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A NEW PYRROLIZIDINE AMINOALCOHOL IN ALKALOIDS FROM CROTALARIA SPECIES

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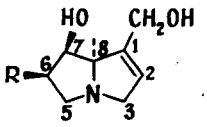
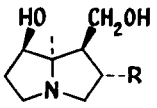
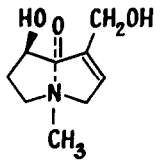
The macrocyclic pyrrolizidine diester alkaloids known so far are based on four aminoalcohols: retronecine (I), platynecine (II), rosmarinecine (III) and otonecine (IV)[1,2]. We have now isolated from Crotalaria species, two alkaloids which are diesters of a new aminoalcohol, 6β,7β-dihydroxy-1-hydroxymethyl-1,2-dehydro-8a-pyrrolizidine (V), hereafter called crotanecine. Madurensine, isolated from Crotalaria madurensis and C. agatiflora growing in India, and anacrotine, isolated from seed of C. anagyroides obtained from Ceylon, are respectively the 6β-hydroxy derivatives of integerrimine (VI) and senecionine (VII). Senecionine is also present in C. anagyroides[3,4].



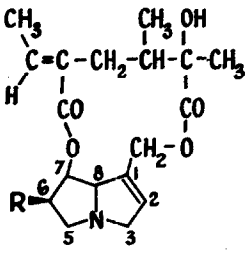
(I) R=H
(V) R=OH



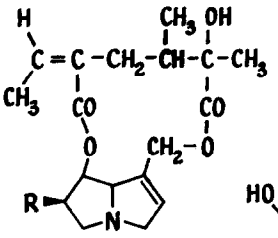
(II) R=H
(III) R=OH



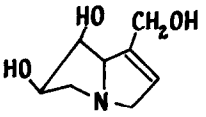
(IV)



(VI) R = H
(IX) R = OH



(VII) R = H
(X) R = OH



(VIII)

Anacrotine, m.p. 191-192°, $[\alpha]_D$ + 30° (ethanol), and madurensine, m.p. 175-176°, were shown by microanalysis and mass spectra to have the empirical formula, $C_{18}H_{25}O_6N$, one oxygen atom more than senecionine and integerrimine. They are not N-oxides since they do not show the appropriate reaction with acetic anhydride[5]. Their infra-red spectra resembled those of senecionine and integerrimine and had a strong single carbonyl peak at 1720 cm^{-1} (in CCl_4; the absorptions of the two ester groups overlap because of hydrogen bonding of the saturated ester carbonyl[6]). Enhanced absorption at 3300-3500 cm^{-1} indicated that anacrotine and madurensine contain an additional hydroxyl group.

The nuclear magnetic resonance spectra of anacrotine and madurensine (Fig. 1a,b), also closely resembling those of senecionine (Fig. 1c) and integerrimine, exhibit the appropriate multiplets for CH-O-CO and magnetically non-equivalent CH_2-O-CO protons (as marked on the spectra); these together with the easily recognised signals for the groups, $C\underline{H}_3$-CH, $C\underline{H}_3$-C-OH and CH_3-CH = C(CO)-CH_2- , of the esterifying acids (also marked on spectra) leave little doubt that the two alkaloids are diesters of a pyrrolizidine aminoalcohol with senecic and integerrinecic acids, respectively. The presence of two hydroxyl groups is demonstrated by the loss

