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General Methods of Alkaloid Synthesis. A New Approach to the Synthesis of the 5,10b-Ethanophenanthridine *Amaryllidaceae* Alkaloids. The Total Synthesis of (±)-3-*epi*-Elwesine

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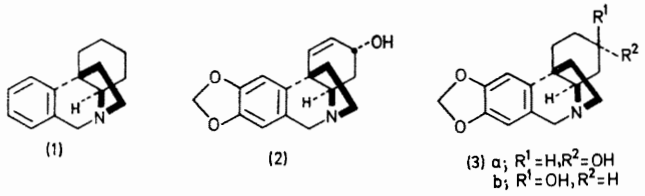
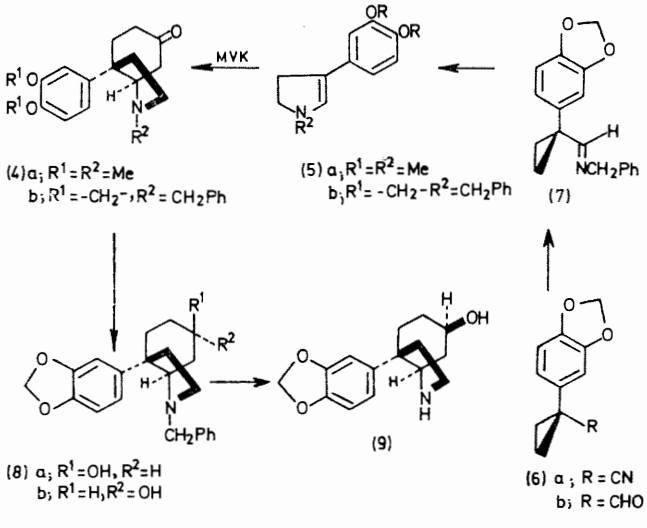
Summary Methyl vinyl ketone annelation of the Δ^2-pyrroline (**5b**) prepared by acid-catalysed thermal rearrangement of the cyclopropyl imine (**7**) has been exploited in an efficient eight-step stereoselective total synthesis of racemic 3-*epi*-elwesine (**3b**).

Members of one major group of the *Amaryllidaceae* alkaloids[1] contain the 5,10b-ethanophenanthridine nucleus (**1**) as exemplified by crinine (**2**). We report a synthesis of 3-*epi*-elwesine (**3a**), a minor alkaloid of *Galanthus elwesii* Hook. f.,[2] which might be employed with only minor modification in the synthesis of a number of the crinine family of alkaloids.



The method of approach we envisaged was a logical extension of two fundamental and increasingly important general principles of alkaloid synthesis which we and others have been developing. The first of these exploits the acid-catalysed, thermally induced rearrangement of cyclopropyl imines as a useful general approach to pyrrolines and has provided simple efficient syntheses of the pyridine alkaloid myosmine and apoferrorosamine[3] and was a key step[4a,b] in a five-stage synthesis of the *Aizoaceae* alkaloid mesembrine (**4a**).[4] Also of importance in the latter synthesis was the application of the methyl vinyl ketone annelation to an endocyclic enamine (*cf.* **5a** to **4a**); a reaction which has also been exploited in the synthesis of the *Erythrina*[5] and hasubanan[6] skeletons as well as a useful *Aspidosperma* alkaloid precursor. The somewhat deceptive similar structural features of mesembrine (**4a**) and the crinine-type alkaloids such as elwesine (**3a**) had, from the very beginning of our investigation,[7] not escaped our attention.



Our synthesis begins with piperonyl cyanide, whose conversion into the cyclopropane carbonitrile (**6a**)† (m.p.

† Each intermediate reported in this communication had been subjected to i.r., and n.m.r. analysis. Supporting data were obtained from low-resolution mass spectral data and/or combustion analysis.

74·5—75·5°) was achieved in 65—75% yield by using $(CH_2Br)_2$ and $LiNH_2$ in glyme at room temperature. This result is in contrast to the employment of $NaNH_2$/glyme which gave only low yields of the cyclopropane and is in consonance with our previous studies.[4a] Di-isobutylaluminium hydride reduction of (**6a**) yielded aldehyde (**6b**) (m.p. 62·5—63·5°, 75—85%) whose transformation into aldimine (**7**) (m.p. 67—67·5°) was accomplished by simply stirring a benzene solution with anhydrous $CaCl_2$ for 2—3 days (72—90%). Thermal rearrangement of this cyclopropyl imine proceeded smoothly in 72—80% yield by employing NH_4Cl as the acidic catalyst. The methyl vinyl ketone annelation of this endocyclic enamine (m.p. 62·5—63°) gave only complex unstable mixtures containing little if any of the desired product. However, 55—65% yields of the pure *cis*-octahydroindole (**4b**) (m.p. 98·5—101°) could be secured by employing acid catalysis.[6c] $NaBH_4$ reduction of (**4b**) provided a 3 : 1 mixture of two epimeric alcohols. Debenzylation[9] of the major product (**8a**, *vide infra*, m.p. 229—231°) yielded (**9**) (m.p. 179—180°, 100%) whose HCHO-induced Pictet–Spengler[10] cyclization completed the synthesis of (±)-3-*epi*-elwesine (**3b**, m.p. 187—188·5°, 65%). The structural and stereochemical assignments were confirmed by comparison with an authentic optically active sample‡ and by oxidation to the known racemic ketone m.p. 171·5—174·5 (lit.[11] 171—173°).

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