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Adina Alkaloids: the Structure of Rubenine

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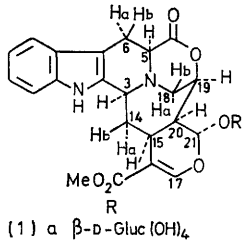
Summary Rubenine, a carboxy-indole alkaloid derived from tetrahydrodeoxycordifoline (**6**) with a unique N(b)–C-18 linkage, has been isolated from *Adina rubescens* and its structure established as (**1a**).

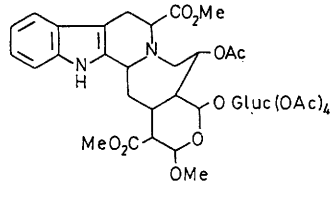
By a combination of gel-permeation and ion-exchange chromatography a new glycoalkaloid, rubenine, $C_{28}H_{32}N_2O_{11}$† $[\alpha]_D^{25}$ — 42° (MeOH) was isolated from *Adina rubescens* heartwood and assigned structure (**1a**) on the basis of chemical and spectroscopic evidence of which only the salient features are outlined below.

U.v., i.r., and n.m.r. spectra readily established the presence of indole and methyl β-alkoxyacrylate functions. Acetylation afforded a tetra-acetate (**1b**) $[\alpha]_D^{25}$ — 46° ($CHCl_3$) which had a crystalline picrolonate salt, m.p. 154—156°. Characteristic ions in the mass spectrum of the acetate at *m/e* 409 (*M* — 331), 393 (*M* — 347) and 331 were consistent with a glucoside tetra-acetate unit, and those at *m/e* 182, 169, 168 indicated a 5-substituted tetrahydro-β-carboline,[1] both of which were substantiated by appropriate n.m.r. signals. However, the most distinctive feature of the mass spectrum was the ready expulsion of CO and CO_2 from the molecular ion, with subsequent loss of a hydrogen in each case, which was attributed to the breakdown of a lactone. Accordingly, treatment with sodium methoxide followed by re-acetylation gave the ring-opened penta-acetate (**2**) where simultaneous addition of methanol to the β-alkoxyacrylate system had occurred, as evidenced by the u.v., n.m.r., and mass spectra.

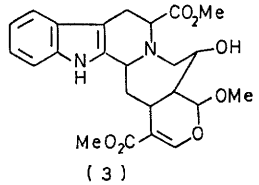
The nature of the sugar in rubenine was established by cleavage with β-glucosidase to the aglycone (**1c**) $[\alpha]_D^{25}$ — 11° (MeOH), which revealed a δ-lactone function with a strong i.r. band at 1740 cm^{-1}. Furthermore, the newly liberated hydroxy-group had to be linked to the β-alkoxyacrylate *via* a hemi-acetal system, since addition of alkali produced a marked enhancement at *ca.* 275 nm in the u.v. absorption



(1) a β-D-Gluc(OH)$_4$
b β-D-Gluc(OAc)$_4$
c H
d Me



(2)



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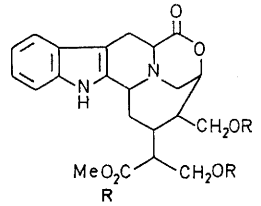
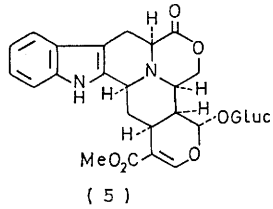


(4) a H
b Ac



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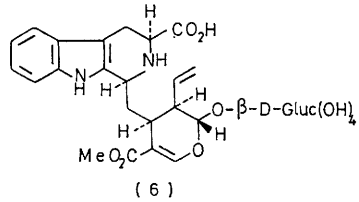

(6)

attributable to an ionised β-hydroxyacrylate chromophore. Treatment of the aglycone with diazomethane afforded

† Molecular formulae for all compounds were determined by accurate mass measurement.

mainly the methyl acetal (**1d**), together with a minor product corresponding to (**3**), neither of which showed a base shift in the u.v. spectrum. Reduction of the aglycone with sodium borohydride removed the β-alkoxyacrylate absorption at 238 nm and gave a diol (**4a**) which could be acetylated to (**4b**).

TABLE

Proton assignments for rubenine from 100 MHz n.m.r. spectrum in $(CD_3)_2SO$–D_2O

Proton	Chemical shift (τ) multiplicity	*J* (Hz)
NH	−0·63s	—
3-H	5·67br d	9, *ca.* 1
5-H	5·85br d	7, *ca.* 1
6-H_a	6·85	7, ?
6-H_b	*ca.* 6·5	*ca.* 1, ?
9-H–12-H	2·5—3·2m	—
14-H_a	*ca.* 8·7	*ca.* 1, ?, ?
14-H_b	8·2m	9, ?, ?
15-H	*ca.* 6·8	*ca.* 5, ?
17-H	2·50s	—
18-H_a	*ca.* 6·4	<1, ?
18-H_b	6·25	6·5, ?
19-H	4·85br dd	6·5, 4·5, <1
20-H	7·8m	9, 4·5, *ca.* 5
21-H	4·65d	9
CO_2Me	6·24s	—

At this stage two plausible structures could be advanced for rubenine—(**1a**) and (**5**)—the latter seeming more likely from examination of models. However, it was not supported by the mass spectra of rubenine derivatives, since, for example, the ready loss of CH_2OAc from the position α to N(b) expected for the acetylated ring-opened derivative of (**5**) was not observed. Eventually, conclusive evidence excluding (**5**) was obtained from n.m.r. spectra which showed that the lactone was derived from a secondary rather than a primary alcohol.

A detailed examination of the n.m.r. spectra of rubenine and its derivatives enabled composite assignments to be made for virtually all the protons which could be confirmed by decoupling experiments. Furthermore, comparison of the observed coupling constants with values calculated from dihedral angles on Dreiding models provided information about the relative stereochemistry. Thus in rubenine (see Table) 20-H was coupled with 21-H (*trans a-a*), 15-H (*cis a-e*), and 19-H (*cis a-e*); 19-H was further strongly coupled to 18-H_b (*trans e-e*) but only weakly to 18-H_a (*cis a-e*); 14-H_b was strongly coupled to both 3-H (*trans a-a*) and 15-H (*trans a-a*), whereas 14-H_a had only slight interactions (*cis a-e*) with them; 5-H again had a substantial coupling with 6-H_a (*cis a-e*) and a small with 6-H_b (*trans e-e*). This provided a body of data which could only be satisfied by the structure and relative configuration (**1a**). Finally, a positive Cotton effect in the c.d. spectrum between 300 and 250 nm established the α-orientation for 3-H[2] and hence proved the absolute configuration of the molecule to be as shown.

Rubenine is thus a derivative of 3α,5α-tetrahydrodesoxycordifoline (**6**)[3] with a unique N-4–C-18 bond in a seven-membered ring. Its immediate precursor could well be the 18,19-epoxide in which nucleophilic attack by N-4 at C-18 is followed by lactonisation.

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