Madurensine, a Macrocyclic Pyrrolizidine Diester with the Secondary Ester Attachment at C-6

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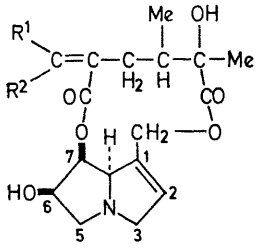
Summary N.m.r. measurements show that madurensine has the secondary ester grouping (and bridgehead of the macrocyclic ring) at C-6 rather than at C-7 as previously supposed.

MADURENSINE AND ANACROTINE are macrocyclic diesters of the trihydroxypyrrolizidine, crotanecine, and were previously assigned the 12-membered ring structures (I) and (II), differing only in the configuration of the ethylidene group in the esterifying acid.[1] Closure of the macro-ring by esterification of the hydroxy-group at C-7 was established only for anacrotine by a detailed comparison of the mass spectrum with that of senecionine. Doubts about the structure (I) for madurensine arose during an examination of the crotanecine ester alkaloids of *Crotalaria agatiflora*, and we have now shown that madurensine is (III), the first known macrocyclic pyrrolizidine diester in which the macro-ring is attached through C-6.

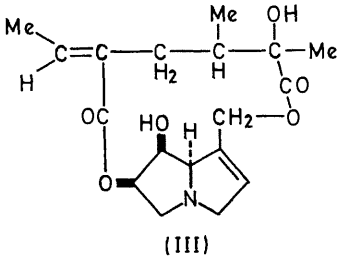
An important clue was provided by the appearance of the H-5β multiplet as a doublet ($J_{5\alpha,5\beta}$ −15·0 Hz) in the n.m.r. spectrum of madurensine, whereas it is a triplet ($J_{5\alpha,5\beta}$ −9·5 Hz, $J_{5\beta,6\alpha}$ 9·5 Hz) in the spectrum of anacrotine. As noted previously,[1] this implies that the saturated ring is *exo*-buckled (normal for diesters of retronecine[2]) in anacrotine, but *endo*-buckled in madurensine. Geometrical isomerism in the esterifying acid is an insufficient reason for this conformational difference but closure of the diester ring in madurensine at C-6 would account for it well. The

C*H*–OCOR multiplet of madurensine,[1] δ 5·02 ($CDCl_3$), is a triplet appropriate to a proton on either C-7 (two neighbouring CH protons) or C-6 (three neighbouring CH protons



(I) R^1 = Me, R^2 = H

(II) R^1 = H, R^2 = Me



(III)

but H-5β not visibly coupled). Decoupling experiments at 100 MHz show that this proton is located at C-6. Irradiation at δ 5·02 collapses a quartet at δ 3·49 to a doublet (*J* 15·0 Hz). This quartet must be due to H-5α since the 15·0 Hz coupling is the same as in the H-5β doublet, δ 2·80, and irradiation at δ 3·49 collapses the H-5β doublet to a singlet. Thus the C*H*–OCOR proton is vicinal to the H-5 protons. Irradiation of H-2 (δ 6·24) confirms the assignment of a multiplet, δ *ca.* 4·3 to H-8, and the multiplet, δ *ca.* 3·50, overlapping the H-5α multiplet, to H-3β; both have one coupling removed. In pyridine as solvent, the H-6α and H-7α multiplets are slightly further apart than in $CDCl_3$ and may be decoupled; irradiation of H-6α (δ 5·31) causes the H-7α quartet (δ 4·75) to collapse to a doublet but has no effect on the H-8 multiplet. These observations allow of no interpretation other than that madurensine has the secondary ester grouping at C-6 as in (III).

Similar decoupling experiments confirm that the C-7-ester structure previously assigned to anacrotine is correct. Irradiation of the C*H*–OCOR triplet, δ 5·24 ($CDCl_3$), collapses the CHOH multiplet (δ 4·56, two overlapping quartets) to a single quartet, removes a small splitting from the H-8 multiplet, δ 4·35, and has no effect in the H-5 region, δ 2·5—3·5.

Models indicate that the macro-ring of madurensine involves no undue steric strain. There is a possibility of acyl-transfer between the 6β- and 7β-OH groups of crotanecine, either in the plant or after extraction, but the natural occurrence of madurensine type alkaloids is confirmed by the co-occurrence in *C. agatiflora* of 6-acetylanacrotine and 7-acetylmadurensine.[3]

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[1] C. K. Atal, K. K. Kapur, C. C. J. Culvenor, and L. W. Smith, *Tetrahedron Letters*, 1966, 537.
[2] C. C. J. Culvenor and W. G. Woods, *Austral. J. Chem.*, 1965, **18**, 1625.
[3] C. C. J. Culvenor and L. W. Smith, unpublished results.