

Photolytic Syntheses of *dl*-Laurotetanine, *dl*-Schefferine & *dl*-Corytenchine*†

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Debenzylation of 1-(5'-benzyloxy-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 *dl*-laurotetanine (I), 12-bromoschefferine (VII), *dl*-schefferine (III), *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 *dl*-schefferine (III) was identical with a natural sample of (-)-schefferine.

LAUROTETANINE, isolated by Greshoff¹ from *Litsea chryscoma*, was assigned structure (I) independently by Barger *et al.*² and by Späth and Tharrer³ on the basis of degradation studies. Later it was isolated by Bick and coworkers⁴. The alkaloid (I) was first synthesized by Kikkawa⁵ employing Pschorr reaction whereas its N-methyl derivative (II) was synthesized by Kametani *et al.*⁶. We report in this paper the photolytic synthesis of *dl*-laurotetanine (I).

Schefferine, a phenolic tetrahydroprotoberberine alkaloid, was isolated from *Schefferomitra subaequalis* by Gellert and Rudzats⁷ and was assigned structure (III) on the basis of spectral data. Kametani and coworkers⁸ isolated corytenchine from *Corydalis ochotensis* and assigned structure (IV) to it. Syntheses of *dl*-schefferine (III) and *dl*-corytenchine (IV) have been reported earlier⁹⁻¹¹.

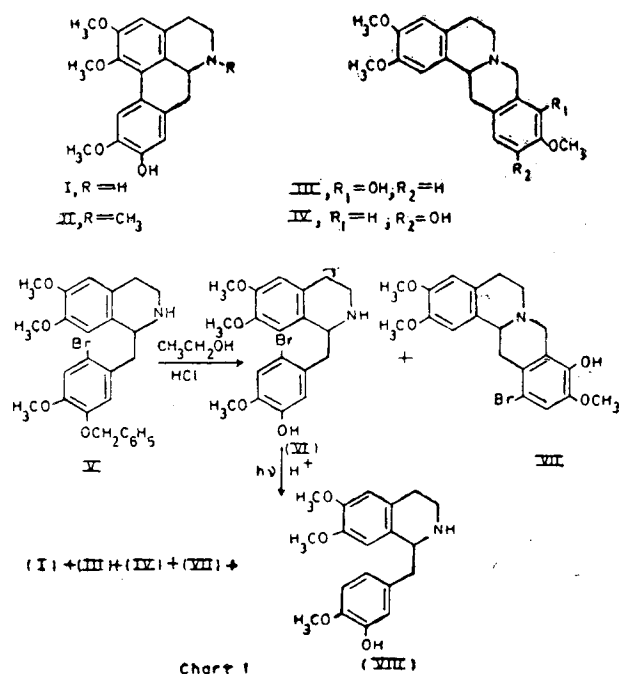
In continuation of our studies^{12a-e} on debenzyla-tion of 1-benzyltetrahydroisoquinolines containing a free imino group and an activating hydroxyl group at position-3' (or 5') of ring-C, we chose compound V for the present study. It was expected that compound V would give, by debenzyla-tion with ethanolic hydrochloric acid, the phenolic tetrahydroisoquinoline (VI) and also 12-bromoschefferine (VII) by the Mannich reaction of VI with formal-dehyde generated *in situ*^{12b}. This was in fact realized as shown in Chart 1. 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^{12b-e}. However, the results of photolysis of VI were found to be more interesting

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in that, besides the expected *dl*-laurotetanine (I) and 12-bromoschefferine (VII), we were able to isolate *dl*-schefferine (III), *dl*-corytenchine (IV) and 1-(3'-hydroxy-4'-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII). Obviously the formation of VIII is due to photolytic loss of bromine from V, while III and IV are formed by the reaction of VIII with formaldehyde formed during photolysis. Formation of III and IV from VIII during photolysis has been reported earlier by Kametani *et al.*^{12b}. In our previous studies^{12a-e} we had not been able to isolate all the five compounds, but we could isolate the debrominated tetrahydroisoquinoline in one case^{12d}.

dl-Laurotetanine (I) obtained in the present study melted at 128-30°; showed $\lambda_{\text{max}}^{\text{EtOH}}$ at 214,

283, 303 nm ($\log \epsilon$ 4.24, 4.00, 3.97) and $\lambda_{\max}^{\text{EtOH}+\text{NaOH}}$ 315 nm ($\log \epsilon$ 4.14). The above bathochromic shift in alkaline solution confirms the presence of a C₉-hydroxyl group¹³ 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 alkaloid¹⁴.

