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Crispatine Monohydrate, $C_{16}H_{23}NO_5.H_2O$, a Pyrrolizidine Alkaloid

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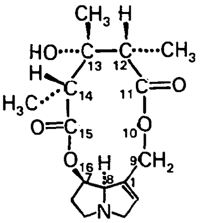
Abstract. $M_r = 327{\cdot}4$, triclinic, $P1$, $a = 5{\cdot}670\,(1)$, $b = 8{\cdot}020\,(1)$, $c = 9{\cdot}943\,(1)$ Å, $\alpha = 91{\cdot}25\,(1)$, $\beta = 103{\cdot}03\,(1)$, $\gamma = 106{\cdot}81\,(1)°$, $U = 419{\cdot}9\,(1)$ Å^3, $Z = 1$, $D_x = 1{\cdot}295$ Mg m^{-3}, $\lambda(\mathrm{Cu}\,K\alpha) = 1{\cdot}5418$ Å, $\mu = 0{\cdot}73$ mm^{-1}, $F(000) = 176$, $T = 291$ K. Final $R = 0{\cdot}037$ for 1367 observed terms. The conformation of the 11-membered macroring is similar to that observed in the related alkaloids, monocrotaline and fulvine. The hydroxyl substituent forms an intramolecular hydrogen bond with the carbonyl O of the secondary ester and forms an intermolecular hydrogen bond with the water molecule.

Introduction. Crispatine (I; stereochemistry of esterifying acid determined herein) has been isolated together with fulvine and monocrotaline from *Crotalaria crispata* (family Leguminosae). The alkaloid hydrolyses to retronecine and crispatic acid (Culvenor & Smith, 1963). The almost identical NMR spectra of fulvinic and crispatic acids and their lack of detectable optical activity led to the conclusion that the two acids were the symmetrical diastereoisomers of 3-hydroxy-2,3,4-trimethylglutaric acid. This conclusion was confirmed and the relative configuration established by synthesis of the diastereoisomers by Matsumoto, Fukui & Edwards (1973). The X-ray structure of fulvine has been determined by Sussman & Wodak (1973), leaving two possible structures for crispatine, the C(13)-epimer (I) of fulvine and the C(12),C(14)-epimer which would result if the crispatic acid were incorporated the other way in the macrocyclic ring. This present X-ray study defines the stereochemistry of crispatine and provides further conformational detail in the series of hepatotoxic pyrrolizidine alkaloids.



(I)

Experimental. Crystals grown from aqueous methanol; as they proved to be unstable in air, crystal *ca* 0·39 × 0·25 × 0·37 mm sealed in a thin-walled Lindemann-glass tube. Rigaku-AFC diffractometer, Cu $K\alpha$ radiation, graphite-crystal monochromator. Cell parameters determined by least squares from 2θ values measured for 25 strong reflections. Integrated intensities recorded by an ω–2θ scan, 2θ scan rate 2° min^{-1}, scan range ($\Delta\omega$) $1{\cdot}2° + 0{\cdot}5°\tan\theta$, 10s stationary background counts. Three reference reflections monitored every 50 reflections showed no significant variation in intensity during data collection. $2\theta_{\max} = 130°$. Range of hkl: 0–6, −9–9, −11–10. 1406 non-equivalent terms, 1367 with $|F_o| > 2\sigma|F_o|$ used for structure refinement. No correction for absorption or extinction. Attempts to solve structure by direct methods not successful and structure eventually solved by vector superposition with the program of Hubbard & Jacobson (1970). Full-matrix least-squares refinement with *SHELX*76 (Sheldrick, 1976). All H-atom sites (including water molecule) located on difference maps. Refinement with anisotropic temperature factors for C, N and O atoms and isotropic for H atoms converged at $R = 0{\cdot}037$, $R_w = 0{\cdot}036$; $\sum w(|F_o| - |F_c|)^2$ minimized with weights $(\sigma^2|F_o| + 5\times10^{-5}|F_o|^2)^{-1}$. At convergence mean parameter shift-to-error ratios 0·13:1 for H and 0·06:1 for all other parameters. Largest peaks on final difference map +0·16 and −0·25 e Å^{-3}. Scattering factors for O, N and C from Cromer & Mann (1968), for H from Stewart, Davidson & Simpson (1965); anomalous-dispersion corrections made with values of Cromer & Liberman (1970).

Discussion. Final atomic coordinates are given in Table 1.* Fig. 1 which contains the atom numbering and Fig. 2 have been prepared from the output of *ORTEP* (Johnson, 1965). The molecular stereochemistry and conformation of crispatine are illustrated in Fig. 1 and torsional angles are given in Table 2. The conformation of the macrocyclic diester system is similar to that observed in the C(13)-epimer, fulvine (Sussman & Wodak, 1973), and in monocrotaline (Stoeckli-Evans, 1979; Wang, 1981) – see Table 2.

