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STUDIES ON TOTAL PHOTOLYTIC SYNTHESES OF ALKALOIDS—IV*

MODIFIED TOTAL SYNTHESES OF FLAVINANTINE, BRACTEOLINE, ISOBOLDINE AND MECAMBRINE BY PHOTOLYSIS

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Abstract—Photolysis of the diazonium salt from 6'-aminoorientaline (**10**) gave flavinantine (**1**) and bracteoline (**5**). The same reaction of 6'-bromoreticuline (**17**) and its analog (**21**) afforded isoboldine (**6**) and mecambrine (fugapavine) (**7**), respectively.

PREVIOUSLY[1] we reported a total synthesis of flavinantine (**1**) by debenzylation of the morphinandienone (**2**), which was obtained by a modified Pschorr reaction[2-4] of the aminoisoquinoline (**3**) derived from the 1-(2-nitrobenzyl)-isoquinoline (**4**). The nature of the reaction of the above synthesis, however, possessed fundamental defects. The first one was regarding the reduction of **4** to the aminoisoquinoline (**3**); the debenzylation occurred as a side reaction, and therefore, it was necessary to separate **4** from by-products. The second defect was that, in the debenzylation of **2** to flavinantine (**1**), several rearranged products were obtained because the morphinandienone was unstable in acid. Therefore, we examined the modified synthesis of the morphinandienone alkaloids. Herein we wish to report a one-step synthesis of flavinantine (**1**) and bracteoline (**5**) by a photo-Pschorr reaction,[5] and also describe the total syntheses of isoboldine (**6**) and mecambrine (**7**) by photolysis of the phenolic bromoisoquinolines.

The nitration of O,O-dibenzylorientaline (**8**),[6] followed by the reaction of the 2'-nitrobenzylisoquinoline (**9**) with Zn and hot HCl gave 6'-aminoorientaline (**10**). The diazotization as usual[1-4] of **10**, followed by irradiation of the resulting diazonium salt (**11**) in diluted H_2SO_4 with a Hanovia 450 W mercury lamp at 5–10° using a pyrex filter, gave two products. One of them, obtained in 2% yield, was flavinantine (**1**), which was identical with the authentic sample[1] according to spectroscopic data. The other one, $C_{19}H_{21}NO_4$ (M^+, *m/e* 327 and microanalysis), m.p. 210–211°, in 2% yield was assigned bracteoline (**5**), an alkaloid from *Papaver bracteatum*,[8] by the UV [λ_{max} 270, 279 and 305 mμ], NMR [τ 3·52 (C_3—H), 3·30 (C_8—H) and 2·03 (C_{11}—H)] and mass spectra [(*m/e* 327 (M^+), 326, 312, 296].[7]

It is interesting that although the thermal decomposition of the diazotized phenolic isoquinoline (**12**) gave 3-nitropredicentrine (**13**), an abnormal product, as a main product,[9] the photo-Pschorr reaction yielded a different result.

In the above photolytic reaction, an aromatic radical (**14**), derived from the decomposition of **11** by photolysis, was hypothesized to be a key intermediate in the synthesis of **1** and **5**. Therefore, a radical formation of the C_6-position from an

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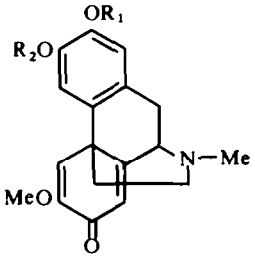
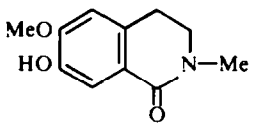
SCHEME I





