Photolytic Syntheses of \textit{dl}-Laurotetanine, \textit{dl}-Schefferine & \textit{dl}-Corytenchine\textsuperscript{*†}

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Debenzylation of 1-(5'-benzylxoy-2'-bromo-4'-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V) gave the phenolic tetrahydroisoquinoline (VI) and 12-bromoschefferine (VII). Photolysis of the hydrochloride of 1-(2'-bromo-5'-hydroxy-4'-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IV) gave \textit{dl}-laurotetanine (I), 12-bromoschefferine (VII), \textit{dl}-schefferine (III), \textit{dl}-corytenchine (IV) and 1-(3'-hydroxy-4'-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII). Compounds III, IV, VII and VIII obtained during photolysis were identical with authentic synthetic samples. Synthetic \textit{dl}-schefferine (III) was identical with a natural sample of (-)schefferine.

Laurotetanine, isolated by Greshoff\textsuperscript{2} from \textit{Listera chrysopoma}, was assigned structure (I) independently by Barger \textit{et al.}\textsuperscript{2} and by Späth and Tharrer\textsuperscript{3} on the basis of degradation studies. Later it was isolated by Bick and coworkers\textsuperscript{4}. The alkaloid (I) was first synthesized by Kikkawa\textsuperscript{4} employing Pschorr reaction whereas its N-methyl derivative (II) was synthesized by Kametani \textit{et al.}\textsuperscript{5}. We report in this paper the photolytic synthesis of \textit{dl}-laurotetanine (I).

Schefferine, a phenolic tetrahydroprotoberine alkaloid, was isolated from \textit{Schefferomitra subaequais} by Gellert and Rudatsz\textsuperscript{6} and was assigned structure (III) on the basis of spectral data. Kametani and coworkers\textsuperscript{7} isolated corytenchine from \textit{Corydalis ochotensis} and assigned structure (IV) to it. Syntheses of \textit{dl}-schefferine (III) and \textit{dl}-corytenchine (IV) have been reported earlier\textsuperscript{8,11}.

In continuation of our studies\textsuperscript{12a-e} on debenzylation of 1-benzyltetrahydroisoquinolines containing a free amino group and an activating hydroxy group at position-3' (or 5') of ring-C, we chose compound V for the present study. It was expected that compound V would give, by debenzylation with ethanolic hydrochloric acid, the phenolic tetrahydroisoquinoline (VI) and also 12-bromoschefferine (VII) by the Mannich reaction of VI with formaldehyde generated in situ\textsuperscript{12b}. This was in fact realized as shown in Chart I. Photolysis of VI should give I besides VII which is expected to be formed by a 'dark' reaction of VI with formaldehyde formed by the photolysis\textsuperscript{12b}. However, the results of photolysis of VI were found to be more interesting

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283, 303 nm (log ε 4.24, 4.00, 3.97) and $\lambda_{max}^{\text{EIOH} + \text{NaOH}}$ 315 nm (log ε 4.14). The above bathochromic shift in alkaline solution confirms the presence of a C₆ hydroxyl group in I. The mass spectrum of I showing peaks at m/e 327 (M⁺), 326 (M⁻-1) (base peak), 298, 296, 283, 267 and 253, confirmed 1,2,9,10-oxygenation pattern of the aporphine alkaloid.

12-Bromoscheffereine (VII) formed during debenzoylation of V was identical (m.p., mixed m.p., mass and IR) with that obtained by the photolysis of VI. The band at 2840-2780 cm⁻¹ in the IR (KBr) spectrum of VII was characteristic of trans-quinolizinidine systems. The mass spectrum of VII showed peaks at m/e 421 and 419 (M⁺, 88Br and 99Br), 192, 190 and 176. The fragmentation pattern agreed well with that expected for tetrahydropropotropermine derivatives. The NMR spectrum (DMSO-d₆) showed signals at 8 3.3-8.0 (6H, s, 3½ OCH₃), 4.10 (1H, d, J₁₈=16 Hz, C₆-H), 6.73 (1H, s, C₆-H), 6.90 (1H, s, C₆-H) and 7.10 (1H, s, C₆-H), consistent with those reported in the literature for 12-bromoscheffereine (VII). In order to confirm the structure, VII was prepared by VI by Mannich cyclization; and indeed it was identical with that obtained during debenzoylation of V or photolysis of VI.

**Experimental Procedure**

**Debenzoylation** of 1-(5'-benzoxyl-2'-bromo-4'-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V) — Compound V (2 g) was refluxed with abs. ethanol (100 ml) and conc. HCl (100 ml) for 12 hr, and the solution evaporated to dryness by distillation in vacuo. The residue was extracted with benzene-ethanol (1:1; 50 ml) and the solvents removed in vacuo to give a residue which on crystallization from methanol-ether yielded the phenolic tetrahydroisoquinoline (VI) as its hydrochloride (1.25 g), m.p. 190°. The liberated base was crystallized from methanol-chloroform m.p. 203-4° (lit. 10 m.p. 203-4°); UV (EtOH): 235 (sh), 285 nm (log ε 4.16, 3.80); UV (EtOH + NaOH) 290 nm (log ε 3.82); mass spectrum: m/e 408 and 406 (M⁻-1); 88Br and 99Br; 326, 217, 215, 192, 190 and 176 (Found: C, 55.65; H, 5.60; N, 3.31. C₁₄H₁₂O₄N Br requires C, 55.90; H, 5.45; N, 3.45%).

