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A FACILE SYNTHESIS OF QUINOLIZIDINES AND INDOLIZIDINES

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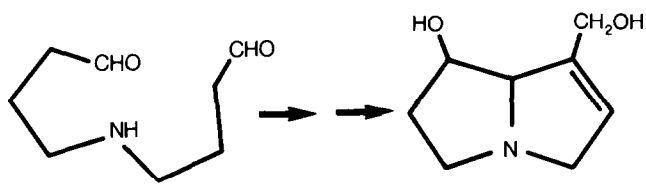
Summary: A biomimetic synthesis of quinolizidines and indolizidines via an intramolecular Mannich reaction is described.

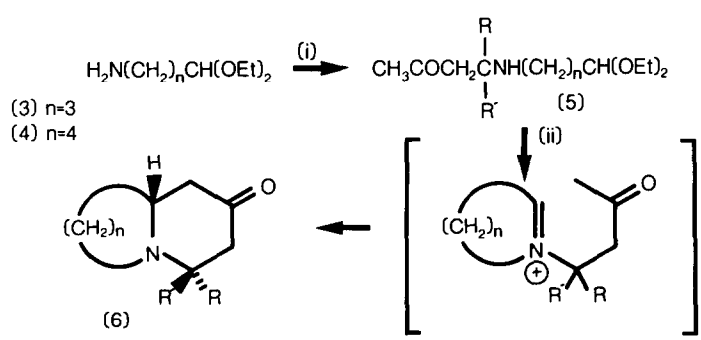
It has been proposed[1] that the symmetrical amino-dialdehyde (1) is an important intermediate in the biosynthesis of retronecine (2).



(1) (2)

Although similar intramolecular Mannich reactions have been utilised in the synthesis of the polycyclic alkaloids myrrhine[2], coccinelline[3,4], porantherine[5] and lycopodine[6], no synthesis of simple bicyclic alkaloids using this method has been reported.

The commercial availability of 4,4-diethoxybutan-1-amine (3) and the facile synthesis of 5,5-diethoxypentan-1-amine (4)[7] make these attractive precursors for the synthesis of quinolizidines and indolizidines. The introduction of a carbon nucleophile is achieved by the conjugate addition of the amine to an α, β-unsaturated ketone. Acidolysis of the resultant addition products afford the bicyclic ketones as follows:



(i) RR'C=CHCOCH$_3$ (ii) 2M HCl

In a typical procedure the amino-acetal (3,20 mmol) is stirred with excess 3-penten-2-one (40 mmol) in ether (10 ml) at ambient temperature until the addition is complete (ca 1h). The addition product (5; n=3; R,R'=H, Me) is partitioned between ether and a large excess (200 ml) of 2N hydrochloric acid. The aqueous layer is separated and heated on a steam bath in an open flask for 2 h. The product is isolated by concentration, basification with potassium carbonate and extraction with chloroform. Purification is achieved either by distillation or, if isomer separation is required, by chromatography (silica gel, diethyl ether).

Table: Synthesis of Quinolizidines and Indolizidines (6)

n	R	R'	% Yield	mp°C Picrate (lit)
3	H	H	55	198 (198–200)[9]
3 (a)	Me	H	60	179 [10]
	H	Me	15	191 [10]
3	Me	Me	60	179
3 (a)	Pr^i	H	45	169
	H	Pr^i	20	171
4	H	H	50	210 (208–10)[11]
4 (a)	Me	H (b)	55	178 (177–9)[12]
	H	Me (c)	20	190 (190–2)[12]

(a) For stereochemical assignment of crystalline derivatives[13]
(b) (±) Epimyrtine
(c) (±) Myrtine

Although both *trans*-4-phenyl-3-buten-2-one and 2-cyclohexen-1-one gave initial adducts (5), both failed to cyclise on acidolysis. This suggests that a fine balance probably exists between the cyclisation and the amine elimination.

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