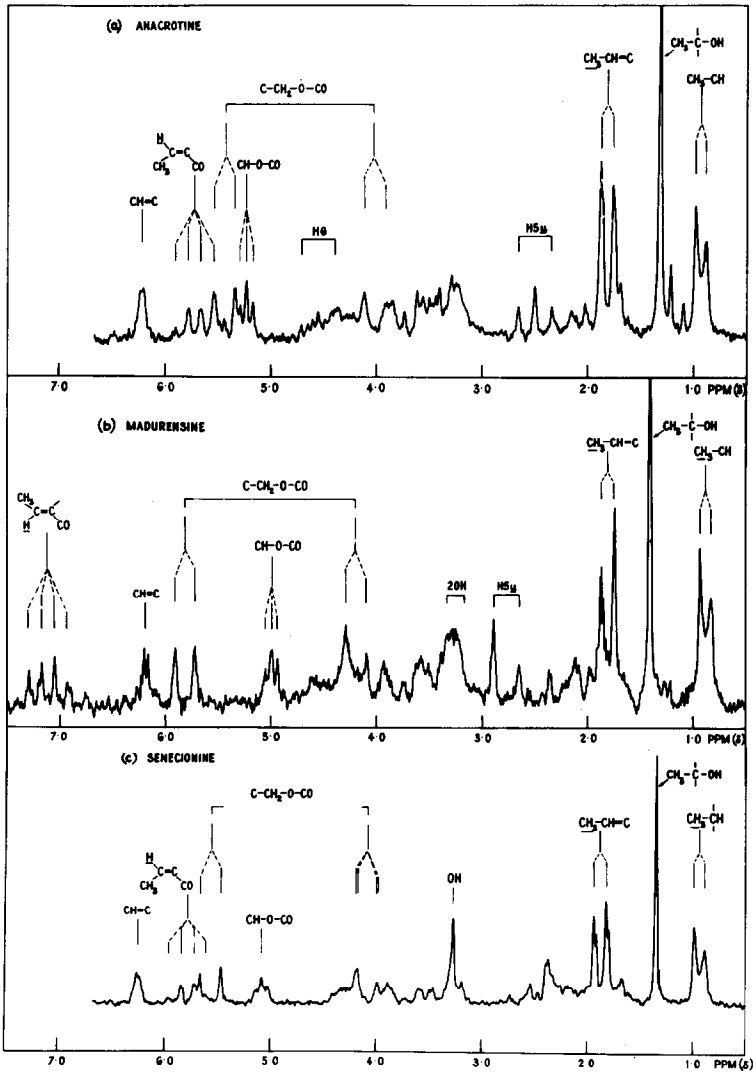


FIG. 1

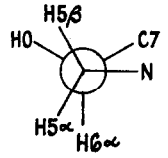
NMR Spectra (at 60 Mc/s in $CDCl_3$) of (a) Anacrotine, (b) Madurensine, (c) Senecionine.

of signals centred at δ3.22, corresponding to two protons, on exchange with deuterium oxide.

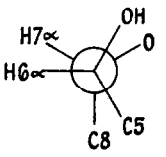
Alkaline hydrolysis of anacrotine gave senecic acid and a new amino-alcohol, crotanecine, $C_8H_{13}O_3N$, m.p. 202-203-5°. Madurensine similarly gave integerrimecic acid and crotanecine. Crotanecine thus contains the additional hydroxyl group and is isomeric with hydroxy-retronecine. Signals for an olefinic proton typical of a 1,2-dehydro-pyrrolizidine are apparent in the δ6.0 region of the NMR spectra of crotanecine (Fig. 2) and the parent alkaloids. One hydroxyl group is present as the 1-hydroxymethyl grouping. It can be shown from the NMR and mass spectra that the other two hydroxyls are attached to C6 and C7.

The NMR spectra of anacrotine and madurensine (Fig. 1a,b) differ from those of senecionine (Fig. 1c) and integerrimine in having signals for two fewer protons in the δ2.0 region, one more proton in the δ4.0-4.5 region and less complicated H5u (u signifies the upfield, d the downfield multiplet of a geminal pair) and CHOCOR multiplets. The latter are essentially simple triplets indicative of only two, approximately equal, splittings (3.5 c/s), whereas in retronecine derivatives an additional small splitting is evident. The H5u multiplet in the spectrum of anacrotine, δ2.60, has the appearance of a triplet with 9.5 c/s line separations. The possibility of confusion between these and other signals adjacent upfield was removed in a multiple-scan, computer-averaged spectrum which also revealed a multiplet due to CHOH as a group of eight lines centred at δ4.6 with splittings of 9.5, 6.5 and 3.5 c/s. This data can be accommodated only in a 6-hydroxy-7-acyloxypyrrolizidine system. The H5 protons have closely similar chemical shifts to the H5 protons of retronecine and other pyrrolizidine derivatives[7,8] and can therefore be assigned in the same way: H5u = H5β and H5d = H5α. The magnitude of the vicinal couplings of H5β and H5α with H6, 9.5 and 6.5 c/s respectively, are consistent only with the proton

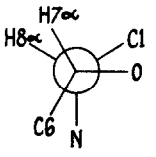
arrangement (XI) which corresponds to a 6β-hydroxyl group and an exo-buckled ring (c.f. discussion of conformation of retronecine and heliotridine[8]).



