

Pyrrolizidine Alkaloids. Synthesis of 13,13-Dimethyl-1,2-didehydrocrotalanine†

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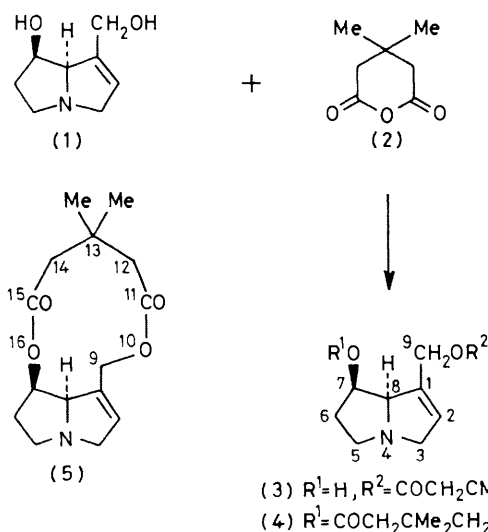
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Summary The first synthesis of an 11-membered macrocyclic pyrrolizidine diester has been achieved from (+)-retronecine and 3,3-dimethylglutaric anhydride.

MORE than 20 naturally occurring 11-membered macrocyclic pyrrolizidine diester alkaloids have been characterised.^{1,2} Most of these alkaloids contain (+)-retronecine (**1**) as the base portion ('necine'). Many syntheses of the naturally occurring necines have been published.³ We report the first synthesis of an 11-membered macrocyclic diester of (+)-retronecine (**1**).

(+)-Retronecine was obtained by alkaline hydrolysis of retrorsine, which is produced by *Senecio isatideus* plants. Reaction of (+)-retronecine with glutaric ester derivatives in the presence of dicyclohexylcarbodi-imide or carbonyldiimidazole⁴ gave complex mixtures of products in low to moderate yield, containing appreciable quantities of the acyclic 7,9-diester of (+)-retronecine (t.l.c. data)⁴. Diester formation was not observed when (+)-retronecine (**1**) was treated with 3,3-dimethylglutaric anhydride (**2**) in chloroform. A quantitative mixture of the 9-(**3**) and 7-(**4**) monoesters of (+)-retronecine was produced. The n.m.r. spectrum of this mixture in deuteriomethanol showed signals for (**3**) at δ 4.71 (s, H-9) and 5.76 (m, H-2); and for (**4**) at δ 4.52 (m, H-7) and 5.68 (m, H-2). From the integrations

for these signals,⁴ the ratio of (**3**) to (**4**) is 2:1. A single ester carbonyl absorption at 1726 cm^{-1} was observed in the i.r. spectrum of the mixture of monoesters in carbon tetrachloride.



† The scheme proposed by Culvenor *et al.* is used for naming and numbering the macrocyclic pyrrolizidine diester alkaloid [C. C. J. Culvenor, D. H. G. Crout, W. Klyne, W. P. Mose, J. D. Renwick, and P. M. Scopes, *J. Chem. Soc. (C)*, 1971, 3653].

Intramolecular esterification of the crude mixture of C-7 and C-9 monoesters was achieved by the Corey-Nicolaou double activation method,⁵ but the choice of solvent was crucial. The high-boiling inert solvents usually employed were all unsatisfactory. Slow addition of the 2-pyridine-thiol esters derived from (3) + (4) to refluxing dimethyl-formamide followed by 20 h at reflux gave one major product. Purification by preparative t.l.c. (CHCl₃-MeOH-NH₃, 85:14:1, R_f 0.58) afforded a 50% yield of 13,13-dimethyl-1,2-didehydrocrotalanine (5) as an oil, $[\alpha]_D^{22} + 42.4^\circ$ (CHCl₃). An accurate mass measurement on the base (5) gave M^+ 279.1469 (C₁₅H₂₁NO₄ requires M 279.1470). The base was characterised as its picrate, ‡ m.p. 191–192 °C.

In the mass spectrum of the free base (5), a typical fragmentation pattern for a macrocyclic pyrrolizidine diester was observed with peaks at m/e 279 (M^+), 138, 137, 136, 120, 119, 117, 94, 93, 83, and 80.¹ The crucial feature in the n.m.r. spectrum of (5) in deuteriochloroform is an AB quartet at δ 4.08 and 5.32 (J 12 Hz) due to the non-equivalent protons at C-9. The chemical shift difference of 1.24 p.p.m. is unusually large for an 11-membered macrocyclic

diester alkaloid (values of 0.0 to 0.92 p.p.m. have been recorded).¹ In the i.r. spectrum of the free base (5) in carbon tetrachloride, a single ester carbonyl absorption was observed at 1738 cm⁻¹ (a value of 1737 cm⁻¹ has been recorded for monocrotaline, which is an 11-membered macrocyclic diester of retronecine)¹. The increase in frequency of the ester carbonyl absorption from 1726 cm⁻¹ in the mixture of monoesters to 1738 cm⁻¹ is attributed to the formation of the macrocyclic diester (5).

The characteristic mass spectrum of (5), the i.r. data, and the non-equivalence of the protons at C-9 in the n.m.r. spectrum of (5) are taken as convincing evidence that an 11-membered macrocyclic diester of retronecine has been formed. Total syntheses of some naturally occurring macrocyclic pyrrolizidine diesters can now be envisaged.

We are grateful to Dr. D. H. G. Crout, Department of Chemistry, University of Exeter, for a sample of retrorsine. We thank the University of Glasgow for a studentship (to S.S.).

(Received, 17th December 1979; Com. 1305.)

‡ Satisfactory spectroscopic and analytical data were obtained for this compound.

¹ L. B. Bull, C. C. J. Culvenor, and A. T. Dick, 'The Pyrrolizidine Alkaloids,' North-Holland, Amsterdam, 1968.

² 'The Alkaloids,' Specialist Periodical Reports, The Chemical Society, London, 1971–1979, vols. 1–9.

³ D. J. Robins, *Adv. Heterocyclic Chem.*, 1979, **24**, 247; D. J. Robins and S. Sakdarat, *J.C.S. Perkin I*, 1979, 1734; *J.C.S. Chem. Comm.*, 1979, 1181.

⁴ W. M. Hoskins and D. H. G. Crout, *J.C.S. Perkin I*, 1977, 538.

⁵ E. J. Corey and K. C. Nicolaou, *J. Amer. Chem. Soc.*, 1974, **96**, 5614.