

The Crystal and Molecular Structure of Nitroleonurine Monohydrate

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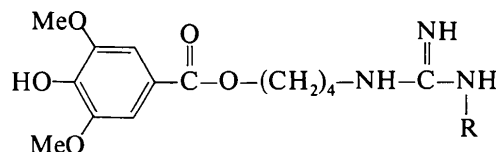
Abstract

$C_{14}H_{20}N_4O_7 \cdot H_2O$ is monoclinic, space group $P2_1/c$, with $a = 9.240$ (5), $b = 13.587$ (3), $c = 14.968$ (4) Å, $\beta = 111.41$ (2)°, $Z = 4$. The structure was solved by direct methods and refined with 2670 observed Cu $K\alpha$ diffractometer data to $R = 0.071$. The molecule assumes a flat chain-like conformation. In contrast to the planar, symmetrical structure of nitroguanidine, the nitroguanidyl moiety in the nitroleonurine molecule assumes the hitherto unobserved unsymmetric form (containing a formal imino group) and deviates significantly from exact planarity. Extensive hydrogen bonding involving both the nitroleonurine and the water molecules results in a layer structure with weak van der Waals interactions between neighbouring layers.

Introduction

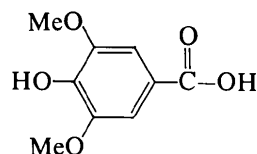
The Chinese herb I-mu Ts'ao, *Leonurus artemisia*, has been used as a drug to cure obstetrical and gynecological disorders for over two thousand years. Recently its urotropic principle has been isolated and identified as leonurine, $C_{14}H_{21}N_3O_5$ (Ia) (Yeung, Kong, Lay & Cheng, 1977). This alkaloid has previously been isolated from *Leonurus sibiricus* grown in north-east China (Kubota & Nakajima, 1930) and in Japan (Goto, Kato, Hirata & Hayashi, 1962), and shown from chemical and spectroscopic evidence to be an acylguanidino derivative of syringic acid (II) and 4-guanidino-1-butanol (III) (Sugiura, Inoue, Hayashi, Kishi & Goto, 1969).

It has been suggested that (Ia) exists as a zwitterion since its pK_a' value of 7.9 is lower than that of a normal phenol group (Sugiura *et al.*, 1969). Our initial attempt to verify this by X-ray crystallography proved unsuccessful due to difficulty in growing good crystals of (Ia). In the present work, we determined the structure of its *N*-nitro derivative (Ib), which crystallizes as the monohydrate. Introduction of the electron-withdrawing nitro group is expected to alter the electronic properties of the strongly basic guanidino

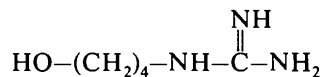


(Ia) R = H

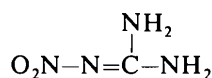
(Ib) R = NO₂



(II)



(III)



(IVa)



(IVb)

group, and possibly the conformation of the leonurine molecule. Nevertheless, we hope to confirm the correctness of the leonurine molecular skeleton and elucidate the role played by the water molecule in crystal packing. Furthermore, the precise location of the H atoms in the terminal nitroguanidyl moiety is of interest since nitroguanidine has been shown to exist in the symmetrical form (IVa) rather than the unsymmetrical form (IVb) (Bryden, Burkardt, Hughes & Donohue, 1956).

Experimental

Nitroleonurine was synthesized by condensation of 4-ethoxycarbonylsyringic acid chloride with 4-(*N*-nitro)guanidino-1-butanol (Sugiura *et al.*, 1969). Samples

suitable for diffraction study were recrystallized from aqueous methanol as colourless prisms elongated along [010], m.p. 405 K (with decomposition).

Crystal data

$C_{14}H_{20}N_4O_7 \cdot H_2O$, $M_r = 374.36$, monoclinic, space group $P2_1/c$, $a = 9.240(5)$, $b = 13.587(3)$, $c = 14.968(4)$ Å, $\beta = 111.41(2)^\circ$, $V = 1749.5$ Å³, $Z = 4$, $D_m = 1.43(1)$ (by flotation in hexane/ CCl_4), $D_x = 1.421$ Mg m⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 1.016$ mm⁻¹.

A crystal of dimensions $0.29 \times 0.54 \times 0.45$ mm was chosen for data collection and the intensities of all reflections having $2\theta(\text{Cu } K\alpha) \leq 132^\circ$ were measured on an automated four-circle diffractometer with Ni-filtered Cu $K\alpha$ radiation using the $2\theta-\theta$ scan technique. The intensities were corrected for background, and Lorentz and polarization corrections were applied; 3070 unique reflections were measured, of which 2670 had $I > 3\sigma(I)$ and were considered to be observed.

Structure determination

The structure determination was not accomplished routinely. The normalized structure amplitudes, $|E|$, for reflections $0k0$, $k = 4n$, were very large ($040 = 7.31$, $080 = 6.22$, $0,12,0 = 4.79$, $0,16,0 = 4.28$), indicating that most or all of the molecule lay on the plane $y = \frac{1}{8}$, and that these reflections would dominate direct phasing attempts. Accordingly, they were omitted from subsequent phase-determining procedures. The 244 planes with $|E| > 1.70$ were input to the program *MULTAN* (Germain, Main & Woolfson, 1971) and eight sets of phases were produced from a starting set of three origin-determining and three arbitrary reflections. The reliability criteria for and discrimination between the sets were not very good: $R(\text{Karle})$ ranged from 37.3 to 42.3% and the figure-of-merit from 0.94 to 1.06 with several solutions having similar indices. E maps produced for the best two sets showed possible molecular fragments but failed to refine.

