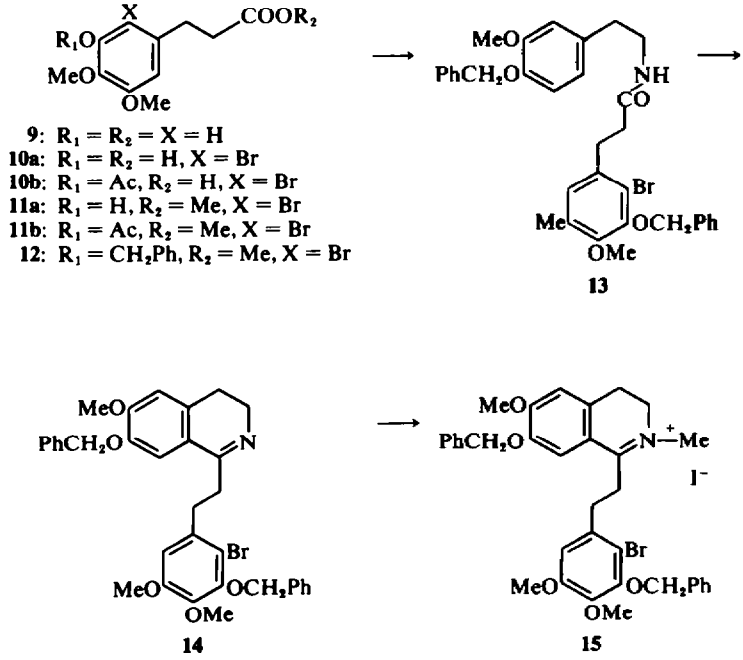

CHART 2

be identical, but IR and NMR spectral* comparisons could not be done due to its low solubility and a very small amount of CC-24.

EXPERIMENTAL

M.p.s were determined on a Yanagimoto microapparatus (MP-S2) and are not corrected. IR spectra were obtained on a Hitachi EPI-3 recording spectrophotometer in $CHCl_3$ soln. UV spectra were recorded on a Hitachi recording spectrophotometer (EPS-3) in MeOH. NMR spectra were measured with a Hitachi H-60 spectrometer with TMS as an internal standard. Mass spectra were taken on a Hitachi RMU-7 spectrometer.

2-Bromo-3-hydroxy-4,5-dimethoxyphenylpropionic acid **10a**. To stirred soln of **9** (45 g) in 50 ml AcOH was added dropwise a soln of Br_2 (32 g) in 50 ml AcOH at 10–15° during 30 min, and the stirring was continued for 2 hr at room temp. The mixture was poured into ice-water, the separated crystals were collected by filtration and recrystallization from benzene gave 55 g of **10a** as colorless needles, m.p. 170–171°; $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1715 (C=O); NMR δ ($CDCl_3$) ppm: 3·82, 3·88 (6H, each s, 2×OMe), 6·45 (1H, s, aromatic proton). (Found: C, 43·42; H, 4·15. $C_{11}H_{13}BrO_5$ requires: C, 43·30; H, 4·29%).

3-Acetoxy-2-bromo-4,5-dimethoxyphenylpropionic acid (**10b**). A mixture of **10a** (50 mg), 2 ml Ac_2O, and 1 drop pyridine was allowed to stand for 12 hr. The mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated. The crystals were recrystallized from benzene–hexane to give 40 mg of **10b** as colorless needles, m.p. 135–136°; $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (ArOCOMe), 1715 (CH_2CO_2H); NMR δ ($CDCl_3$) ppm: 2·38 (3H, s, COMe), 3·80, 3·85 (6H, each s, 2×MeO), 6·76 (1H, s, aromatic proton). (Found: C, 45·14; H, 4·22. $C_{13}H_{15}BrO_6$ requires: C, 44·97; H, 4·36%).

Methyl 2-bromo-3-hydroxy-4,5-dimethoxyphenylpropionate (**11a**). A mixture of **10a** (45 g), 5 ml conc H_2SO_4 and 450 ml dry MeOH was refluxed for 5 hr. The solvent was evaporated and the remaining residue was diluted with water and extracted with ether. The extract was washed with sat $NaHCO_3$ aq and water, dried over Na_2SO_4, and evaporated. The residual oil was crystallized from benzene–hexane to afford 40 g of **11a** as colorless needles, m.p. 74–76°; $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1730 (C=O); NMR δ ($CDCl_3$) ppm: 3·68 (3H, s, COOMe), 3·83, 3·88 (6H, each s, 2×OMe), 6·46 (1H, s, aromatic proton). (Found: C, 45·56; H, 4·72. $C_{12}H_{15}BrO_5$ requires: C, 45·16; H, 4·74%).

Methyl 3-acetoxy-2-bromo-4,5-dimethoxyphenylpropionate (**11b**). The same acetylation of **11a** (50 mg) gave 40 mg of **11b** as colorless prisms (from n-hexane), m.p. 84–85°; $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (COOMe), 1730 (CH_2CO_2Me); NMR δ ($CDCl_3$) ppm: 2·37 (3H, s, COMe), 3·68 (3H, s, (COOMe), 3·80, 3·85 (6H, each s, 2×OMe), 6·77 (1H, s, aromatic proton). (Found: C, 46·34; H, 4·65. $C_{14}H_{17}BrO_6$ requires: C, 46·55; H, 4·75%).

