

THE TOTAL SYNTHESIS OF RAC-SCELETIUM ALKALOID A₄ AND ITS
3'-DEMETHOXY ANALOGUE

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In our continuing studies of the structural elucidation,¹ synthesis,^{2a,b} and biosynthesis³ of alkaloids obtained from Sceletium species, we now report in this letter the first total syntheses of Sceletium alkaloid A₄ (1)^{1,4} and its 3'-demethoxy analogue (2)

A ready synthetic pathway to the mesembranone ring system, involving the annelation of a 3-aryl substituted 2-pyrroline (e.g. 3) with a vinyl ketone, has been ably demonstrated by Professor Robert V Stevens⁵ and others

Accordingly, the hydrochloride of 3-anisyl 2-pyrroline⁵ (3, HCl salt) was annelated with 7-ethylenedioxy-hept-1-ene-3-one (5) in refluxing acetonitrile to afford a mixture (total) of epimeric (at C-7) keto-acetals (6) in 80% yield. Deacetalization of (6) with a molar quantity of para-toluene sulphonic acid in refluxing aqueous dioxane afforded the intermediate 1,5-keto-aldehyde α -enolether hemiacetal mixture (8 \neq 9). The isolated crude reaction mixture subsequently was refluxed with a threefold molar excess of hydroxylamine hydrochloride in absolute ethanol⁶ to give, after chromatography over neutral alumina, compound (2) in 52% yield. The constitution of synthetic rac-(2) is fully corroborated by its spectral (uv, ir, ¹H nmr, and ms) properties. Compound (2), although hitherto not isolated from natural sources, was synthesized to test biosynthetic proposals made elsewhere²

Similarly, annelation of 2-pyrroline hydrochloride (4, HCl salt) with the enone-acetal (5) in refluxing acetonitrile gave a mixture of epimeric (at C-7) keto-acetals (7) in 85% yield. Deacetalization of (7), as before, provided a keto-aldehyde α -enolether hemiacetal mixture (10 \neq 11) which subsequently was treated with excess of hydroxylamine hydrochloride in refluxing ethanol to give rac-Sceletium alkaloid A₄ (1). Synthetic rac-(1) is identical (uv, ir, ¹H nmr, ms, glpc) in all respects with the natural product.

Enone acetal (5) was synthesized by exclusive γ -alkylation of the dianion of 3-phenylsulphonylbutan-2-one⁸ with 3-bromopropanal ethylenedioxyacetal⁹ and subsequent thermal elimination of benzenesulphonic acid in refluxing carbon tetrachloride for 22 hours.

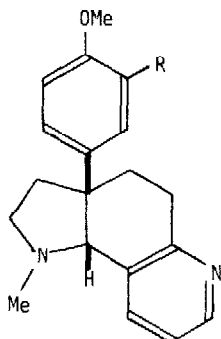
All new compounds e.g. (2),(5),(6),(7),(8),(9),(10), and (11) have spectral properties in accord with the assigned structures.

Acknowledgements

We thank Professor R V Stevens, Texas University, for informing us at the 9th International Symposium on Natural Products, Ottawa, June 1974, of his proposed total synthesis of

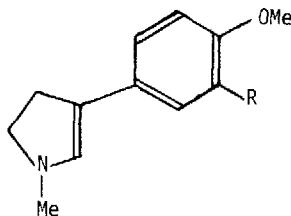
Sceletium alkaloid A_4 employing acid-catalysed annelation of 2-pyrroline (4) with methyl 5-oxohept-6-enoate

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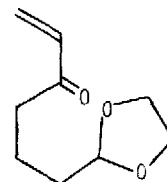
(1) R = OMe

(2) R = H

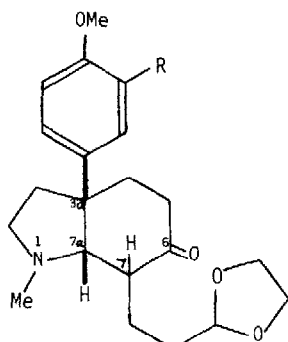


(3) R = H

(4) R = OMe

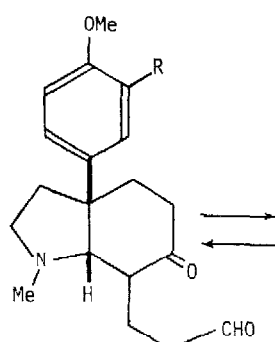


(5)



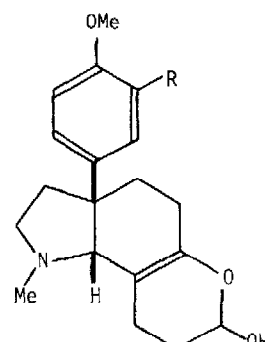
(6) R = H

(7) R = OMe



(8) R = H-CHO

(10) R = OMe



(9) R = H-OH

(11) R = OMe

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