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

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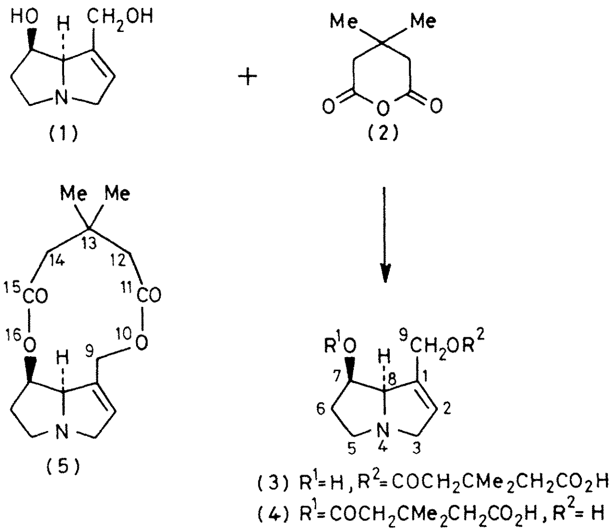
Summary The first synthesis of an 11-membered macrocyclic pyrrolizidine diester has been achieved from (+)-retronecine and 3,3-dimethylglutaric anhydride.

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 carbonyldi-imidazole[4] gave complex mixtures of products in low to moderate yield, containing appreciable quantities of the acyclic 7,9-diesters 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.



(1)

(2)

(5)

(3) $R^1 = H, R^2 = COCH_2CMe_2CH_2CO_2H$

(4) $R^1 = COCH_2CMe_2CH_2CO_2H, R^2 = H$

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† 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-pyridinethiol esters derived from (**3**) + (**4**) to refluxing dimethylformamide followed by 20 h at reflux gave one major product. Purification by preparative t.l.c. ($CHCl_3$–MeOH–NH_3, 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° ($CHCl_3$). An accurate mass measurement on the base (**5**) gave M^+ 279·1469 ($C_{15}H_{21}NO_4$ 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.

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

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