Acta Cryst. (1979). B35, 3004-3007

# The Crystal and Molecular Structure of Nitroleonurine Monohydrate

By Norman Camerman and Lilian Y. Y. Chan

Department of Biochemistry, University of Toronto, Toronto, Canada M5S 1A8

AND H. W. YEUNG AND THOMAS C. W. MAK

Science Center, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

(Received 5 June 1979; accepted 7 August 1979)

#### Abstract

 $C_{14}H_{20}N_4O_7$ .  $H_2O$  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 4guanidino-1-butanol (III) (Sugiura, Inoue, Hayashi, Kishi & Goto, 1969).

It has been suggested that (Ia) exists as a zwitterion since its pKa' 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 electronwithdrawing nitro group is expected to alter the electronic properties of the strongly basic guanidino 0567-7408/79/123004-04\$01.00



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 (IV*a*) rather than the unsymmetrical form (IV*b*) (Bryden, Burkardt, Hughes & Donohue, 1956).

## Experimental

Nitroleonurine was synthesized by condensation of 4ethoxycarbonylsyringic acid chloride with 4-(*N*-nitro)guanidino-1-butanol (Sugiura *et al.*, 1969). Samples © 1979 International Union of Crystallography suitable for diffraction study were recrystallized from aqueous methanol as colourless prisms elongated along [010], m.p. 405 K (with decomposition).

## Crystal data

 $C_{14}H_{20}N_4O_7 H_2O$ ,  $M_r = 374.36$ , monoclinic, space group  $P2_1/c$ , a = 9.240 (5), b = 13.587 (3), c = 14.968 (4) Å,  $\beta = 111.41$  (2)°, V = 1749.5 Å<sup>3</sup>, Z = 4,  $D_m = 1.43$  (1) (by flotation in hexane/CCl<sub>4</sub>),  $D_x = 1.421$  Mg m<sup>-3</sup>,  $\lambda$ (Cu Ka) = 1.5418 Å,  $\mu = 1.016$  mm<sup>-1</sup>.

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  $2\theta(\operatorname{Cu} K\alpha) \leq 132^\circ$  were measured on an automated four-circle diffractometer with Nifiltered 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 = $7.31,\ 0.80 = 6.22,\ 0.12.0 = 4.79,\ 0.16.0 = 4.28),$ 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(Karle) ranged from 37.3 to 42.3% and the figure-ofmerit 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(Karle) = $26\cdot3\%$  (next best =  $29\cdot2$ ), figure-of-merit =  $1\cdot22$  $(1\cdot20)$ ]. 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  $y = 0\cdot125$ . (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

Tat	ole	1.	Final	atomic	coordinates	$(\times 10^4)$ wi	th e.s.d.'s	
in	ра	irei	ntheses	s, and	equivalent	isotropic	thermal	
parameters $[B_{eq} = (B_{11} + B_{22} + B_{33})/3]$								

	x	у	z	$B_{eq}$ (Å <sup>2</sup> )
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

atoms are given in Table 1.\* The thermal motion of the molecule is strongly anisotropic, with  $B_{22}$  much larger than the other components for most of the atoms.

# Discussion

The molecular structure, conformation, and hydrogenbonding network in nitroleonurine are shown in Fig. 1. The present analysis confirms the structural assignment of leonurine (Ia) by previous workers. In the nitroleonurine molecule (Ib), atoms N(1), N(2) and N(3) all have H atoms bonded to them (Fig. 1). The nitroguanidyl group thus corresponds to the hitherto unobserved unsymmetric form (IVb) of nitroguanidine. Unlike planar, symmetrical nitroguanidine (IVa) (Bryden *et al.*, 1956), the nitroguanidyl group deviates significantly from exact planarity. The normals

\* Lists of structure factors, anisotropic temperature factors, and hydrogen atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34718 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.



