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Genus *Crotalaria*. XVII*
The Stereochemistry of Croalbinecine

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Abstract

The stereochemistry of the pyrrolizidine triol, croalbinecine, is defined as 1α-hydroxymethyl-8α-pyrrolizidine-2β,7β-diol, by means of nuclear magnetic resonance measurements and the conversion of croalbidine into turneforcidine.

Introduction

In our earlier report[1] we have derived the structure of a pyrrolizidine alkaloid croalbidine isolated from *Crotalaria albida* Heyne ex Roth. The alkaloid on acid hydrolysis yields (+)-trichodesmic acid lactone (1) and a new amino alcohol, croalbinecine. The present paper deals with the stereochemistry of croalbinecine which is now shown to be 1α-hydroxymethyl-8α-pyrrolizidine-2β,7β-diol (2). The only other known saturated pyrrolizidine triol is rosmarinecine (1β-hydroxymethyl-8α-pyrrolizidine-2α,7β-diol), which constitutes the basic part of the alkaloids rosmarinine and angularine isolated from *Senecio* (Compositae) species.[2]

Discussion

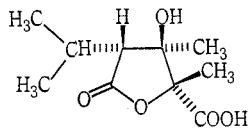
The n.m.r. spectrum of croalbinecine (Fig. 1*a*) measured in deuterium oxide at 100 MHz showed well resolved multiplets in the region δ 2·0–4·5, fully consistent with a 1-hydroxymethylpyrrolizidine-2,7-diol structure. The assignments and approximate coupling constants derived on this basis by first-order analysis are shown in Table 1. The chemical shifts are similar to those observed for equivalent groupings in the saturated pyrrolizidine-7,9- and -2,9-diols.[3,4]

Decoupling experiments provided additional evidence for this substitution pattern. Irradiation at δ 2·03 (H 6) led to collapse of three multiplets (Fig. 1*b*): those at δ 2·76 and 3·14 (H 5β and H 5α respectively), each of which reduced to two lines separated by 10 Hz and with appropriate intensities for an AB system, and a four-line multiplet, δ 4·29 (H 7), which also reduced to two lines. Irradiation at δ 2·35 (multiplet with four splittings assigned to H 1) (Fig. 1*c*) collapsed the multiplet centred

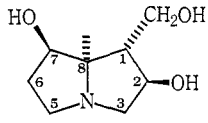
* Part XVI, *J. Indian Chem. Soc.*, in press.

[1] Sawhney, R. S., and Atal, C. K., *Indian J. Chem.*, 1973, **11**, 88.
[2] Bull, L. B., Culvenor, C. C. J., and Dick, A. T., 'The Pyrrolizidine Alkaloids' p. 256 (North Holland Publishing Co.: Amsterdam 1968).
[3] Aasen, A. J., Culvenor, C. C. J., and Smith, L. W., *J. Org. Chem.*, 1969, **34**, 4137.
[4] Aasen, A. J., and Culvenor, C. C. J., *J. Org. Chem.*, 1969, **34**, 4143.

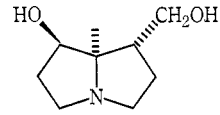
near δ 3·7 (H 9) from eight lines to four lines appropriate for an AB pair, J 11·5 Hz; it also reduced the four-line multiplet, δ 4·18 (H 2), to two lines, and altered, though in a non-interpretable manner, a group of multiplets centred near δ 3·25 (H 8, H 3α,



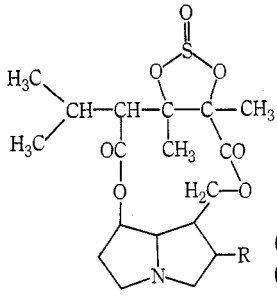
(1)



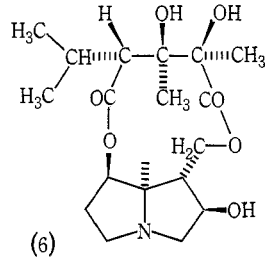
(2)



(5)



(3) R = Cl
(4) R = H



(6)

