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TOTAL SYNTHESIS OF (±)-ANGUSTOLINE

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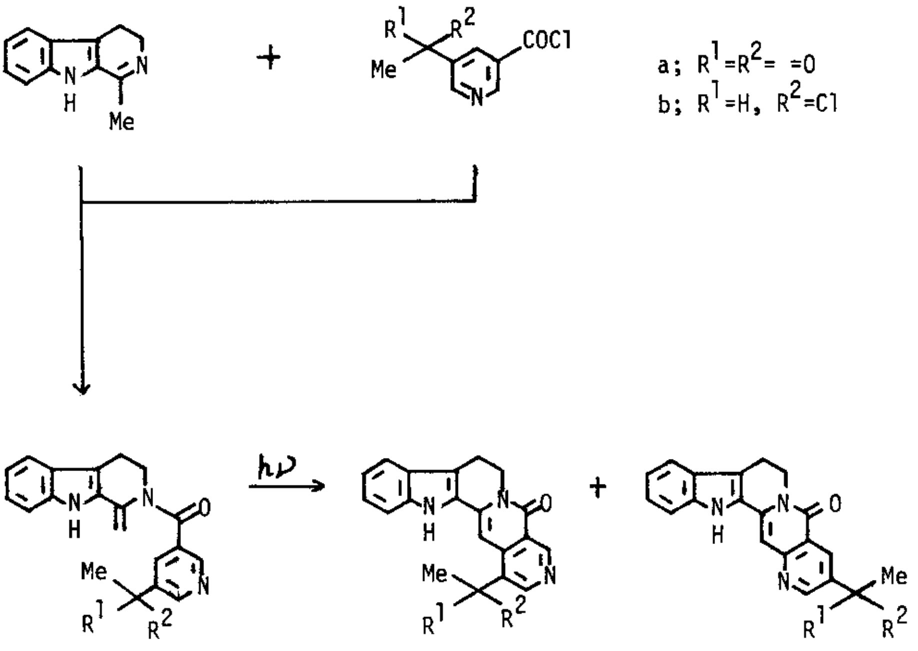
(±)-Angustoline, an alkaloid of Strychnos angustiflora, was synthesized via the route including enamide photocyclization.

As an extension of synthetic work on angustidine,[1] we report the first total synthesis of (±)-angustoline, a major alkaloid of Strychnos angustiflora,[2] thus completing formal synthesis of all three alkaloids so far isolated.

Treatment of sodium 5-acetylnicotinate[3] with oxalyl chloride produced the acid achloride, which without purification was reacted with harmalane to afford the enamide (Ia) as a yellow solid, $\nu_{max}^{cm^{-1}}$ ($CHCl_3$) 3520 (NH), 1695 (Ac), and 1640 (NCO). A 0.02 M methanolic solution of (Ia) was irradiated with a low pressure mercury lamp at room temperature for 5 h. Chromatography of the reaction mixture on alumina separated two products (IIa and IIIa) in 30 and 8 % yields respectively; (IIa), m.p. $>$ 300°, M^+ 329; (IIIa), m.p. $>$300°, M^+ 329.

Sodium borohydride reduction of (IIa) afforded the alcohol (IIb), m.p. 292-294° (lit. 310-314°)[2], M^+ 331, which was shown to be (±)-angustoline by comparisons of i.r., n.m.r., and mass spectra. Since angustoline had been converted into angustine and dihydroangustine,[4] this synthesis formally completed the total synthesis of all three alkaloids so far isolated.[2]



a; $R^1=R^2=\ =O$
b; $R^1=H$, $R^2=Cl$

(I)

a; $R^1=R^2=\ =O$
b; $R^1=H$, $R^2=Cl$

(II)

a; $R^1=R^2=\ =O$
b; $R^1=H$, $R^2=OH$
c; $R^1=H$, $R^2=OMe$

(III)

a; $R^1=R^2=\ =O$
b; $R^1=R^2=H$
c; $R^1=H$, $R^2=OMe$

In relation to the above synthesis, photocyclization of the enamide (Ib), which was obtained from harmalane and 5-(1-chloroethyl)nicotinoyl chloride, was carried out and afforded three photocyclized products (IIc, IIIb, and IIIc), which were separated by chromatography on alumina; (IIc), m.p. 220-223°, M^+ 345; (IIIb), m.p. >300°, M^+ 315; (IIIc), m.p. 266-269°, M^+ 345. The compound (IIc) should be designated as (±)-angustoline methyl ether. The formation of these three photoproducts would seem to be formed either by hydrogenolysis or substitution of the chloride by solvent during the course of irradiation.

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