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Amaryllidaceous Alkaloids: The Total Synthesis of Dihydroxycrinene

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THE alkaloids of the family Amaryllidaceae¹ are a group of over seventy known structures in two main ring systems, none of which have been totally synthesized.² We now report a synthesis of one of these systems, representing the skeleton of haemanthidine (I) and incorporating the requisite functionality for further synthetic elaboration to the natural alkaloids.³

Piperonylic acid was converted into 3,4-methylenedioxyaniline hydrochloride *via* the Curtius reaction and acid hydrolysis. Meerwein arylation of maleic acid by the corresponding diazonium salt (with copper catalysis) led to a mixture of acids which produced (II), m.p. 219—220°; i.r. spectrum 5·40, 5·60, and 5·25 μ ; on refluxing in acetic anhydride. With butadiene this anhydride smoothly (70% yield) afforded the Diels–Alder adduct (III), m.p. 111—112°, i.r. spectrum 5·40 and 5·60 μ . This reaction provides ring c of the natural alkaloids, with the correct stereochemistry. The formation of ring b requires only stereospecific insertion of nitrogen and cyclization, and this is accomplished by first opening the anhydride with methoxide to the half-ester (IV), m.p. 170—171° (78% yield).

[The identity of (IV) was assured by production, comparison, and appropriate interconversions of the four possible ester and acid derivatives of (IV).] The free secondary carboxyl was then converted by the Curtius procedure into the isocyanate and this in turn cyclized with trifluoroacetic acid to the lactam (V) (45% yield), m.p. 280—281°; i.r. spectrum 3·08, 5·80, 6·02, and 6·20 μ . This procedure provides rings a, b, and c with the requisite *trans* b/c junction. The alternative mode of cyclization of the isocyanate *ortho* to the methylenedioxy-group was ruled out by the n.m.r. spectrum of (V).

The oxygenated two-carbon bridge of (I) was next constructed by hydrolysis of the ester group in (V) followed by reaction of the acid chloride with diazomethane to yield the corresponding diazoketone (90% yield), m.p. 161—162°; i.r. spectrum 3·10, 4·65, 6·00, and 6·20 μ . Upon bubbling hydrogen chloride into dry solutions of this diazoketone, nitrogen was evolved and cyclization occurred to form 6,11-dioxocrinene (VIa) in 82% yield, m.p. 217—219°; i.r. spectrum 5·79, 5·85, and 6·20 μ .

This dioxocrinene is of theoretical interest as a

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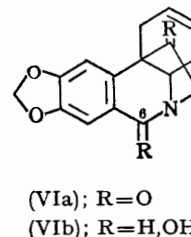
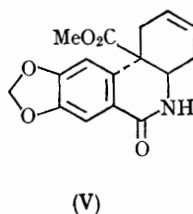
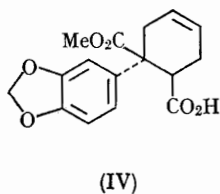
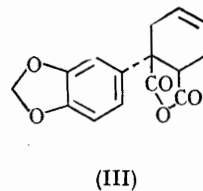
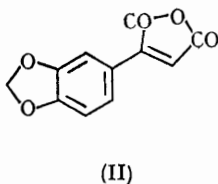
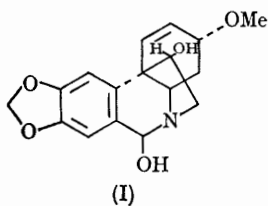
¹ For reviews see H. G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," pp. 410—475, Akad. Verlag, 1961, and W. C. Wildman in R. H. F. Manske, "The Alkaloids," Academic Press, vol. 6, pp. 290—414, 1960.

² Galanthamine, an amaryllidaceous alkaloid with a third, less-common ring system has been synthesized by D. H. R. Barton and G. W. Kirby, *Proc. Chem. Soc.*, 1960, 392.

³ Analyses and spectra are consistent with the given formulations throughout.

relative of 2-quinuclidone, exhibiting no normal amide resonance owing to Bredt's Rule prohibition of the canonical form bearing a π -bond between the carbonyl and the bridgehead nitrogen. This

completely analogous to the several oxohaemanthamines prepared from natural haemanthidine.⁴ Borohydride reduction of 6,11-dioxocrinine (VIa) smoothly affords a crystalline mixture (about 1:1)



is shown in dioxocrinine by the extreme ease of hydrolysis or methanolysis of the quasi-amide link, the ready reduction of this carbonyl by sodium borohydride, and the low infrared absorption ($5.85 \text{ m}\mu$). The dioxocrinine is thus

of the two 6,11-dihydroxycrines (VIb) epimeric at C-11, showing hydroxyl but no carbonyl absorption in the infrared spectrum; the epimers were but slightly resolved in thin-layer chromatograms.

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⁴ S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2590.