(XI)



(XII)



(XIII)

The H6α,H7 and H7,H8 vicinal couplings, each 3.5 c/s, require that the proton on C7 be H7α (c.f. diagrams (XII) and (XIII)), i.e. that the acyloxy grouping is 7β as in retronecine. Thus the aminoalcohol, crotanecine, is 1-hydroxymethyl-6β,7β-dihydroxy-1,2-dihydro-6α-pyrrolizidine (V).

In the spectrum of madurensine (Fig. 1b), the H5u multiplet is reduced to two lines, 15 c/s apart, indicating $J_{5\alpha,5\beta} = -15$ c/s, $J_{5\beta,6\alpha} < 0.5$ c/s, and consistent with a 6β-hydroxyl group in an endo-buckled ring.[8] The spectrum of crotanecine (Fig. 2) is fully consistent with structure (V). Multiplets can be assigned as indicated for the H2, H3 and H5 protons. The signals of the H6, H7, H8 and H9 protons form a band near δ4.2; in retronecine, a similar group near δ4.6 is due to the H7, H8 and H9 protons[8]. The near equality in shift of the H6, H7 and H8 protons results in the presence of strong combination lines in the H5u and H5d multiplets. 5-Spin computer calculations show that the coupling constants, $J_{5\alpha,5\beta}$ -9.5 c/s, $J_{5\alpha,6\alpha}$ 7.0 c/s, $J_{5\beta,6\alpha}$ 9.5 c/s, are in agreement with the observed spectrum. These constants are approximately the same as in anacrotine and we conclude that crotanecine also has an exo-buckled conformation (VIII).

