Acta Cryst. (1989). C45, 1942–1944

Methyl 2-[4-(2-Chloroethyl)-2,3-dihydro-7-nitroquinoxalin-1-yl]benzoate from Intramolecular Cyclization of a Nitroaromatic Mustard

BY JOHN S. BUCKLETON AND GEORGE R. CLARK*

Department of Chemistry, The University of Auckland, Auckland, New Zealand

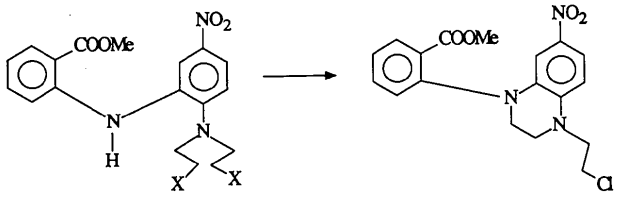
AND DAVID CHAMBERS AND WILLIAM A. DENNY

Cancer Research Laboratory, The University of Auckland School of Medicine, Auckland, New Zealand

(*Received* 2 *December* 1988; *accepted* 10 *April* 1989)

Abstract. $C_{18}H_{18}ClN_3O_4$, $M_r = 375{\cdot}81$, orthorhombic, $P2_12_12_1$, $a = 11{\cdot}000\ (3)$, $b = 8{\cdot}023\ (2)$, $c = 19{\cdot}316\ (5)$ Å, $V = 1704{\cdot}68$ Å^3, $Z = 4$, $D_m = 1{\cdot}46\ (1)$, $D_x = 1{\cdot}417$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 1{\cdot}82$ cm^{-1}, $F(000) = 760$, $T = 293\ (1)$ K, $R = 0{\cdot}051$ for 985 $[I > 2{\cdot}5\sigma(I)]$ reflections. X-ray analysis confirms that the nitroaromatic mustard methyl *N*-{2-[bis(2-chloroethyl)amino]-5-nitrophenyl}anthranilate undergoes rapid intramolecular cyclization, but the product is the 7-nitro rather than the 6-nitro derivative previously reported [Chambers & Denny (1986). *J. Chem. Soc. Perkin Trans.* 1, pp. 1055–1060].

Introduction. Nitroaromatic mustards are of interest as possible hypoxia-selective anticancer drugs since reduction of the nitro group in hypoxic tumour tissue will selectively activate the mustard by electron release (Denny & Wilson, 1986). During the synthesis of compounds of this type the diphenylamine diol (1) was prepared, as a precursor of the mustard (2). However, following treatment of the diol (1) with a number of reagents the mustard (2) could not be isolated, owing to its rapid intramolecular cyclization to the dihydroquinazoline (3) (Chambers & Denny, 1986). To confirm this reaction, the crystal structure of the corresponding acid was determined by X-ray crystallography, and is shown to be methyl 2-[4-(2-chloroethyl)-2,3-dihydro-7-nitroquinoxalin-1-yl]benzoate.



(1) X = OH
(2) X = Cl

(3)

* To whom correspondence should be addressed.

0108-2701/89/121942-03$03.00

Experimental. Crystals were prepared from ethyl acetate/acetone. Density measured by flotation in aqueous KI. Diffractometer crystal 0·35 × 0·32 × 0·14 mm mounted on Nonius CAD-4 diffractometer; Zr-filtered Mo $K\alpha$ radiation; unit-cell dimensions from 25 reflections, $10{\cdot}0 < \theta < 12{\cdot}2°$; systematic absences $h00$, $h \neq 2n$; $0k0$, $k \neq 2n$; $00l$, $l \neq 2n$ defined space group as $P2_12_12_1$; 1910 unique reflections, $2 \leq \theta \leq 27°$, $[(\sin\theta)/\lambda]_{max}$ 0·6388 Å^{-1}; 985 with $I > 2{\cdot}5\sigma(I)$, $0 \leq h \leq 14$, $0 \leq k \leq 10$, $0 \leq l \leq 24$; three intensity standards checked every 100 reflections showed no non-statistical variation during X-ray exposure; Lorentz and polarization corrections applied, absorption corrections by empirical ψ scan data, max. and min. correction factors 0·8975 and 0·7759 respectively. The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1986), H atoms in calculated positions (C—H 1·0 Å). F_{obs} refinement of atomic positions and anisotropic temperature factors, scale factor and weighting parameter; $w = 2{\cdot}4439/[\sigma^2(F) + gF^2]$, $g = 1{\cdot}50 \times 10^{-4}$; $R = 0{\cdot}051$, $wR = 0{\cdot}048$, $(\Delta/\sigma)_{max} = 0{\cdot}14$ for positions; max. $\Delta\rho$ excursion in final difference map 0·33 e Å^{-3}; atomic scattering factors from *International Tables for X-ray Crystallography* (1974). Calculations performed with the Enraf–Nonius (1981) *Structure Determination Package* on a PDP-11 computer for initial data reduction and with *SHELX*76 (Sheldrick, 1976), on the University of Auckland IBM 4341 computer for refinement. Diagrams were produced using *ORTEP* (Johnson, 1965).