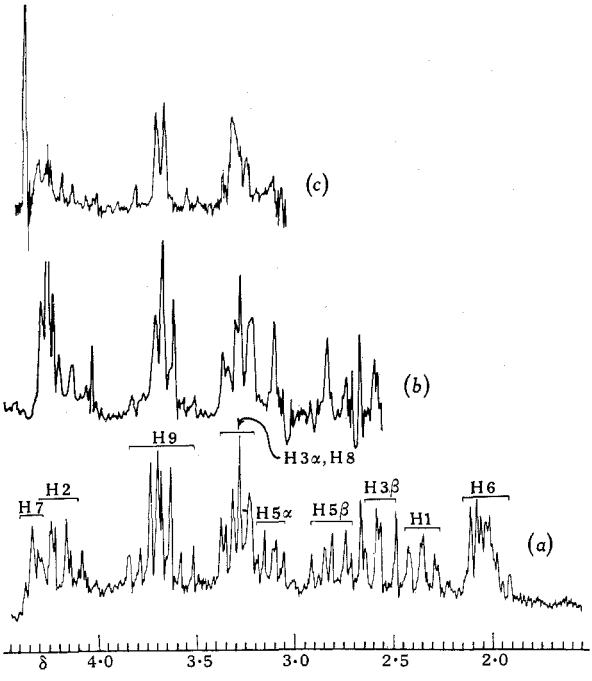


Fig. 1. N.m.r. spectrum of croalbinecine measured in D_2O at 100 MHz: (*a*) under standard conditions; (*b*) during irradiation at frequency δ 2·03; (*c*) during irradiation at frequency δ 2·35.

H 5α). A spectrum of the hydrochloride of the amino alcohol was interpretable on the basis of the structure (2) with appropriate deshielding of the protons in the pyrrolizidine ring (Table 1).

A direct correlation of croalbinecine with the saturated pyrrolizidine-2,9-diols has been achieved by elimination of the hydroxyl at C2. Reaction of the alkaloid croalbidine with thionyl chloride leads to replacement of the C2 hydroxyl by chlorine although the hydroxyl groups in the trichodesmic acid moiety are simultaneously esterified to form the cyclic sulphite (3). Trichodesmine, an ester of trichodesmic acid with retronecine, also yields a cyclic sulphite with thionyl chloride.[5] Catalytic reduction removes the chlorine from (3) to give (4) which is hydrolysed in acid to trichodesmic acid and an amino diol. This was found to be identical with turneforcidine, 1α-hydroxymethyl-8α-pyrrolizidin-7β-ol (5), in all respects including sign of specific rotation.

Table 1. N.m.r. parameters for croalbinecine and its hydrochloride measured in deuterium oxide at 100 MHz

δ refers to chemical shifts relative to the methyl signals of sodium 3-trimethylsilylpropane-1-sulphonate as zero. H9u and H9d are the designations for the H9 protons at higher and lower field, respectively

Proton	Croalbinecine base δ (p.p.m.)	Croalbinecine base Coupling constants (Hz)	Hydrochloride δ (p.p.m.)
H2	2·35	$J_{1,2}$ 8·0; $J_{1,8}$ 8·0; $J_{1,9u}$ 6·2; $J_{1,9d}$ 5·5	2·63
H2	4·18	$J_{1,2}$ 8·0; $J_{2,3\beta}$ 8·0; $J_{2,3\alpha}$ 5·8	4·36
H3β	2·55	$J_{2,3\beta}$ 8·0; $J_{3\alpha,3\beta}$ 10·0	3·06
H3α	3·29	$J_{2,3\alpha}$ 5·8; $J_{3\alpha,3\beta}$ 10·0	3·85
H5β	2·76	$J_{5\alpha,5\beta}$ 10·0; $J_{5\beta,6}$ 7·0, 10·0[A]	*c.* 3·40
H5α	3·14	$J_{5\alpha,5\beta}$ 10·0; $J_{5\alpha,6}$ 4·0, 5·5[A]	*c.* 4·10
H6	*c.* 2·03		*c.* 2·28
H7	4·29	$J_{6,7}$ *c.* 4·0; $J_{7,8}$ *c.* 4·0	*c.* 4·60
H8	3·28	$J_{7,8}$ 4·0; $J_{1,8}$ 8·0	*c.* 3·85
H9u	3·63	$J_{9u,9d}$ 11·5; $J_{1,9u}$ 6·4	*c.* 3·71
H9d	3·73	$J_{9u,9d}$ 11·5; $J_{1,9d}$ 5·8	*c.* 3·76

[A] Values quoted are observed splittings, not necessarily true coupling constants.

Evidence for the configuration of croalbinecine at C2 is provided by the relevant vicinal coupling constants (Table 1). The couplings, $J_{1\beta,2}$ 8·0 and $J_{2,3\beta}$ 8·0 Hz, in pyrrolizidine derivatives agree best with *trans* hydrogens which spend most of their time in a near-diaxial situation ($\theta \approx 160°$). This consideration applies especially when as in this instance, the magnitude of the coupling constants is expected to be reduced by the electronegativity of a hydroxyl group attached to one carbon atom. The other value, $J_{2,3\alpha}$ 5·8 Hz, is more appropriate to *cis* hydrogens ($\theta \approx 30$–$40°$). On this basis, H2 will be H2α and the ring concerned predominantly *exo*-buckled. This conclusion is supported by the fact that the H2 coupling constants of macronecine, 1β-hydroxymethyl-8β-pyrrolizidin-2β-ol and thus a model for the alternative 1α-hydroxymethyl-8α-pyrrolizidin-2α-ol structure for croalbinecine, have rather different values (5–6, 5–6 and 1 Hz).[3] In the hope of finding the ring in a different conformation with unambiguously interpretable coupling constants, the n.m.r. spectrum of the parent alkaloid croalbidine, was also measured. In deuterochloroform–deuteromethanol solution, the H2 multiplet was clearly observable (width 25 Hz) and the approximate coupling constants were $J_{1\beta,2}$ 9·2, $J_{2,3\alpha}$ 6·5, $J_{2,3\beta}$ 9·2 Hz. These

