Adina Alkaloids: The Structure of Macrolidine

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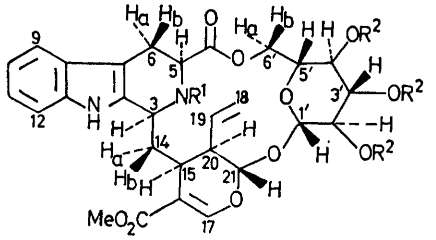
Summary A new glycosidic indole alkaloid, macrolidine, has been obtained from *Adina rubescens* and shown to have a novel lactone structure (**1a**) containing a 14-membered ring.

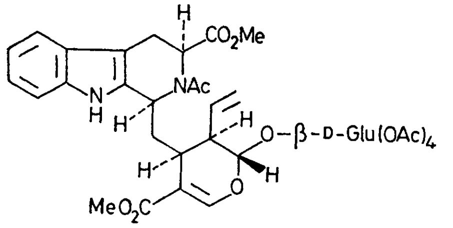
Macrolidine was isolated from *A. rubescens* heartwood and characterised as the acetate derivative (**1b**) $C_{36}H_{40}N_2O_{14}$ $[\alpha]^{25}_{D}$ + 2° ($CHCl_3$). Since the corresponding propionate differed by 56 m.u., this was a tetra-acetate, which Zemplen deacetylation followed by propionylation showed to contain one *N*-acetyl and three *O*-acetyl groups. It was unaffected by diazomethane, and catalytic hydrogenation afforded a dihydro derivative (**1c**) $[\alpha]^{25}_{D}$ $-5°$ ($CHCl_3$).

Indole and β-alkoxyacrylate chromophores shown in u.v. and i.r. spectra had appropriate signals in the n.m.r. spectrum, which also indicated vinyl, methoxy, and four acetyl groups and an acetylated hexoside. The mass spectral fragmentation of macrolidine tetra-acetate had ions at $M^+ - CH_3CO$, *m/e* 182, 169, and 168, characteristic of a 3,5-disubstituted tetrahydro-β-carboline N^b-acetamide such as methyl tetrahydrodeoxycordifoline penta-acetate (**2**).[1] The spectral resemblance extended to common ions at *m/e* 165, derived from a methoxycarbonyldihydropyran group (*m/e* 167 in the dihydro derivatives) and at *m/e* 169 and 109, due to fragments from an acetylated hexoside. A striking difference in the mass spectrum of macrolidine tetra-acetate was that ions at *m/e* 331, $M - 331$ and $M - 347$ corresponding to loss of a glucoside tetra-acetate group were totally absent. Taken in conjunction with the presence of only three *O*-acetyl groups this feature suggested



(1)

	R^1	R^2	
a;	H	H	
b;	Ac	Ac	
c;	Ac	Ac	18,19-dihydro
d;	Ac	H	18,19-dihydro



(2)

that one of the sugar hydroxyls could be linked to the 5-carboxy function as a lactone.

Prolonged reaction with methanolic sodium methoxide followed by re-acetylation gave the starting material and two products, both of which were consistent with opening of a lactone ring. One was identical with the known methyl 3α,5α-tetrahydrodesoxycordifoline penta-acetate (**2**), and the other corresponded to subsequent conjugate addition of methanol to the acrylate ester.

It remained to find which hydroxyl group was involved in the lactone ring. Since protons α to primary and secondary alcohols undergo marked downfield shifts on acylation,[2] examination of the n.m.r. spectrum of a macrolidine derivative in which the sugar was not acetylated should enable a distinction to be made. Brief treatment of dihydromacrolidine tetra-acetate with sodium methoxide gave *N*-acetyldihydromacrolidine (**1d**) $[\alpha]_D^{25}$ + 39·5° (MeOH) for which virtually every proton could be assigned in the n.m.r. spectrum $[(CD_3)_2CO]$. The secondary hydrogens of the sugar at C-2′, 3′ and 4′ were all in the high-field region τ 6·15—6·6, compared with τ 4·7—5·1 for the tetra-acetate; hence signals at τ 5·40 (dd, *J* 12 and 2·5 Hz) and 6·06 (dd, *J* 12 and *ca.* 8 Hz) were attributed to the 6′-methylene group moved downfield by acylation from *ca.* τ 6·5 in the alcohol.

Thus macrolidine has structure (**1a**) with a novel fourteen-membered lactone ring. The absolute configuration follows from the correlation with (**2**) except that C-5 might have been inverted in the process. However, this is unlikely since examination of models of macrolidine indicate that the usual 5α-orientation gives the best agreement between dihedral angles and coupling constants.

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[1] W. P. Blackstock, R. T. Brown, C. L. Chapple, and S. B. Fraser, *J.C.S. Chem. Comm.*, 1972, 1006 and refs. therein.

[2] *E.g.* L. M. Jackman and S. Sternhell, 'NMR Spectroscopy in Organic Chemistry,' Pergamon, 1969, p. 179.