Adina Alkaloids: Desoxycordifoline, 3α,5α- and 3β,5α-Tetrahydrodesoxycordifoline Lactam

By W. P. BLACKSTOCK, R. T. BROWN,* C. L. CHAPPLE, and S. B. FRASER
(*Department of Chemistry, The University, Manchester* M13 9PL)

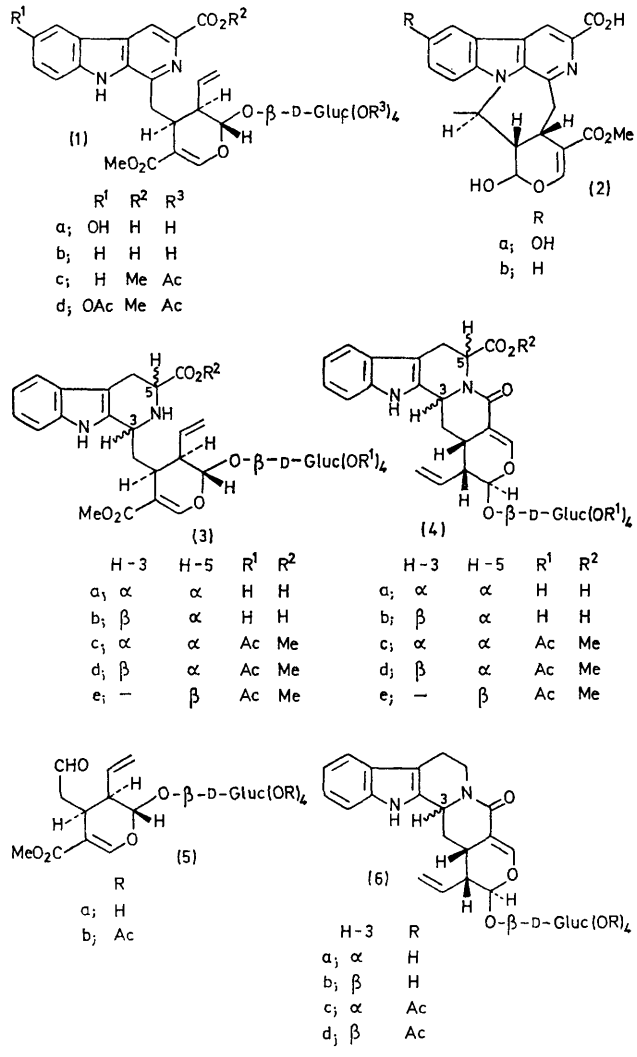
Summary Derivatives of both epimeric tetrahydrodesoxycordifolines (**3a**) and (**3b**) have been isolated and the structures determined; partial synthesis of methyldesoxycordifoline tetra-acetate (**1c**) has established the predicted structure and the absolute configuration of the cordifolines.

CONSEQUENT on the discovery in *Adina cordifolia* of the carboxy-alkaloids cordifoline[1] (**1a**), adifoline[2] (**2a**), and the corresponding 10-deoxy analogues[3] (**1b**) and (**2b**) was the obvious inference that their biogenetic precursor would have to be a hypothetical tetrahydrodesoxycordifoline (TDC) (**3a**) and/or (**3b**) formed by condensation between L-tryptophan and secologanin[4] (**5a**). We now report the isolation and structure elucidation of both 3α,5α- and 3β,5α-TDC lactams (**4a**) and (**4b**), and the partial syntheses of TDC and desoxycordifoline derivatives.

From a methanolic extract of *Adina rubescens* we had previously isolated vincoside lactam[5] (**6b**) and a series of related glycosides,[6] as well as desoxycordifoline. Continued fractionation by gel-permeation and partition chromatography, followed by acetylation and further chromatography afforded two acids, which were converted by diazomethane into two isomeric esters, $C_{36}H_{40}N_2O_{14}$,† (A) $[\alpha]_D^{25}$ −84° and (B) $[\alpha]_D^{25}$ −79°. Since diazoethane gave ethyl esters, $C_{37}H_{42}N_2O_{14}$, only one carboxy-group was present in each acid. Since the u.v. spectra of (A) and (B) (λ_{max} 227·5, 273, 282, and 290 nm) were the same as those of vincoside lactam and strictosamide (**6a**) the presence of indole and β-alkoxyacrylamide chromophores was indicated, the latter being substantiated by the i.r. spectra. The mass spectra were indistinghishable with an intense molecular ion at *m/e* 724 and other fragments at *m/e* 393 (*M* − 331), 377 (*M* − 347) 347, and 331 consistent with the presence of a glucoside tetra-acetate portion, and, overall, corresponded to that expected for a vincoside lactam or strictosamide tetra-acetate substituted by a methoxycarbonyl group. This impression was reinforced by the n.m.r. spectra, ester (B) showing similarities to the former (**6d**) and ester (A) to the latter (**6c**).

