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Structure of Crotanecine

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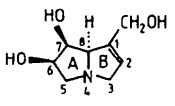
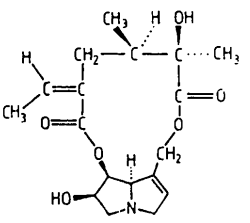
Abstract. $C_8H_{13}NO_3$, $M_r = 171{\cdot}20$, orthorhombic, $P2_12_12_1$, $a = 10{\cdot}9526\ (9)$, $b = 12{\cdot}4628\ (9)$, $c = 6{\cdot}0816\ (7)$ Å, $V = 830{\cdot}1\ (1)$ Å^3, $Z = 4$, $D_x = 1{\cdot}37$ g cm^{-3}, λ(Mo $K\alpha$) $= 0{\cdot}71069$ Å, $\mu = 1{\cdot}13$ cm^{-1}, $F(000) = 368{\cdot}0$, $T = 294$ K; $R = 0{\cdot}034$ for 861 unique reflections. The *A* ring is found to be *exo*-buckled [with a pucker angle of 40·8 (2)°], in agreement with the conformation in solution, as deduced from NMR studies. The relative stereochemistry is also confirmed. Each molecule is linked to three others by intermolecular hydrogen bonds.

Introduction. Esterified derivatives of the pyrrolizidinetriol crotanecine have been identified as alkaloids of some species of *Crotalaria* (Atal, Kapur, Culvenor & Smith, 1966; Culvenor & Smith, 1972). Largely on the basis of ^{1}H NMR spectroscopy, structure (1) was proposed for the necine (Atal *et al.*, 1966) and this has recently been confirmed by synthesis (Yadav, Rüeger & Benn, 1984) and X-ray structural characterizations of the parent alkaloids anacrotine (2) and madurensine (3) (Mackay, Sadek & Culvenor, 1984). We report herein an X-ray crystallographic examination of crotanecine which provides additional data on its structure and should prove of value to those concerned with structure–activity relationships among the hepatotoxic pyrrolizidine derivatives.



(1)



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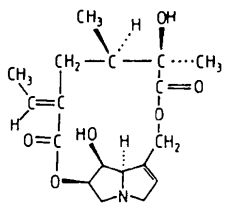

(3)

Experimental. Colourless crystal, 0·2 × 0·2 × 0·3 mm, Enraf–Nonius CAD-4F diffractometer, graphite-monochromated Mo $K\alpha$; lattice parameters from least-squares refinement of 25 reflections with $12 \le \theta \le 18°$; 1023 unique reflections, 680 considered observed at the $3\sigma(I)$ level, $\theta_{max} = 25°$, $\omega/2\theta$ scans, scan range 1·5 × (0·60 + 0·347 tanθ)°, scan speed 3·7 ranging to 0·7° min^{-1}; three standard reflections ($\bar{4}11$, $1\bar{3}2$, 411) measured every 1500 s of X-ray exposure time, max. variation in intensity of +4·0%; data collected: $+h\ -k\ \pm l$ to max. indices of 13, 15, 7 (Friedel pairs collected and averaged). Data corrected for background, Lp and decay; no absorption correction applied. Structure solved using *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), refined by full-matrix least squares based on *F*, minimizing function $\sum w(|F_o| - |F_c|)^2$, w defined as $[\sigma^2(F_o) + 0{\cdot}00004(F_o^2)]^{-1}$ where $\sigma(F_o)$ was derived from counting statistics; *XRAY*76 system of computer programs (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976); H atoms included in positions located from difference Fourier synthesis, isotropic thermal parameters of H set to 1·1 times that of bonded atom, H parameters not refined, all non-H anisotropic. Model converged with: 861 reflections [observed plus those for which $I_c > 3\sigma(I_o)$], 109 variables, $R = 0{\cdot}034$, $wR = 0{\cdot}027$, max. $(\Delta/\sigma) = 0{\cdot}002$, $S = 1{\cdot}02$, max. residual electron density $= \pm 0{\cdot}25$ e Å^{-3}; an isotropic extinction parameter could not be refined. Scattering factors those of Cromer & Mann (1968) for non-H and Stewart, Davidson & Simpson (1965) for H atoms. Anomalous-dispersion corrections included for non-H atoms (*International Tables for X-ray Crystallography*, 1974).

