Novel Total Synthesis of Protoberberine-type Alkaloids

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Summary Benzoylation of 1-alkyl-3,4-dihydroisoquinolines followed by photocyclisation provides a useful route to protoberberine alkaloids, as exemplified by the synthesis of (\pm) -xylopinine (X).

As an extension of the photocyclisation of unsaturated enamides,¹ we found that photocyclisation of the isoquinolines (IIa,b) and (VI) readily provides the 8-oxoberbine structures (IIIa,b), (VII), and (VIII).

N-Benzoylation of the isoquinolines (Ia and b)² in solution in boiling benzene in the presence of triethylamine with benzoyl chloride afforded quantitatively the N-benzoylisoquinolines (IIa and b), which showed characteristic *exo*-methylene n.m.r. peaks at δ *ca*. 5—6. A 0.02Mmethanolic solution of the enamides (IIa and b) was irradiated with a low-pressure mercury lamp at room temperature. T.l.c. of the reaction mixture showed complete conversion after 1—20 h depending on the amount of the enamide used. The 8-oxoberbines (IIIa and b) were obtained as sole photoproducts in *ca*. 70% yield. Structure (IIIa)³ was assigned from i.r. and n.m.r. evidence and was unequivocally established by conversion into berbine (IVa), m.p. 83—85°,⁴ which was identical with an authentic specimen.

This process was then used in the preparation of (+)xylopinine (X). Thus, N-acylation of the isoquinoline (V) with 3,4-dimethoxybenzoyl chloride proceeded smoothly to afford the N-benzamide (VI) $[v_{max.} 1620 \text{ and } 1585 \text{ cm}^{-1}; \delta$ 5.50 and 4.43 (each br. s, $C=CH_2$)], which was unstable and was irradiated as above without further purification. Irradiation for 3 h provided the lactam (VII), m.p. $190-192^{\circ}$ (5%) (ν_{max} , 1640 and 1605 cm⁻¹) and the didehydrolactam (VIII), m.p. 196.5-198°5 (40%) vmax. 1640, 1610 sh, and 1595 cm⁻¹. Reduction (LiAlH₄) of the lactam (VII) in ether solution afforded the corresponding tertiary amine (X), m.p. 157-158°,6 identical with an authentic specimen of (\pm) -xylopinine. Reduction of the second photoproduct (VIII) with LiAlH₄ followed by NaBH₄⁷ also afforded (X). The above process thus provides a convenient route to a group of protoberberine alkaloids.



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