The recent discovery[7] of an abundant source of secologanin enabled us to synthesise the possible structures (**4c**) and (**4d**) for comparison. Condensation of methyl L-tryptophanate with secologanin tetra-acetate (**5b**) gave methyl 5α-TDC tetra-acetate, $C_{37}H_{44}N_2O_{15}$, as a mixture of C-3 epimers (**3c**) and (**3d**), which were separated by t.l.c. on silica. Treatment of the higher R_F epimer with K_2CO_3 followed by re-acetylation and re-methylation afforded a lactam (**4c**) or (**4d**), identical in every respect with ester (B) [comparative t.l.c., i.r., n.m.r., c.d., mass spectra, and rotation]. Similarly, the lower R_F epimer gave a lactam (**4c**) or (**4d**) identical with ester (A). The stereochemistry at C-5 was confirmed by a parallel sequence using D-tryptophan to obtain the two 5β-isomers (**4e**) which were readily shown to differ from the natural products. Since the structures of the starting materials are known[4] the configurations of the two lactams thus follow at every centre except C-3.

Recently we established the C-3 configurations in vincoside lactam and strictosamide by reduction of the β-alkoxyacrylamide functions and measuring the o.r.d. curves of the products.[5] By analogy with standard tetracyclic indole alkaloids a positive Cotton effect between 240 and 300 nm



	R¹	R²	R³
a;	OH	H	H
b;	H	H	H
c;	H	Me	Ac
d;	OAc	Me	Ac

	R
a;	OH
b;	H

	H-3	H-5	R¹	R²
a;	α	α	H	H
b;	β	α	H	H
c;	α	α	Ac	Me
d;	β	α	Ac	Me
e;	—	β	Ac	Me

	H-3	H-5	R¹	R²
a;	α	α	H	H
b;	β	α	H	H
c;	α	α	Ac	Me
d;	β	α	Ac	Me
e;	—	β	Ac	Me

	R
a;	H
b;	Ac

	H-3	R
a;	α	H
b;	β	H
c;	α	Ac
d;	β	Ac

denoted a 3α- configuration and a negative one a 3β.[8] Since the acrylamide chromophore is attached to the same C-3 centre as the aromatic system the associated Cotton effects might be additive in the same sense so that it would be possible to obtain the same information directly. It was found that the c.d. curves of the 3α-lactams were invariably

† All molecular formulae were determined by accurate mass measurement.

positive and those of the 3β-lactams were negative between 250 and 300 nm. One of the TDC lactams had a strongly positive ($[\theta]_{271} + 5{\cdot}3 \times 10^4$) and the other a strongly negative absorption ($[\theta]_{265} - 2{\cdot}4 \times 10^4$) and permitted ready assignment of configuration at C-3. Thus ester (A) is methyl 3α,5α-tetrahydrodesoxycordifoline tetra-acetate (**4c**) and ester (B) the 3β-epimer (**4d**); the naturally occurring compounds are presumably the corresponding acids (**4a**) and (**4b**).

Since suitable TDC derivatives were available from the above syntheses we established unambiguously the structure and absolute configuration of desoxycordifoline. The presence of sensitive functional groups in the molecule meant that methods which had previously been used to aromatise tetrahydro-β-carbolines were too drastic and hence a mixture of the C-3 epimers of methyl 5β-TDC tetra-acetate (**3e**) was treated with chlorobenztriazole[9] in methylene chloride at room temperature to give (albeit in low yield) methyl desoxycordifoline tetra-acetate (**1c**) identical by the usual criteria with that derived from the natural product. In particular the c.d. spectra ($[\theta]_{307} + 7{\cdot}2 \times 10^3$, $[\theta]_{270} - 2{\cdot}5 \times 10^4$, and $[\theta]_{239} + 2{\cdot}0 \times 10^4$) were superimposable, and it was noteworthy that methylcordifoline penta-acetate (**1d**) had a virtually identical c.d. spectrum, indicating the same absolute configuration. The expected stereochemical relationship between the cordifolines and secolaganin was thus confirmed.

The isolation of both TDCs as lactams suggests that they exist as such in the plant and are not artefacts of the isolation procedure, since only the 3β-isomer lactamises readily (*e.g.* upon attempted acetylation) and the 3α-isomer has been isolated uncyclised from *Rhazia orientalis*[10] as well as from *A. rubescens*. It will be of interest to see whether the 3β-TDC (**3b**) fulfils a similar function to vincoside[11] (**3b**; H replaces CO_2R^2) as a precursor of more sophisticated alkaloids and this aspect is currently under investigation.

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