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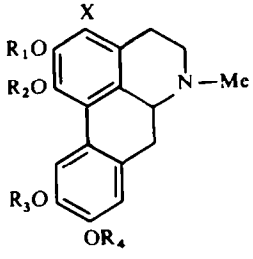
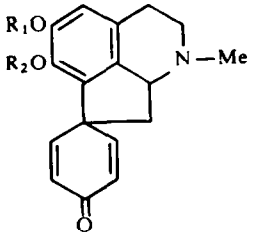
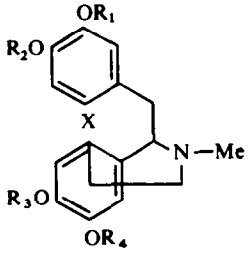
1: R_1 = Me; R_2 = H
2: R_1 = Me; R_2 = CH_2Ph
20: R_1 = H; R_2 = Me



5: R_1 = R_4 = Me; R_2 = R_3 = X = H
6: R_1 = R_3 = Me; R_2 = R_4 = X = H
13: R_1 = H; R_2 = R_3 = R_4 = Me; X = NO_2



7: R_1 + R_2 = —CH_2—



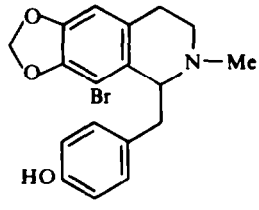
3: R_1 = R_3 = R_4 = Me; R_2 = CH_2Ph; X = NH_2
4: R_1 = R_3 = R_4 = Me; R_2 = CH_2Ph; X = NO_2
8: R_1 = R_3 = Me; R_2 = R_4 = CH_2Ph; X = H
9: R_1 = R_3 = Me; R_2 = R_4 = CH_2Ph; X = NO_2
10: R_1 = R_3 = Me; R_2 = R_4 = H; X = NH_2
11: R_1 = R_3 = Me; R_2 = R_4 = H; X = N_2^+
12: R_1 = R_2 = R_4 = Me; R_3 = H; X = N_2^+
14: R_1 = R_3 = Me; R_2 = R_4 = H; X = radical
15: R_1 + R_2 = —CH_2—; R_3 = Me; R_4 = CH_2Ph; X = Br
16: R_1 + R_2 = —CH_2—; R_3 = Me; R_4 = H; X = Br
17: R_1 = R_4 = H; R_2 = R_3 = Me; X = Br
18: R_1 = R_4 = X = H; R_2 = R_3 = Me

appropriate compound would promise formation of a carbon–carbon bond. As a radial formation under photolysis could occur in a cleavage of a carbon–halogen bond,[10] we first investigated the photolytic electrocyclic reaction of the bromoisoquinoline (**15**),[11] the most easily obtained among the halogenoisoquinoline, however, the expected compound was not obtained.

The coupling reaction of the C_6-radical with an isoquinoline ring would proceed more smoothly in a phenolic isoquinoline than in a methoxylated one. Thus, the phenolic bromoisoquinoline (**16**)[11] was irradiated in the usual way[5,12], but the morphinandienone and/or aporphine could not be obtained. The third attempt was by photolysis in basic media. We presumed that coupling of a radical formed in a reaction would occur more easily in the phenolate anion than in the phenolic hydroxyl. Thus, 6′-bromorecticuline (**17**)[13] was irradiated for 7 hr at room temperature in the presence of NaOH with a Hanovia 450 W mercury lamp, using a pyrex filter. Thus, isoboldine (**6**)[14] was obtained in 19·5% yield in addition to reticuline (**18**) and the cleaved products isovanillin and thalifoline (**19**).[15] These compounds were identical, according to spectroscopic and chromatographic comparisons, with authentic samples. In this reaction, the compound (M^+ 327) showing the α, β-unsaturated ketone system in its IR spectrum was obtained as a trace, the structure of which remained unclear, but was perhaps formed by photo-rearrangement of pallidine (**20**). Moreover, the desired morphinandienone, pallidine (**20**), was formed, but could not be separated in a chromatographically pure state because of contamination with isoboldine.

