A Biogenetically Patterned Synthesis of the Indolizidine Alkaloid Septicine

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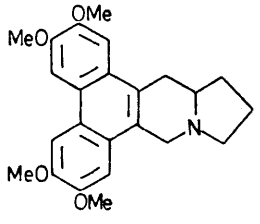
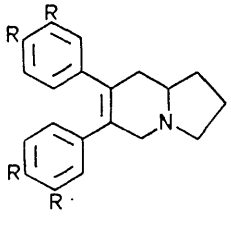
Summary An economical synthesis of septicine (**3**) is described which is patterned on the likely biosynthetic pathway to alkaloids of this type.

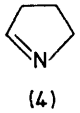
IT is a reasonable assumption that compounds of type (**7**) and (**2**) are key intermediates in the biosynthesis of indolizidine alkaloids of the tylophorine (**1**) type.[1] Consideration of the suggested pathway has led us to develop a simple synthetic route to compounds of type (**2**) and we report here its application in the synthesis of the alkaloid septicine (**3**).[2]



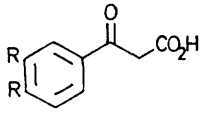
(1)



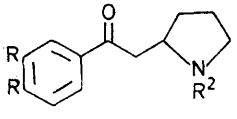
(2) R = H
(3) R = OMe



(4)

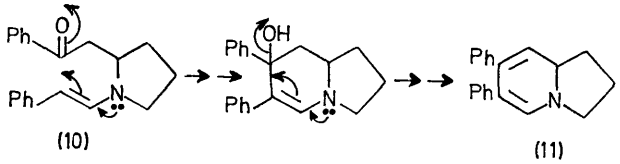


(5) R = H
(6) R = OMe

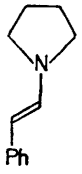


(7) $R^1 = R^2 = H$
(8) $R^1 = H, R^2 = Me$
(9) $R^1 = OMe, R^2 = H$

Condensation of Δ^1-pyrroline (**4**)[3] with benzoylacetic acid (**5**)[4] in aqueous methanolic solution (optimum pH 7) afforded 2-phenacylpyrrolidine (**7**) (65%). [Reaction of (**7**) with formic acid and formaldehyde gave (**8**) identical with an authentic sample[5]]. Formation of the enamine (**10**) from (**7**) and phenylacetaldehyde in benzene (without catalyst at room temperature) was complete within minutes (n.m.r. analysis), the results being similar to those we obtained for the condensation of phenylacetaldehyde and pyrrolidine which



(10) (11)



(12)

affords (**12**).[6] Addition of enamines to carbonyl groups is fairly uncommon[7] but cyclisation of (**10**) was simply achieved when it was set aside in methanol (room temp., 1 h) and the product, presumed to be (**11**) was reduced with sodium borohydride (MeOH, 2 h, room temp.). The major product was isolated by chromatography and was shown to be (**2**) by comparison with an authentic sample.[8] Enamine formation also occurred in methanol and so the entire reaction sequence beginning with (**7**) and phenylacetaldehyde could be carried out in this solvent when the isolated yield of (**2**) was 30%.

Septicine (**3**) was synthesised under similar conditions. 3,4-Dimethoxybenzoylacetic acid (**6**) was prepared by

hydrolysis of the corresponding ethyl ester, itself prepared by adaptation of a convenient procedure.[9] Reaction of (**6**) with Δ^1-pyrroline (**4**) gave (**9**) which on condensation with 3,4-dimethoxyphenylacetaldehyde[10] (benzene solution, room temp. 30 min; MeOH, 60 min) and subsequent reduction with sodium borohydride gave a compound (24%) which was identical with an authentic sample of natural septicine (**3**) (apart from optical activity).

Since Δ^1-pyrroline may be prepared from either ornithine[3] or putrescine,[11] both of which are available with a variety of labels, and since the reaction sequence is an economical one, the route lends itself to the synthesis of labelled compounds of biosynthetic interest.

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[7] For examples see: P. Houdewind, J. C. L. Armande, and U. K. Pandit, *Tetrahedron Letters*, 1974, 591; T. A. Spencer and K. K. Schmiegel, *Chem. and Ind.*, 1963, 1765; W. D. Burrows and E. P. Burrows, *J. Org. Chem.*, 1963, **28**, 1180; L. Birkofer, S. M. Kim, and H. D. Engels, *Chem. Ber.*, 1962, **95**, 1495.
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