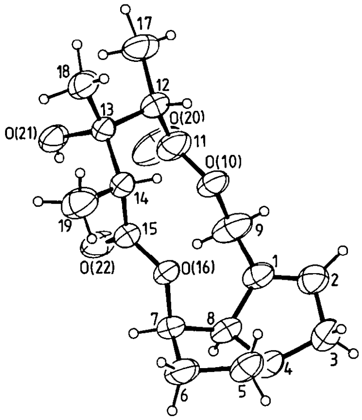


Fig. 1. Perspective view of the molecule with thermal ellipsoids scaled to 50% probability. The C atoms are denoted by numerals only.

Table 1. *Final atomic coordinates* (×10^4, *for* H ×10^3) *and isotropic temperature factors with e.s.d.'s in parentheses*

For non-H atoms $B_{eq} = 8\pi^2U_{eq} = \frac{8}{3}\pi^2\sum_i\sum_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}/B_{iso}(Å^2)
C(1)	−669 (13)	−1725 (6)	−838 (6)	3·5 (1)
C(2)	295 (13)	−2018 (6)	−1869 (6)	4·2 (2)
C(3)	−941 (13)	−3828 (6)	−2566 (6)	4·4 (2)
N(4)	−2730 (12)	−4699 (6)	−1738 (5)	3·5 (1)
C(5)	−1931 (13)	−6032 (6)	−916 (6)	4·0 (2)
C(6)	−3208 (13)	−6090 (6)	265 (6)	4·3 (2)
C(7)	−2728 (12)	−4155 (6)	674 (6)	3·4 (2)
C(8)	−2828 (12)	−3324 (6)	−719 (6)	3·3 (2)
C(9)	0	0	0	4·4 (2)
O(10)	2181 (11)	106 (6)	1160 (5)	3·7 (1)
C(11)	2594 (13)	1298 (6)	2241 (6)	4·3 (2)
C(12)	4779 (12)	1215 (6)	3392 (5)	3·7 (2)
C(13)	3922 (12)	−178 (6)	4393 (5)	3·2 (2)
C(14)	2799 (12)	−2044 (6)	3594 (6)	3·1 (2)
C(15)	214 (12)	−2371 (6)	2658 (5)	3·3 (2)
O(16)	−177 (11)	−3532 (5)	1584 (5)	3·1 (1)
C(17)	6131 (15)	3052 (8)	4159 (6)	5·2 (2)
C(18)	6159 (13)	−122 (8)	5598 (6)	4·3 (2)
C(19)	2534 (15)	−3553 (6)	4564 (6)	5·1 (2)
O(20)	1353 (13)	2270 (6)	2237 (5)	6·1 (1)
O(21)	2136 (12)	228 (6)	5043 (6)	4·0 (2)
O(22)	−1407 (11)	−1758 (6)	2855 (5)	4·3 (2)
O(*W*)	2177 (13)	2946 (6)	7085 (6)	5·6 (2)
H(2)†	165 (8)	−115 (5)	−217 (4)	4·7 (9)
H(3*a*)	29 (8)	−445 (5)	−253 (4)	5·1 (9)
H(3*b*)	−177 (7)	−363 (4)	−350 (4)	4·1 (8)
H(5*a*)	−13 (9)	−570 (5)	−62 (4)	5·1 (10)
H(5*b*)	−240 (7)	−721 (5)	−152 (4)	4·5 (8)
H(6*a*)	−240 (9)	−667 (5)	103 (4)	5·5 (10)
H(6*b*)	−514 (9)	−659 (6)	−10 (4)	6·6 (11)
H(7)	−389 (7)	−395 (5)	122 (4)	3·6 (7)
H(8)	−447 (8)	−309 (5)	−93 (4)	4·8 (9)
H(9*a*)	−150 (8)	0 (5)	38 (4)	4·4 (10)
H(9*b*)	51 (10)	101 (6)	−63 (4)	7·4 (12)
H(12)	582 (6)	82 (4)	294 (4)	3·4 (7)
H(14)	383 (6)	−212 (4)	307 (3)	2·5 (6)
H(17*a*)	485 (10)	328 (6)	468 (5)	7·3 (13)
H(17*b*)	802 (18)	321 (11)	513 (9)	15·8 (16)
H(17*c*)	654 (12)	391 (8)	354 (6)	10·0 (16)
H(18*a*)	712 (9)	121 (6)	604 (4)	5·8 (9)
H(18*b*)	557 (8)	−102 (6)	638 (4)	6·4 (11)
H(18*c*)	718 (10)	−42 (6)	543 (4)	5·4 (12)
H(19*a*)	172 (9)	−463 (6)	402 (5)	7·8 (13)
H(19*b*)	167 (11)	−328 (8)	530 (6)	10·0 (16)
H(19*c*)	427 (11)	−350 (6)	511 (5)	6·5 (11)
H(21)	120 (10)	11 (7)	461 (5)	3·5 (14)
H(*Wa*)	359 (11)	341 (7)	738 (6)	7·7 (16)
H(*Wb*)	243 (15)	250 (9)	637 (7)	10·3 (16)

† H atoms have the same numbering as the atoms to which they are bonded.

Table 2. *Torsional angles* (°) *in the macroring*

E.s.d.'s are about 0·6°. Atoms are represented by their identification number. Corresponding values for monocrotaline* and fulvine are included.