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Discussion. Atomic parameters for non-H atoms are given in Table 1.* The molecular structure of crotanecine is shown in Fig. 1 (Johnson, 1965). The *A* ring is found to be *exo*-buckled with a pucker angle of 40·8 (2)° and an angle of 125·2 (2)° between the mean planes defined by ring *B* atoms and atoms C(5), N(4), C(8) and C(7) of ring *A*. This conformation was also observed in the solid state for anacrotine and senecionine, which differs from the former in having an H rather than an OH at C(6) (Mackay & Culvenor, 1982). The respective pucker and mean-plane angles for these latter two compounds are 37·9 (6), 127·1 (7) and 35·3 (4), 127·9 (4)° respectively, in excellent agreement with those found in the present study. An analysis of the *J* values for the couplings observed between H(5)α, H(5)β and H(6) had previously led to the conclusion that crotanecine exists in solution as the *exo*-buckled conformer. In contrast, madurensine has been shown to have the less common *endo*-buckled conformation both in solution (Atal *et al.*, 1966) and in the solid state (Mackay *et al.*, 1984), due, most likely, to the attachment of the ester macrocycle at C(6).

Bond lengths and angles for crotanecine are summarized in Table 2. Comparison of these with the appropriate values found in the pyrrolizidine nucleus of both anacrotine and madurenesine shows only minor deviations. The major differences, as expected, involve C—O bonds where the ester grouping is attached. The crystal packing is such that each molecule of crotanecine is linked to three others by intermolecular hydrogen bonds. These include O(10)—H(10)···N(4) (at x, y, $1+z$), O(11)—H(11)···O(10) (at $1-x$, $\frac{1}{2}+y$, $\frac{3}{2}-z$), and O(12)—H(12)···O(11) (at $\frac{3}{2}-x$, $1-y$, $\frac{1}{2}+z$). The values of O···*X*, O—H, H···*X* and the angle O—H···*X* are: 2·72, 0·94, 1·80 Å, 165·6°; 2·74, 0·88, 1·89 Å, 162·7°; and 2·72, 0·87, 1·87 Å, 165·7°, respectively.

The absolute configuration of crotanecine cannot be rigorously determined in this study as the *R* factors for the enantiomeric models are indistinguishable. However, the relative configuration is confirmed. Moreover, the successful synthesis of crotanecine from (2*S*,4*R*)-4-hydroxyproline (Yadav *et al.*, 1984) and the structure of anacrotine (Mackay *et al.*, 1984), in which the senecic acid moiety is of known configuration, leave no doubt that this necine belongs to the 8α-series and that Fig. 1 thus correctly represents its absolute stereochemistry also.

* Tables containing the anisotropic thermal parameters, H-atom coordinates and isotropic thermal parameters, bond lengths and angles associated with H atoms, and structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42282 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Final atomic coordinates* (×10⁴) *and equivalent isotropic thermal parameters* (×10) *for the non*-H *atoms*

	x	*y*	*z*	B_{eq}*(Å²)
C(1)	4057 (2)	2913 (2)	6508 (4)	2·4 (1)
C(2)	2986 (2)	3378 (2)	6294 (4)	3·0 (1)
C(3)	2877 (2)	3981 (2)	4199 (4)	3·8 (1)
N(4)	4020 (2)	3721 (1)	2992 (3)	2·7 (1)
C(5)	4711 (2)	4657 (2)	2168 (4)	3·2 (1)
C(6)	6036 (2)	4385 (2)	2634 (4)	2·8 (1)
C(7)	5972 (2)	3815 (2)	4862 (4)	2·5 (1)
C(8)	4832 (2)	3116 (2)	4544 (4)	2·4 (1)
C(9)	4510 (2)	2229 (2)	8334 (5)	3·4 (1)
O(10)	3635 (2)	2108 (1)	10053 (3)	3·8 (1)
O(11)	6821 (1)	5282 (1)	2588 (3)	3·5 (1)
O(12)	5768 (1)	4560 (1)	6560 (3)	3·0 (1)

* B_{eq} is calculated from $\frac{1}{3}$ the trace of the B_{ij} matrix.

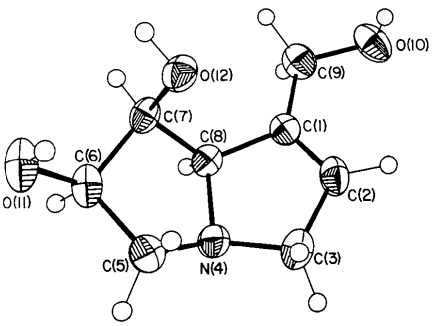

Fig. 1. *ORTEP* plot (Johnson, 1965) of crotanecine showing the atomic-labelling scheme. H atoms are included as spheres of radius 0·1 Å.