This photolytic electrocyclic reaction was also applied to a synthesis of the proaporphine. Irradiation of 8-bromo-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-2-methyl-6,7-methylenedioxyisoquinoline (**21**),[16,17] as in the synthesis of isoboldine, gave mecambrine (fugapavine) (**7**) in 1% yield, an alkaloid from the *Papaver* species.[18–20] Structural assignment was by spectroscopic methods. The IR spectrum showed the presence of a cross-conjugated cyclohexadienone system,[21,22] which conclusion was supported by the UV[13] and mass spectra.[18,19,21,22,24] The NMR spectrum[18] revealed the olefinic protons at τ 3·55–3·90 (α, α′) and 2·90–3·35 (β, β′) as two AB quartets with fine structure[21,22] and a pattern closely similar to that of pronuciferine

SCHEME II



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(**22**).[21] These data indicated the product to be (±)-mecambrine (**7**), and, in fact, synthetic and natural mecambrines were proved to be identical by IR($CHCl_3$), UV(MeOH), NMR($CDCl_3$) and chromatographic comparisons, which corroborated the structure suggested by Bick.[25]

EXPERIMENTAL

IR spectra ($CDCl_3$) with a Hitachi EPI-3 recording spectrometer, and UV (MeOH) spectra with a Hitachi EPS-3 recording spectrometer. Mass spectra were measured with a Hitachi RMU-7 spectrometer. NMR spectra were taken with a Hitachi R-20 in $CDCl_3$ with TMS as internal standard.

O,O-*Dibenzyl-6'-nitroorientaline* (**9**). To a stirred solution of 9·6 g of *O,O*-dibenzylorientaline (**8**)[6] in $CHCl_3$ (100 ml) was added a solution of 13 ml of HNO_3 (d = 1·42) in 25 ml of glacial AcOH at 0–5° during 15 min. After stirring for 45 min at constant temperature, the mixture was poured into ice-water, basified with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. Evaporation of solvent afforded 11 g of brownish oil, recrystallized from $CHCl_3$/MeOH to give 8 g of **9** as pale yellow needles: m.p. 146–147°; τ 7·64 ($NC\underline{H}_3$, 3, s), 6·27 and 6·39 ($2OC\underline{H}_3$, 6, each s), 5·0 and 5·15 ($2OC\underline{H}_2Ph$, 4, each s), 3·57, 3·68 and 3·78 (aromatic protons, 3, each s), 2·54 (C_5-H, 1, s). (Calcd. for $C_{33}H_{34}N_2O_6$: C, 71·46; H, 6·18; N, 5·05. Found: C, 71·02; H, 5·82; N, 5·17%).

6'-Aminoorientaline (**10**). To a stirred solution of 2 g of nitroisoquinoline (**9**) in a mixture of 30 ml of AcOH, conc. HCl (40 ml) and water (10 ml) was added in portions 12 g of Zn powder during 15 min at room temperature. After stirring for 30 min at room temperature, the mixture was heated on a water-bath for 30 min. After removal of Zn by filtration, the mixture was basified with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent gave 700 mg of **10** as brownish powder. ν_{max} 3500 cm^{-1} (OH), τ 7·55 ($N—C\underline{H}_3$, 3, s), 6·21 and 6·37 ($2OC\underline{H}_3$, 6, each s), 4·98 ($2O\underline{H}$, $N\underline{H}_2$, 4, broad s), 3·55, 3·57, 3·72 and 3·79 (aromatic protons, 4, each s). Used for the following reaction without further purification.

Photolysis of diazotized 6'-aminoorientaline (**10**). To a stirred solution of 2 g of the above aminoisoquinoline (**10**) in 100 ml of 5% H_2SO_4 was added dropwise a solution of 420 mg of $NaNO_2$ in 7 ml of water at 0–5° during 20 min. After the stirring for 1 hr, the mixture was diluted with 900 ml of water below 5°. The stirred mixture was irradiated with a Hanovia 450 W mercury lamp using a pyrex filter for 4 hr below 10°. After reaction, the mixture was made basic with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to leave 220 mg of brownish syrup, chromatographed on 5 g of silica gel. Removal of the elution with 2% MeOH-$CHCl_3$ afforded 60 mg of a mixture of flavinantine (**1**)[1] and bracteoline (**5**), which was successively chromatographed on 5 g of neutral alumina. Evaporation of the elution with 1% MeOH-$CHCl_3$ left 10 mg of flavinantine (**1**), spectroscopic data identical with those of the authentic specimen.[1] Successive elution with 3% MeOH-$CHCl_3$ gave 15 mg of bracteoline (**5**) as colorless needles, m.p. 210–211° (MeOH), identified with an authentic specimen[11] by spectroscopic comparison.