	Crispatine	Fulvine	Monocrotaline
7–8–1–9	−62·5	−60·6	−61·0
8–1–9–10	99·7	112·1	111·8
1–9–10–11	−161·4	−155·5	−157·4
9–10–11–12	176·8	172·4	175·1
10–11–12–13	−86·3	−87·0	−84·6
11–12–13–14	62·1	54·9	53·5
12–13–14–15	−74·0	−72·2	−73·9
13–14–15–16	151·4	155·4	155·4
14–15–16–7	172·4	−176·0	−177·7
15–16–7–8	105·6	110·6	113·2
16–7–8–1	−15·4	−28·6	−27·8
2–1–9–10	−88·5	−63·7	−66·4
6–7–16–15	−142·3	−138·3	−137·2

* Values calculated from the coordinates derived by Wang (1981).

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* Lists of structure amplitudes, anisotropic temperature factors, bond lengths and angles, and intermolecular contacts have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38892 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The pyrrolizidine nucleus exhibits the usual *exo*-buckling of retronecine alkaloids with a pucker angle 47·5 (6)° and an angle 123·1 (7)° between the mean planes defined by the atoms C(5), N(4), C(8), C(7) and C(1), C(2), C(3), N(4), C(8). The atoms in the latter group are coplanar to within ±0·06 (1) Å and C(9) lies within the plane. A similar situation was noted in the 11-membered macrocyclic alkaloid grantaline (Mackay & Culvenor, 1983) in which the atoms of the unsaturated ring and C(9) are coplanar to within ±0·04 (1) Å, and in fulvine and monocrotaline* the atoms are coplanar to within ±0·02 (1) and ±0·00 (1) Å respectively with C(9) lying only 0·07 (1) and 0·09 (1) Å from their associated plane. In the 12-membered macrocyclic alkaloids, however, C(9) lies significantly from the unsaturated ring plane, for example 0·25 (1) Å in both senecionine (Mackay & Culvenor, 1982) and jacobine (Pérez-Salazar, Cano & García-Blanco, 1978).

Atoms in the primary-ester group, C(9), O(10), C(11), C(12), O(20), are coplanar to within ±0·03 (1) Å. The C(9) methylene group is orientated somewhat less asymmetrically in relation to the ester plane than in fulvine; the torsional angle H(9*a*)—C(9)—O(10)—C(11) being −45 (5) and −35 (3)° respectively in the two alkaloids. The secondary-ester system at C(7) has the atoms C(7), O(16), C(15), C(14), O(22) coplanar within ±0·06 (1) Å, but the H atom at C(7) is substantially out-of-plane, the torsional angle H(7)—C(7)—O(16)—C(15) being −22 (5)°, compared with the values of −18 (3) and −13 (5)° in fulvine and monocrotaline respectively. As in the latter two compounds, the carbonyl bonds of the ester function are *syn*-parallel. The angle between the bonds is 18·9 (5)° compared with the value 15·2 (5)° in monocrotaline and 12·0 (3)° in fulvine. The intramolecular O(10)···O(16) distance 2·921 (6) Å is shorter than the values 3·040 (8) and 2·957 (5) Å in monocrotaline and fulvine respectively. Similarly, the O(10)···C(15) distance of 2·647 (7) Å is shorter than the corresponding values, 2·741 (9) Å in monocrotaline and 2·765 (7) Å in fulvine.

The hydroxyl substituent at C(13) lies on the same side of the macroring as the H atom at C(8) and the O(22) of the carbonyl group of the secondary-ester system with which it forms an intramolecular hydrogen bond; the O(21)···O(22), H(21)···O(22) and O(21)—H(21) distances are 2·708 (7), 2·22 (5) and 0·58 (5) Å, respectively and the O(21)—H(21)···O(22) angle is 143 (6)°. In both monocrotaline and fulvine the configuration at C(13) is opposite to that in crispatine so that in the two former compounds the associated hydroxyl group is directed outwards from the macroring and is involved only in an intermolecular hydrogen-bonding interaction. All bond lengths and angles are similar to those reported for comparable structures.

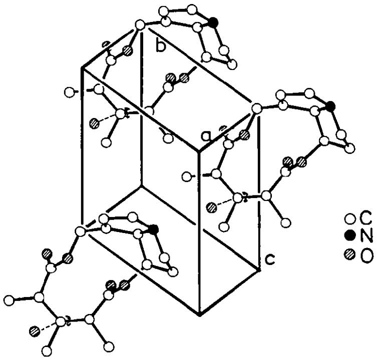

Fig. 2. The crystal packing.

The crystal packing is illustrated in Fig. 2. There is only one intermolecular hydrogen-bonding interaction. The O atom of the hydroxyl substituent is the acceptor in a hydrogen bond with the water molecule; the O(21)···O(*W*), O(21)···H(*Wb*) and O(*W*)—H(*Wb*) distances have the respective values 2·938 (8), 2·17 (5) and 0·85 (7) Å and the O(21)···H(*Wb*)—O(*W*) angle is 151 (6)°. All other intermolecular contacts are greater than 3·47 Å.

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* All numerical values refer to the more recent analysis by Wang (1981).