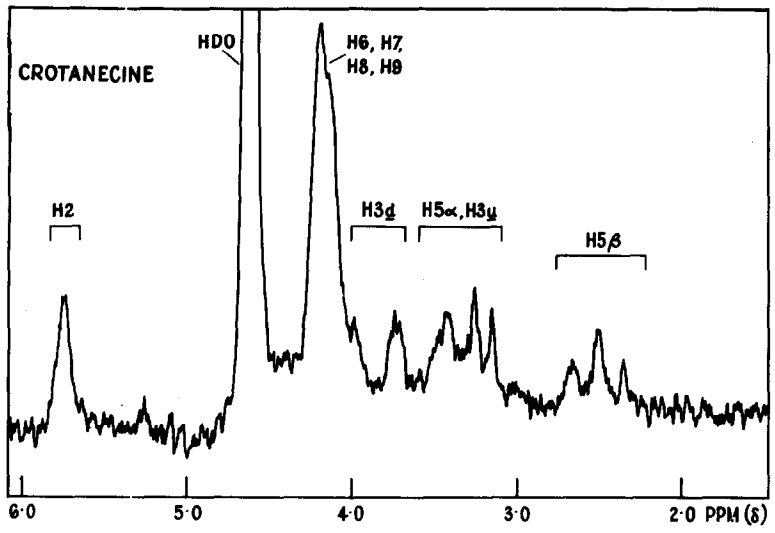
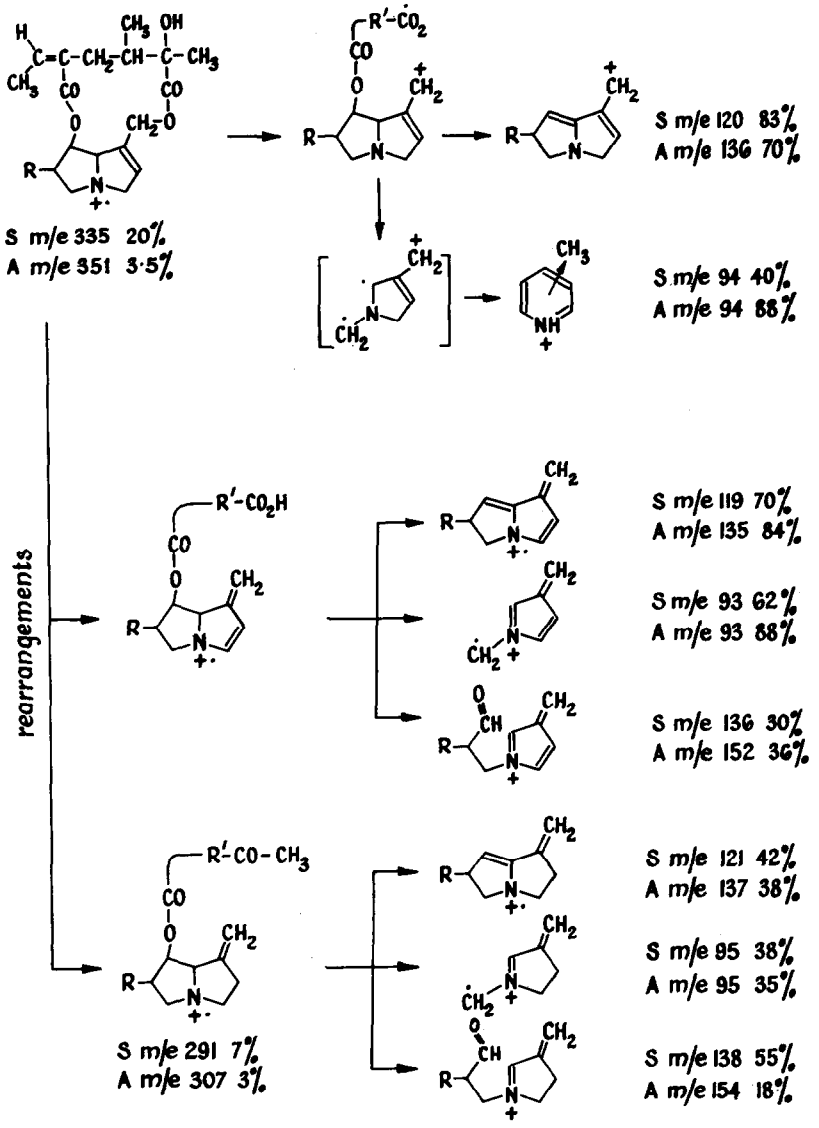


FIG. 2

NMR Spectrum (at 60 Mc/s in D_2O) of Crotanecine.

The conclusion that anacrotine and madurensine have structures (X) and (IX) respectively, is well supported by their mass spectra. The main fragmentation pathways of the macrocyclic diesters[9,10] leave the saturated ring of the nucleus intact until a late stage. In accord with this, the spectra of anacrotine and senecionine exhibit parallel series of peaks 16 mass numbers apart until the point is reached where C6 is lost. This is illustrated by the following fragmentation sequences in which tentative structures are assigned to the main peaks (S and A indicate peaks in the spectra of senecionine (R = H) and anacrotine (R = OH) respectively):


S m/e 335 20%
A m/e 351 3·5%
S m/e 120 83%
A m/e 136 70%
S m/e 94 40%
A m/e 94 88%
rearrangements
S m/e 119 70%
A m/e 135 84%
S m/e 93 62%
A m/e 93 88%
S m/e 136 30%
A m/e 152 36%
S m/e 291 7%
A m/e 307 3%
S m/e 121 42%
A m/e 137 38%
S m/e 95 38%
A m/e 95 35%
S m/e 138 55%
A m/e 154 18%

It is remarkable that the pyrrolizidine ring should be exo-buckled in crotanecine and anacrotine, yet endo-buckled in madurensine, and that the difference in conformation results in a change in the geminal coupling constant, $J_{5\alpha,5\beta}$, from -9.5 to -15.0 c/s.

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