Methyl 3-benzyloxy-2-bromo-4,5-dimethoxyphenylpropionate (**12**). A mixture of 35 g of **11a**, 17 g of benzyl chloride, 15 g K_2CO_3, and 300 ml MeOH was refluxed for 5 hr and the solvent was evaporated. The remaining residue was poured into water and extracted with ether. The extract was washed with 2% NaOH and water, dried over Na_2SO_4, and evaporated to give 36 g of **12** as a yellowish oil; $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O). This was converted into its hydrazide by usual method to afford colorless prisms, m.p. 110–112°; $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1670, 1625 (CONH). (Found: C, 53 26; H, 5·22; N, 7·17. $C_{18}H_{21}BrN_2O_4$ requires: C, 52·82; H, 5·17; N, 6·85%).

N-(4-Benzyloxy-3-methoxyphenethyl)-3-(3-benzyloxy-2-bromo-4,5-dimethoxyphenyl)propionamide (**13**). A mixture of 4-benzyloxy-3-methoxyphenethylamine (25 g) and 30 g of ester **12** was heated at 180° for 2 hr and the mixture was extracted with benzene. The extract was washed with 5% HCl and water, dried over Na_2SO_4, and evaporated. The residual oil was crystallized from benzene–hexane to give 38 g of **13** as colorless needles, m.p. 113·5–114·5°; $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1660 (NHCO). (Found: C, 64·61; H, 5·62; N, 2·48. $C_{34}H_{36}BrNO_6$ requires: C, 64·35; H, 5·72; N, 2·21%).

7-Benzyloxy-1-(3-benzyloxy-2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (**14**). A mixture of amide **13** (30 g), 30 ml $POCl_3$ and 150 ml dry $CHCl_3$ was refluxed for 2 hr. The solvent was evaporated and the residual oil was washed with hexane. Recrystallization of the crude hydrochloride from MeOH–ether afforded 21 g of the hydrochloride of **14** as colorless needles, m.p. 188–189°; $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 (>C=N–). (Found: C, 62·30; H, 5·73; N, 2·39. $C_{34}H_{35}BrClNO_5$ requires: C, 62·35; H, 5·40; N, 2·15%).

A soln of the above hydrochloride (20 g) in 100 ml $CHCl_3$ was washed with 10% NH_4OH and water. The solvent was evaporated off to give 16 g of **14** as a pale brownish oil; $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630 (–C=N–); NMR δ ($CDCl_3$) ppm: 3·77, 3·82, 3·87 (9H, each s, 3×OMe), 5·01, 5·08 (4H, each s, 2×OCH_2Ph), 7·08, 6·60, 6·66 (3H, each s, aromatic protons), 7·18–7·56 (10H, m, aromatic protons).

7-Benzyloxy-1-(3-benzyloxy-2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline methiodide (**15**). A mixture of **14** (15 g), 10 ml MeI, and 50 ml MeOH was allowed to stand at room temp. The solvent was evaporated off to give an orange syrup, which was washed with ether to leave a yellow powder. Recrystallization from MeOH gave 12 g of **15** as pale yellowish prisms, m.p. 187–188°; $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630 (–C=N–). (Found: C, 55·50; H, 4·85; N, 2·08. $C_{35}H_{37}BrINO_5$ requires: C, 55·42; H, 4·92; N, 1·85%).

7-Benzyloxy-1-(3-benzyloxy-2-bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (**16**). To a cooled mixture of **15** (11 g), 100 ml MeOH, 50 ml $CHCl_3$, and 1 drop of water was added in portions 4 g of $NaBH_4$ under stirring. The mixture was stirred for a further 1 hr at room temp. The solvent was evaporated off, and the remaining residue was diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried over K_2CO_3, and evaporated to give 8 g of **16** as a yellow oil; $\nu_{max}^{CHCl_3}$ cm^{-1}: 2780 (NMe); NMR δ ($CDCl_3$) ppm: 2·46 (3H, s, NMe), 3·75 ~ 3·84 (9H, s, 3×OMe), 5·01, 5·05 (4H, each s, 2×OCH_2Ph), 6·50, 6·55, 6·62 (3H, each s, aromatic protons), 7·25–7·65 (10H, m, aromatic protons).

1-(2-Bromo-3-hydroxy-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-2-methylisoquinoline (**8**). A mixture of the isoquinoline **16** (4 g), 25 ml conc HCl and 25 ml EtOH was refluxed for 4 hr. The solvent was evaporated, and the remaining residue was made basic with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with water and dried over K_2CO_3. Evaporation of

*The NMR data on CC-24 were reported in ref. 10, but not on the solvent for this determination.

the solvent afforded 1·8 g of **8** as a pale brownish oil, which was difficult for crystallization and therefore used in the following reaction without purification; $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 2750 (NMe).

Photolysis of **8**. A cooled mixture of 1·8 g of **8**, 0·8 g NaOH, 50 ml EtOH, and 900 ml water was irradiated for 7 hr with a Riko 400 W high pressure mercury lamp (Pyrex filter). After the addition of an excess NH_4Cl, the mixture was extracted with $CHCl_3$. The extract was washed with water, dried over K_2CO_3, and evaporated to leave 1·6 g of a brownish oil, which was chromatographed on 50 g of silica gel. Removal of MeOH–$CHCl_3$ (2:98) as an eluant gave a homoaporphine fraction, which was recrystallized from EtOH to afford **7** (80 mg), m.p. 223–225°; $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH); λ_{max}^{MeOH} nm (log ϵ): 221 (4·45), 258 (4·12), 289 (3·84), 298 (3·76). Mass spectrum: *m/e* 371 (M^+), 354 (base peak); NMR ($CDCl_3$) ppm: 2·45 (3H, s, NMe), 3·78 (6H), 3·83 (3H) (each s, 3×OMe), 6·30, 6·55 (2H, each s, aromatic protons). (Found: C, 64·52; H, 7·22; N, 3·53. $C_{21}H_{25}NO_5 \cdot H_2O$ requires: C, 64·76; H, 6·99; N, 3·60%).

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