The probable positioning of the molecule at $y = \frac{1}{8}$ suggested that overlapping vectors in the Patterson distribution could be a contributing cause to the poor results with direct phasing methods. An $E^2 - 1$ Patterson map confirmed this, exhibiting a concentration of peaks on the $y = 0, 0.25$ and 0.50 sections, and virtually nothing elsewhere. We attempted to overcome this by modifying the $|E|$'s by the method of Nixon (1978); the procedure we followed was to reduce the sizes of the overlapping peaks in an E^2 Patterson distribution and Fourier transform to obtain modified $|E|$ values. The set of 244 reflections originally

used for direct phasing, now with modified $|E|$'s, were again input to *MULTAN*; a starting set of six reflections, three of which were contained in the original starting set, produced eight solution sets of which one had clearly superior indices of merit [$R(\text{Karle}) = 26.3\%$ (next best = 29.2), figure-of-merit = 1.22 (1.20)]. An E map based on these 244 phased E 's revealed positions of 21 of the 26 non-hydrogen atoms of nitroleonurine monohydrate, all lying at approximately $y = 0.125$. (That the successful solution was due to the modified $|E|$'s and not to the altered set of starting reflections was verified by recalculating phase sets using the new starting reflections and the unmodified $|E|$'s; no improvement in indices-of-merit or discrimination between sets occurred.)

The remaining five heavy atoms were found on a difference Fourier map and least-squares refinement resulted in $R = 0.17$ (isotropic), and $R = 0.105$ (anisotropic). Difference electron density maps revealed the positions of the 22 H atoms and further refinement of the non-hydrogen atom parameters led to convergence at $R = 0.071$. Statistical counter weights, $w = 1/\sigma^2$, were used; the final $[\sum w(|F_o| - |F_c|)^2 / (m - n)]^{1/2} = 1.07$, and the final maximum shift/error = 0.05. The atomic scattering factors were taken from Cromer & Mann (1968), and from Stewart, Davidson & Simpson (1965) for H. The positional parameters and equivalent isotropic temperature factors for the non-hydrogen

Table 1. *Final atomic coordinates* ($\times 10^4$) *with e.s.d.'s in parentheses, and equivalent isotropic thermal parameters* [$B_{\text{eq}} = (B_{11} + B_{22} + B_{33})/3$]

	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq} (Å ²)
C(1)	8003 (3)	1256 (2)	6609 (2)	2.5
C(2)	8440 (3)	1281 (2)	5817 (2)	2.6
C(3)	7338 (3)	1290 (2)	4898 (2)	2.9
C(4)	5767 (3)	1278 (1)	4772 (2)	2.4
C(5)	5301 (3)	1246 (2)	5554 (2)	2.5
C(6)	6414 (3)	1235 (1)	6467 (2)	2.5
C(7)	4645 (3)	1285 (2)	3770 (2)	2.8
C(8)	2029 (3)	1259 (2)	2724 (2)	2.9
C(9)	419 (3)	1228 (2)	2776 (2)	2.9
C(10)	-774 (3)	1183 (2)	1746 (2)	3.0
C(11)	-2446 (3)	1186 (2)	1719 (2)	2.9
C(12)	-5046 (3)	1221 (1)	439 (2)	2.6
C(13)	10558 (4)	1472 (3)	5280 (3)	5.8
C(14)	4551 (3)	1220 (2)	7235 (2)	4.1
N(1)	-3506 (3)	1216 (1)	714 (2)	3.0
N(2)	-5732 (3)	1177 (2)	1067 (2)	3.9
N(3)	-5760 (2)	1266 (1)	-538 (2)	2.8
N(4)	-7292 (2)	1318 (1)	-921 (2)	2.9
O(1)	9019 (2)	1259 (1)	7525 (1)	3.2
O(2)	10022 (2)	1300 (1)	6036 (1)	3.5
O(3)	6130 (2)	1209 (1)	7294 (1)	3.9
O(4)	5032 (2)	1276 (1)	3077 (1)	4.2
O(5)	3158 (2)	1291 (1)	3698 (1)	2.9
O(6)	-7851 (2)	1331 (1)	-1815 (1)	3.4
O(7)	-8174 (2)	1356 (2)	-465 (2)	5.3
O(8)	8210 (4)	1079 (3)	9320 (2)	8.3

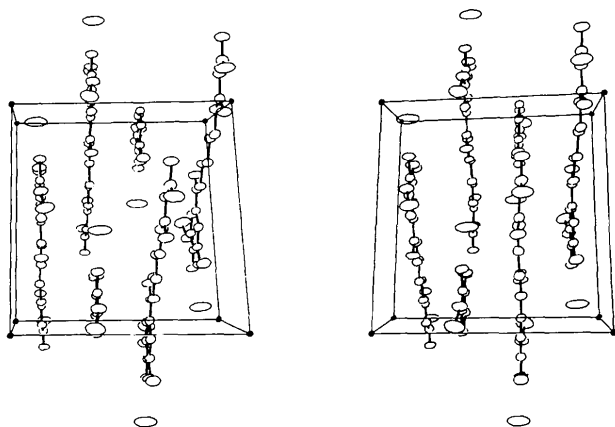


Fig. 3. Stereodrawing showing the molecular packing viewed down a toward the origin of the unit cell at the lower left corner. The b and c axes point to the right and upward respectively. Hydrogen atoms have been omitted for clarity.

connected by O—H...O and N—H...O hydrogen bonds to form layers normal to b (Table 2, Fig. 1). The scheme makes use of all available protons except that bonded to N(3), which is not within hydrogen-bonding range of any negative polar group. Neighbouring layers are related by the c glide, alternate layers are related by the 2_1 screw axis, and the interlayer van der Waals separation is $b/4 = 3.40 \text{ \AA}$ (Fig. 3).

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