12-Bromoschefferine (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*-quinolizidine systems¹⁵. The mass spectrum of VII showed peaks at m/e 421 and 419 (M⁺, ⁸¹Br and ⁷⁹Br), 192, 190 and 176. The fragmentation pattern agreed well with that expected for tetrahydroprotoberberine derivatives¹⁶. The NMR spectrum (DMSO-*d*₆) showed signals at δ 3.80 (9H, s, 3 × OCH₃), 4.10 (1H, *d*, J_{AB} = 16 Hz, C₈-H), 6.73 (1H, s, C₄-H), 6.90 (1H, s, C₁-H) and 7.10 (1H, s, C₁₁-H), consistent with those reported in the literature¹⁰ for 12-bromoschefferine (VII). In order to confirm the structure, VII was prepared from VI by Mannich cyclization; and indeed it was identical with that obtained during debenzoylation of V or photolysis of VI.

dl-Schefferine (III), formed during photolysis showed in its mass spectrum peaks at m/e 341 (M⁺), 340 (M-1)⁺, 192, 190, 150 and 135. The fragmentation pattern was consistent with that expected for a 10-methoxy-tetrahydroprotoberberine derivative^{16,17}. NMR spectrum in DMSO-*d*₆ showed signals at δ 3.78 (3H, s, OCH₃), 3.80 (6H, s, 2 × OCH₃), 4.12 (1H, *d*, J = 16 Hz, C₈-H), 6.70, 6.78 (2H, 2s, Ar-H) and 6.90 (2H, s, Ar-H) which are characteristic of a 9,10-oxygenated tetrahydroprotoberberine derivative¹⁸. Structure (III) assigned to the photolytic product was confirmed by direct comparison (m.p., mixed m.p., TLC and IR) with an authentic sample of *dl*-schefferine (III) prepared by the reductive debromination of VII. The synthetic III was identical (TLC) with natural sample (kindly supplied by Prof. E. Gellert, Department of Chemistry, University College, Wollongong, New South Wales, Australia).

dl-Corytenchine (IV), which was also formed during photolysis, showed in its mass spectrum peaks at m/e 341 (M⁺), 340, 326, 192, 190, 150 and 135. Its IR spectrum showed bands in the region at 2840-2720 cm⁻¹ characteristic of *trans*-quinolizidine structure. Elemental analysis and spectral data suggested it to be a tetrahydroprotoberberine, but it was found to be different (m.p., TLC and IR) from schefferine (III). Hence, it must be a 10,11-oxygenated berberine derivative, i.e. an isomer of schefferine (ψ -schefferine) or, in other words, corytenchine. This was confirmed by comparison of its IR spectrum with an authentic sample of *dl*-corytenchine (IV), which was prepared from VIII, as reported in the literature¹¹.

Compound VIII formed during photolysis showed in its mass spectrum peaks at m/e 328 (M-1)⁺, 192 and 190 suggesting it to be a tetrahydroisoquinoline¹⁹. Its UV spectrum exhibited $\lambda_{\max}^{\text{EtOH}}$ at 233 (sh) and 283 nm ($\log \epsilon$ 4.25, 4.05) and $\lambda_{\max}^{\text{EtOH}+\text{NaOH}}$ at

290 nm ($\log \epsilon$ 4.11) which are also characteristic of 1-benzyltetrahydroisoquinolines. Removal of bromine from VI using 10% Pd-C/H₂ gave 1-(3'-hydroxy-4'-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII) which was identical (m.p., mixed m.p., TLC and IR) with that obtained during photolysis of VI.

Thus, the present study confirmed our earlier observations on the formation of tetrahydroprotoberberines in the debenzoylation of 1-(3'-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinolines and in the photolysis of 1-(3'-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinolines. It also served to highlight the complex course of photolysis of substrates of the type VI.

Experimental Procedure

Debenzoylation of 1-(5'-benzyloxy-2'-bromo-4'-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V) — Compound V¹⁰ (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 were 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 ($\log \epsilon$ 4.16, 3.80), UV (EtOH+NaOH) 290 nm ($\log \epsilon$ 3.82); mass spectrum: m/e 408 and 406 [(M-1)⁺, ⁸¹Br and ⁷⁹Br], 326, 217, 215, 192, 190 and 176 (Found: C, 55.65; H, 5.60; N, 3.31. C₁₉H₂₂O₄NBr requires C, 55.90; H, 5.45; N, 3.45%).

The mother liquor was concentrated, 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-bromoschefferine (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°) (Found: C, 57.37; H, 5.75; N, 2.94. C₂₀H₂₂O₄NBr 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 rechromatographed 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.¹⁰ m.p. 147-48° for pentahydrate III) (Found: C, 70.15; H, 7.06; N, 3.75. C₂₀H₂₃O₄N 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*-corytenchine (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*-corytenchine (Found: C, 70.59; H, 7.09. C₂₀H₂₃O₄N 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-*d*₆): δ 3.80 (9H, s, 3 \times OCH₃), 6.63, 6.69 (2H, Ar-H), 6.87 (2H, Ar-H).

(iii) Elution with chloroform-methanol (98:2, v/v; fractions 17-45) gave a mixture of two compounds. It was rechromatographed 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 Paar 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. C₁₉H₂₃O₄N requires C, 69.27; H, 7.03; N, 4.25%); NMR (CDCl₃): δ 3.80 (6H, s, 2 \times OCH₃), 3.87 (3H, s, OCH₃), 4.08 (1H, *m*, C₁-H), 6.65-6.76 (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. C₁₉H₂₁O₁N.2H₂O requires C, 62.79; H, 6.93%).

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