Table 2. *Bond lengths* (Å) *and angles* (°) *for crotanecine*

C(1)–C(2)	1·314 (3)	C(5)–C(6)	1·517 (3)
C(1)–C(8)	1·487 (3)	C(6)–C(7)	1·532 (4)
C(1)–C(9)	1·486 (4)	C(6)–O(11)	1·411 (3)
C(2)–C(3)	1·484 (4)	C(7)–C(8)	1·535 (3)
C(3)–N(4)	1·487 (3)	C(7)–O(12)	1·407 (3)
N(4)–C(5)	1·479 (3)	C(9)–O(10)	1·426 (3)
N(4)–C(8)	1·500 (3)		
C(2)–C(1)–C(8)	110·8 (2)	C(5)–C(6)–O(11)	113·7 (2)
C(2)–C(1)–C(9)	128·7 (2)	C(7)–C(6)–O(11)	114·4 (2)
C(8)–C(1)–C(9)	120·5 (2)	C(6)–C(7)–C(8)	100·9 (2)
C(1)–C(2)–C(3)	112·4 (2)	C(6)–C(7)–O(12)	110·5 (2)
C(2)–C(3)–N(4)	104·2 (2)	C(8)–C(7)–O(12)	109·8 (2)
C(3)–N(4)–C(5)	115·2 (2)	C(7)–C(8)–C(1)	117·3 (2)
C(3)–N(4)–C(8)	107·4 (2)	C(7)–C(8)–N(4)	106·1 (2)
C(5)–N(4)–C(8)	107·8 (2)	C(1)–C(8)–N(4)	104·6 (2)
N(4)–C(5)–C(6)	104·5 (2)	C(1)–C(9)–O(10)	112·6 (2)
C(5)–C(6)–C(7)	103·0 (2)		

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13,14-Didehydro-11-deoxy-15-ketoprostaglandin E_1 (at 173 K), $C_{20}H_{30}O_4$

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Abstract. $M_r = 334{\cdot}5$, monoclinic, $P2_1/n$, $a = 5{\cdot}544$ (1), $b = 12{\cdot}834$ (2), $c = 27{\cdot}587$ (6) Å, $\beta = 92{\cdot}22$ (2)°, $V = 1961{\cdot}4$ Å^3, $Z = 4$, $D_x = 1{\cdot}13$ g cm^{-3}, Mo $K\bar{\alpha}$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}72$ cm^{-1}, $F(000) = 728$, final $R = 0{\cdot}061$ for 2463 unique reflections above background [$I > 2\sigma(I)$]. The molecule does not have the hairpin conformation that is characteristic of most prostaglandin molecules. Instead, an 'L'-shaped conformation is revealed that is similar to the structure of prostaglandin B_1. The alkyl chains have the fully extended all-*trans* conformation. The five-atom ring has an envelope conformation. The stereochemical features of the title compound are compared with those of prostaglandin E_1 and two other prostaglandin E_1 analogs.

Introduction. The synthesis of the title compound (hereinafter referred to as 7ME1) will be reported separately (Matthews, 1985). Naturally occurring and synthetic prostaglandins* tend to have a hairpin conformation in the solid state. In this conformation the two side chains are approximately parallel. The single reported exception to that generalization is PGB_1 (DeTitta, Langs & Edmonds, 1979), whose crystal structure reveals an 'L' conformation in which the side chains are approximately perpendicular to each other. The crystal structure of a 13-dehydroprostaglandin E_1 analog (Oliver & Strickland, 1983), the only published report of an alkyne-containing prostaglandin structure, revealed a relatively planar hairpin-shaped molecule. The structural analysis of 7ME1 was undertaken in order to determine the conformation of this related molecule in the solid state.

Experimental. Crystals of the compound obtained from Dr R. S. Matthews of these laboratories, seed crystals obtained as a waxy residue from long-term (~1 year) storage of the compound, crystallized by slow evaporation of a diethyl ether–ethyl acetate solution; clear needle-shaped crystal, $0{\cdot}06 \times 0{\cdot}13 \times 0{\cdot}25$ mm, mounted on glass fiber, Syntex $P2_1$ autodiffractometer, data crystal continuously bathed in cold dry nitrogen gas stream maintained at 173 K using a Syntex LT-1 low-temperature attachment, Laue symmetry $2/m$ with systematic absences $0k0$ for k odd and $h0l$ for $h+l$ odd; lattice parameters by least-squares refinement of 23 carefully centered reflections, Miller indexes for data collection $h = 0$ to 6, $k = 0$ to 15, $l = -32$ to 32 using $\theta/2\theta$ scan with variable scan rate of 4·0 to 29·3° min^{-1}; intensities of 4 check reflections (200, 040, 004, $\bar{2}\bar{2}\bar{2}$) monitored every 100 reflections revealed only random variations (<6%) from mean intensities; 3556 unique reflections ($2{\cdot}0 < 2\theta < 50°$), 2463 with $I > 2\sigma(I)$ used in solution and refinement of structure, data corrected for Lorentz and polarization effects, not for absorption;

* Abbreviations employed: PG, prostaglandin; PGE_1, (11*R*,13*E*,15*S*)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid; PGB_1, (13*E*,15*S*)-15-hydroxy-9-oxoprosta-8(12),13-dien-1-oic acid; CE1S, (15*S*)-15-hydroxy-7-oxa-9-oxoprost-13-yn-1-oic acid; 7ME1,9,15-dioxoprost-13-yn-1-oic acid.

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