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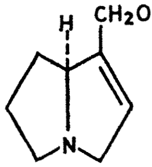
Synthesis of the Alkaloidal Base (±)-Supinidine

By Joseph J. Tufariello* and James P. Tette

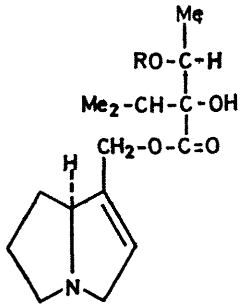
(*Department of Chemistry, State University of New York at Buffalo, Buffalo, New York* 14214)

Summary Supinidine (I), the necine base which has been obtained from supinine, heleurine, and related alkaloids has been synthesized.

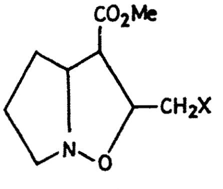
The pyrrolizidine alkaloids, which occur widely in nature and have hepatotoxic properties, in general consist of a pyrrolizidine ("necine") base and a carboxylic ("necic") acid. The synthesis of the necine bases and the necic acids has been much studied.[1]



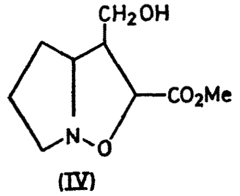
(I)



(II) a; R = H
b; R = Me



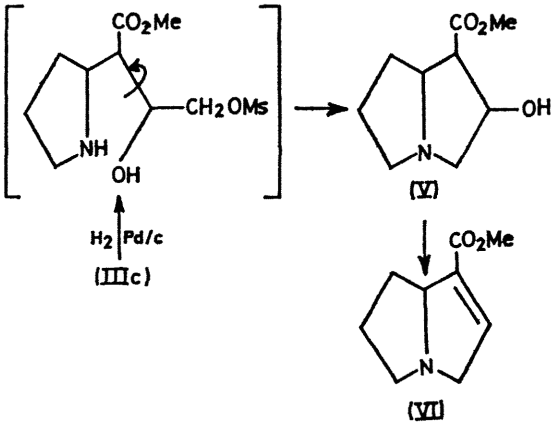
(III) a; X = OH
b; X = H
c; X = OSO₂Me



(IV)

We now report the first synthesis of supinidine[2] (I), the necine base obtained from supinine (IIa), heleurine (IIb), and related alkaloids. The key step in our synthesis involves the 1,3-dipolar addition of Δ^1-pyrroline 1-oxide[3] to methyl γ-hydroxycrotonate[4] to afford a 1 : 1 adduct. The structure of the adduct can, *a priori*, be formulated as either (IIIa) or (IV); however, it has been shown that methyl crotonate reacts with such nitrones to afford adducts with the desired orientation[5] (*i.e.*, IIIb). The n.m.r. spectrum of the hydroxy-substituted isoxazolidine (IIIa) obtained in our study supports our assignment since the proton at C-2 appears as a 6-line pattern centred at δ ($CDCl_3$, Me_4Si) 4·23 p.p.m.

The isoxazolidine (IIIa) was converted into the corresponding methanesulphonate, which affords methyl 2-hydroxypyrrolizidine-1-carboxylate (V) upon hydrogenolysis over Pd/C. This sequence provides a simple entry into the pyrrolizidine ring system.



The dehydration of the hydroxy-ester (V) effected with phosphorus oxychloride at 0°, yields an unsaturated ester, (VI), which exhibits the expected one-proton vinyl signal at δ ($CDCl_3$, Me_4Si) 6·70 p.p.m. Reduction of the $\alpha\beta$-unsaturated ester with lithium aluminium hydride and aluminium chloride[6] gives the desired alkaloid.

The (±)-supinidine so obtained possesses n.m.r. and i.r. spectra identical with the supinidine obtained by the hydrolysis of supinine (IIa).

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