[5] Yunusov, S. Yu., and Plekhanova, N. V., *Dokl. Akad. Nauk Uzb. SSR*, 1957, No. 6, 19 (*Chem. Abstr.*, 1959, **53**, 6276).

values indicate that the ring conformation is the same as in croalbinecine. The slightly larger values for $J_{1\beta,2}$ and $J_{2,3\beta}$ (9·2, rather than 8·0 Hz) increase the probability that these couplings apply to *trans* hydrogens.

Although some uncertainty may still attach to the configuration at C 2, we therefore regard croalbinecine as being 1α-hydroxymethyl-8α-pyrrolizidine-2β,7β-diol (2). The other known saturated pyrrolizidine triol, rosmarinecine (1β-hydroxymethyl-8α-pyrrolizidine-2α,7β-diol), gives a markedly different n.m.r. spectrum in D_2O solution. The absolute configuration of croalbidine may now be represented as (6).

Experimental

Conversion of Croalbidine into the 2-Chloro Derivative (3)

Croalbidine (2 g) was treated with pure thionyl chloride (40 ml) at 5° and then refluxed gently for 5 h after which t.l.c. showed the absence of croalbidine. Excess of reagent was removed under reduced pressure to give a black residue which on washing with acetone yielded colourless crystalline material (1·06 g). The product on recrystallization from ethanol afforded colourless crystals of *(3)-hydrochloride*, m.p. 193–194°. A mass spectrum measured by direct-entry probe shows a molecular ion for the free base, *m/e* 435. Microanalysis indicates that the crystals represent a mono- or sesqui-hydrate, in which the water is not removed by drying at 70° under high vacuum (Found, on a dried sample: C, 43·3, 43·1; H, 5·9, 6·0; N, 2·5; S, 6·6. $C_{18}H_{27}Cl_2NO_7S$ requires C, 45·8; H, 5·8; N, 3·0; S, 6·8; with $1H_2O$ it requires C, 44·1; H, 5·9; N, 2·8; S, 6·5 and with $1·5H_2O$ it requires C, 43·3; H, 6·0; N, 2·8; S, 6·4%). A sample kept in a desiccator for 9 months melted at 211–212° but was unchanged in its C, H content.

Catalytic Reduction of (3)

The chloro compound (200 mg), shaken in absolute ethanol (15 ml) with Raney nickel, absorbed 1 molar equivalent of hydrogen at n.t.p. in 4 h. The product (110 mg) after recrystallization from ethanol yielded colourless crystals of *(4)-hydrochloride*, m.p. 224–225°, M^+ 401 (Found: N, 2·9. $C_{18}H_{28}ClNO_7S$ requires N, 3·2%).

Acid Hydrolysis of (4)

Compound (4) (200 mg) was heated with 12% hydrochloric acid (7 ml) on a steam bath for 60 h. The solution was filtered and the filtrate extracted with ether to yield 58 mg of an acid which after recrystallization from ether–light petroleum had m.p. 214–215° alone or mixed with (+)-trichodesmic acid. The residual acid solution was evaporated to dryness in vacuum and extracted with absolute ethanol. Removal of solvent gave a gummy necine hydrochloride (90 mg) which did not crystallize. The aqueous solution of the necine hydrochloride was passed through Amberlite CG 400 (OH) and elution with water yielded (5), $[\alpha]_D$ −8·5° (*c*, 0·53 in methanol) (cf. lit. values for turneforcidine −10·5°, −18° and −12·5° in the same solvent).[3,6]

An n.m.r. spectrum of (5), measured in $CDCl_3$ at 60 MHz, matches closely the spectrum of turneforcidine in $CDCl_3$ and is dissimilar from the spectra of hastanecine, platynecine, macronecine and dihydroxyheliotridane in the same solvent.[3] The mass spectrum of the diol is also in good agreement with that of turneforcidine.

Acknowledgments

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[6] Aasen, A. J., and Culvenor, C. C. J., *Aust. J. Chem.*, 1969, **22**, 2657.