Photolysis of 6'-bromoreticuline (**17**). A solution of 2 g of 6'-bromoreticuline[13] and 2 g of NaOH in water (820 ml) was irradiated with a Hanovia 450 W mercury lamp using a pyrex filter for 7 hr at room temperature with stirring. This was basified with solid NH_4Cl and extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. Evaporation of solvent left 1·5 g of brown gum, chromatographed on 50 g of silica gel. The first $CHCl_3$ eluant gave 30 mg of isovanillin, identical with an authentic sample. The $CHCl_3$-MeOH (v/v 99·5:0·5) eluate gave 20 mg of thalifoline (**19**), m.p. 210–211°, identical with the authentic sample.[15] The following eluant afforded 4 mg of the unknown compound, m.p. 223–224°, as colorless prisms (MeOH). ν_{max} 3500, 1648 cm^{-1}, λ_{max} 261, 282^{sh} and 299^{sh} mμ; *m/e* 327 (M^+), 310 and 282; τ 7·44 (NCH_3, 3, s), 6·16 (OCH_3, 3, s), 6·10 (OCH_3, 3, s). The $CHCl_3$-MeOH (v/v 99:1) eluant gave 310 mg (19·5%) of isoboldine (6) as pale yellow prisms (MeOH), m.p. 185–190° (decomp.), spectroscopic data superimposable upon those of authentic sample.[14] The successive eluant yielded 258 mg of a mixture of pallidine (**20**) and isoboldine (**6**), not separable by chromatography. The IR spectrum of this mixture was identical with that of a mixture of the authentic pallidine and isoboldine (*ca.* 1:1). The $CHCl_3$-MeOH (v/v 98:2) eluate furnished 350 mg of reticuline (**18**) as a pale yellow viscous syrup, identical with an authentic sample.[26]

Photolysis of 8-bromo-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-2-methyl-6,7-methylenedioxyisoquinoline (**21**). A solution of 2·4 g of the phenolic bromoisoquinoline (**21**)[16,17] and 1·5 g of NaOH in 11 of 50% aqueous EtOH was irradiated as in the synthesis of isoboldine (**6**). Evaporation of solvent gave residue which was treated with excess NH_4Cl and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to leave 2 g of brown gum, which was subjected to column chromatography on 30 g of silica gel. The first $CHCl_3$-MeOH (v/v 99:1) eluant gave 220 mg of a crude mecambrine, and the second eluant recovered 600 mg of starting material.

The crude mecambrine was chromatographed on 10 g alumina (neutral, activity 1) eluting with C_6H_6-$CHCl_3$ (v/v 8:3) to give 13 mg (1%) of mecambrine (**7**) as colorless needles (from $CHCl_3$-ether), m.p. 197–198° (decomp.), ν_{max} 1665, 1648 and 1628 cm^{-1}; λ_{max} 294 and 231 mμ; τ 7·63 (NCH_3, 3, s), 4·22

($-OC\underline{H}_2O-$, 2, q, J = 1·5 Hz), 3·55–3·90 (α,α'-olefinic protons, 2, m), 3·51 (aromatic protons, 1, s), and 2·90–3·35 (β,β'-olefinic protons, 2, m), *m/e* 295 (M^+), 294 (M^+-H), 266 (M^+-H-CO) and 252 ($M^+-CH_2=NMe$). (Calcd. for $C_{18}H_{17}NO_3$: C, 73·20; H, 5·80; N, 4·74. Found: C, 72·94; H, 5·79; N, 4·96%).

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