Novel Total Synthesis of Protoberberine-type Alkaloids

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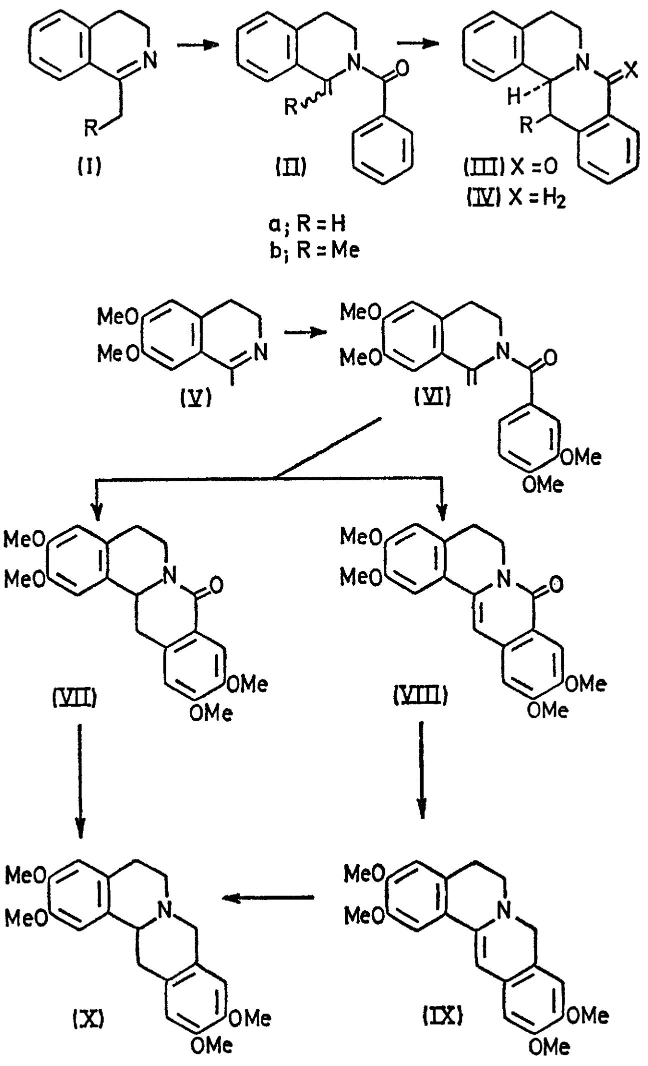
Summary Benzoylation of 1-alkyl-3,4-dihydroisoquinolines followed by photocyclisation provides a useful route to protoberberine alkaloids, as exemplified by the synthesis of (±)-xylopinine (X).

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 0·02M-methanolic 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) [$\nu_{max.}$ 1620 and 1585 cm^{-1}; δ 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° (5%) ($\nu_{max.}$ 1640 and 1605 cm^{-1}) and the didehydrolactam (VIII), m.p. 196·5—198°[5] (40%) $\nu_{max.}$ 1640, 1610 sh, and 1595 cm^{-1}. Reduction ($LiAlH_4$) of the lactam (VII) in ether solution afforded the corresponding tertiary amine (X), m.p. 157—158°,[6] identical with an authentic specimen of (±)-xylopinine. Reduction of the second photoproduct (VIII) with $LiAlH_4$ followed by $NaBH_4$[7] also afforded (X). The above process thus provides a convenient route to a group of protoberberine alkaloids.



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