Fig. 1. The atom numbering, conformational structure, and hydrogen bonding in nitroleonurine monohydrate. Superscripts refer to the equivalent positions given in Table 2.

to mean planes through the two sets of atoms (i) C(12), N(1), N(2) and (ii) N(3), N(4), O(6), O(7) make an angle of  $4 \cdot 3^{\circ}$ . In nitroguanidine, cyanoguanidine (Hope & Kim, 1971), and a variety of compounds containing the protonated guanidyl group (Bhat & Vijayan, 1977, and references therein), the three C-Ndistances are virtually identical and lie in the range 1.34-1.35 Å. In the present uncharged structure, C(12)-N(3) is significantly longer than C(12)-N(1)and C(12)-N(2), which are not significantly different despite the fact that N(2) is formally shown as an imino N atom in structural formula (Ib) (Fig. 2). The N(3)-N(4) bond is short compared to the corresponding length in symmetrical nitroguanidine, and the two N-O distances are indistinguishable. These results indicate that atom sets (i) and (ii) constituting the nitroguanidyl group behave as separate  $\pi$  systems with only weak conjugation across the C(12)-N(3) bond. The dimensions of the remaining portion of the nitroleonurine molecule are normal.

The nitroleonurine molecule adopts an extended, flat configuration; the two largest deviations from a least-squares plane through all 25 non-hydrogen atoms are +0.13 Å for C(10) and -0.21 Å for C(13). The water molecule, which undoubtedly plays a prominent role in determining the observed conformation of nitroleonurine, lies only 0.15 Å from this mean plane. In the crystal packing both types of molecules are inter-

## Table 2. Hydrogen-bond distances (Å) and angles (°)

H atom parameters were not refined; no e.s.d.'s are available.

D	Н	A	X	D–H	H <i>A</i>	$D \cdots A$	<i>D−</i> - H…A	H <i>A</i> -X
O(1)	H(1)	${{ m O}(6)^i} \ {{ m O}(3)} \ {{ m O}(8)^{ii}} \ {{ m O}(4)^{iii}}$	N(4)	0.967	1.835	2.695	146·5	122.6
O(8)	H(3)		C(6)	0.980	1.976	2.943	168·4	129.8
N(1)	H(14)		H(2)	1.010	2.044	3.050	176·1	120.3
N(2)	H(15)		C(7)	0.960	1.921	2.831	157·4	158.0

Superscripts refer to the following symmetry-related positions:

(i) 
$$2 + x, y, 1 + z;$$
 (ii)  $-1 + x, y, -1 + z;$  (iii)  $-1 + x, y, z;$   
(iv)  $1 + x, y, z;$  (v)  $1 + x, y, 1 + z;$  (vi)  $-2 + x, y, -1 + z.$ 



Fig. 2. Bond lengths (Å) and angles (°) in nitroleonurine. Standard deviations are 0.004 Å and  $0.2^{\circ}$ .



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  $O-H\cdots O$  and  $N-H\cdots O$  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 Å (Fig. 3). We thank Dr P. E. Nixon for furnishing us with his program for removing overlapping vectors from Patterson distributions. Support in Toronto was from the Medical Research Council of Canada.

#### References

- BHAT, T. N. & VUAYAN, M. (1977). Acta Cryst. B33, 1754– 1759.
- BRYDEN, J. H., BURKARDT, L. A., HUGHES, E. W. & DONOHUE, J. (1956). Acta Cryst. 9, 573-578.
- CROMER, D. T. & MANN, J. B. (1968). Acta Cryst. A24, 321–324.
- GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). Acta Cryst. A27, 368-376.
- GOTO, T., KATO, N., HIRATA, Y. & HAYASHI, Y. (1962). Tetrahedron Lett. pp. 545-548.
- HOPE, H. & KIM, N. E. (1971). Am. Crystallogr. Assoc. Winter Meet. Abstr. 22.
- Кивота, S. & Nакалма, S. (1930). Nippon Yakubutsugaku Zasshi, 11, 153–158.
- NIXON, P. E. (1978). Acta Cryst. A34, 450-453.
- STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). J. Chem. Phys. 42, 3175–3187.
- SUGIURA, S., INOUE, S., HAYASHI, Y., KISHI, Y. & GOTO, T. (1969). Tetrahedron, 25, 5155–5161.
- YEUNG, H. W., KONG, Y. C., LAY, W. P. & CHENG, K. F. (1977). Planta Med. 31, 51-56.