The mother liquor was concentrated and basified with ammonia and extracted with chloroform. The chloroform extract was washed with water, dried (Na₂SO₄) and evaporated to yield a solid (200 mg) which was chromatographed over silica gel (7.5 g) and eluted with chloroform. Fractions 3-6 were combined and crystallized from chloroform-methanol to give 12-bromoscheffereine (VII), (15 mg), m.p. 187-88° (lit. 10 m.p. 182-84°). Fractions 9-20 were combined and crystallized from methanol-chloroform to give VI (120 mg), m.p. 203-4° (lit. 10 m.p. 203-4°).

**Photolysis** of VI hydrochloride — The hydrochloride of VI (2 g) in distilled water (1200 ml) containing sodium bisulphite (600 mg) was irradiated for 10 hr using an immersion type Hanovia lamp with a pyrex filter. The solution was concentrated in vacuo to about 150 ml, cooled, basified with ammonia and repeatedly extracted with chloroform. The chloroform extract was dried (Na₂SO₄) and the solvent removed to give a brown solid (1.2 g) which was chromatographed over silica gel (30 g) and eluted with chloroform and chloroform-methanol mixtures containing 1-5% methanol.

(i) Elution of the column with chloroform-methanol (99:1); v/v; fractions 3-6) gave VII which crystallized from chloroform-methanol (30 mg), m.p. 187-88° (lit. 10 m.p. 182-84°). For analysis (Found: C, 57.37; H, 5.75; N, 2.94. C₁₄H₁₂O₄NBr requires C, 57.19; H, 5.24; N, 3.35%). UV (EtOH): 220, 280 nm.
(log ε 4:37, 3:85); UV (EtOH+NaOH): 287 nm (log ε 3:91).

(ii) Elution with chloroform-methanol (99:1, v/v; fractions 7-15) gave a mixture containing two compounds. It was recrystallographed over silica gel (7 g) and eluted with chloroform. Fractions 1-6 were combined and crystallized from chloroform-methanol to yield dl-schefferine (III, 15 mg), m.p. 138-40° (lit.6 m.p. 147-49° for pentahydrate III) (Found: C, 70:15; H, 7:06; N, 3:75. C₉H₁₅O₂N requires C, 70:36; H, 6:79; N, 4:10%). IR (KBr): 2840-2720 cm⁻¹ (trans-quinolizidine band). The IR spectrum of the photolytic product was identical with that of an authentic synthetic sample of dl-schefferine whereas TLC behaviour was identical with that of (−)-schefferine. Fractions 8-15 were combined and crystallized from chloroform-methanol to give dl-coryteneine (IV, 15 mg), m.p. 236-37° (lit.11 m.p. 236-37°); IR in KBr was identical with that of an authentic synthetic sample of dl-coryteneine (Found: C, 70:59; H, 7:09. C₉H₁₅O₂N requires C, 70:36; H, 6:79%); UV (EtOH): 287 nm (log ε 3:67); UV (EtOH+NaOH): 293 nm (log ε 3:70); mass spectrum: m/e 341 (M⁺), 340, 326, 192, 190, 176, 150, 135; NMR (DMSO-d₆): δ 3:80 (9H, s, 3 × OCH₃), 6:63, 6:69 (2H, Ar-H), 6:97 (2H, Ar-H).

(iii) Elution with chloroform-methanol (98:2, v/v; fractions 17-45) gave a mixture of two compounds. It was recrystallographed over silica gel (10 g) and eluted with chloroform. Fractions 1-20 gave the starting VI (450 mg), its identity being confirmed by comparison (IR) with an authentic sample. Further elution gave VIII which was crystallized from benzene-pet. ether (40-60°), yield 60 mg, m.p. 131-32°; its identity was confirmed by comparison with an authentic synthetic sample which was prepared as follows: Compound VI (500 mg) in ethanol (200 ml) was hydrogenated in the presence of 10% Pd-C catalyst (200 mg) in a Parr reduction apparatus at 40-50 psi for 5 hr. The catalyst was filtered, solvent removed in vacuo, and the residue basified with ammonia and extracted with chloroform. The chloroform extract was washed with water, dried (Na₂SO₄) and distilled to leave a residue which was crystallized from benzene-pet. ether (40-60° (240 mg), m.p. 131-32° (Found: C, 69:42; H, 7:36; N, 4:60. C₉H₁₅O₂N requires C, 69:27; H, 7:03; N, 4:25%). NMR (CDCl₃): δ 3:80 (6H, s, 2 × OCH₃), 3:87 (3H, s, OCH₃), 4:08 (1H, m, C-H), 6:65-7:76 (5H, Ar-H).

(iv) Elution of the main column with chloroform-methanol (98:2, v/v; fractions 47-56) gave dl-laurotetanine (I) which was crystallized from acetone-

ether (yield 55 mg), m.p. 128-30° (Found: C, 63:19; H, 6:41. C₁₅H₂₃O₃N.H₂O requires C, 62:79; H, 6:93%).

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References

1. GRESHOFF, M., Ber. dt. chem. Ges., 23 (1890), 3537.

875