Discussion. Atomic positions and isotropic (or equivalent isotropic) thermal parameters are given in Table 1.† The molecular geometry and atomic numbering are depicted in Fig. 1. The X-ray analysis

† Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52048 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Non-H-atom coordinates* ($\times 10^4$), *isotropic thermal parameters* ($Å^2 \times 10^3$) *and equivalent isotropic temperature factors* ($Å^2$)

	x	y	z	U	B_{eq}*
Cl	3909 (3)	1178 (3)	9707 (1)		9·1 (2)
O(1''a)	−1291 (5)	6863 (7)	8552 (3)		4·7 (3)
O(1''b)	368 (5)	5255 (7)	8605 (3)		5·3 (2)
O(7a)	2857 (5)	5955 (8)	6247 (3)		4·4 (3)
O(7b)	3929 (6)	3687 (8)	6143 (3)		5·7 (4)
N(1)	2580 (5)	7003 (8)	8784 (3)		3·2 (4)
N(4)	4318 (5)	4962 (7)	9352 (3)		3·2 (3)
N(7)	3475 (6)	4803 (10)	6498 (3)		3·7 (4)
C(1')	579 (7)	8212 (8)	8461 (4)		2·6 (3)
C(1'')	−83 (8)	6617 (11)	8551 (4)		3·9 (4)
C(1''')	5258 (7)	3993 (10)	9709 (4)	47 (2)	
C(1'''')	−2038 (8)	5385 (12)	8581 (5)	67 (3)	
C(2)	2492 (7)	6563 (11)	9508 (4)	55 (2)	
C(2')	1830 (7)	8323 (9)	8525 (4)		2·9 (3)
C(2''')	4748 (8)	2645 (10)	10171 (4)	57 (2)	
C(3)	3716 (7)	6207 (10)	9781 (4)	52 (2)	
C(3')	2400 (7)	9818 (10)	8373 (4)	47 (2)	
C(4a)	4095 (6)	4854 (8)	8656 (4)		2·6 (3)
C(4')	1742 (6)	11227 (10)	8180 (4)	47 (2)	
C(5)	4685 (6)	3720 (9)	8222 (3)	39 (2)	
C(5')	491 (7)	11119 (10)	8137 (4)	48 (2)	
C(6)	4472 (6)	3693 (10)	7519 (4)	44 (2)	
C(6')	−75 (7)	9631 (9)	8265 (4)	42 (2)	
C(7)	3660 (6)	4806 (9)	7234 (3)		2·7 (3)
C(8)	3012 (6)	5903 (9)	7650 (3)	31 (2)	
C(8a)	3213 (6)	5953 (9)	8362 (4)		2·6 (3)

* Temperature factors of anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as $B_{eq} = \frac{8}{3}\pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

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

Cl—C(2''')	1·743 (8)	C(1')—C(2')	1·384 (9)
O(1''a)—C(1'')	1·343 (9)	C(1')—C(6')	1·400 (9)
O(1''a)—C(1'''')	1·444 (9)	C(1''')—C(2''')	1·511 (10)
O(1''b)—C(1'')	1·205 (9)	C(2)—C(3)	1·474 (10)
O(7a)—N(7)	1·246 (8)	C(2')—C(3')	1·386 (10)
O(7b)—N(7)	1·234 (8)	C(3')—C(4')	1·394 (10)
N(1)—C(2)	1·445 (9)	C(4a)—C(5)	1·398 (9)
N(1)—C(2')	1·432 (9)	C(4a)—C(8a)	1·429 (9)
N(1)—C(8a)	1·363 (8)	C(4')—C(5')	1·381 (9)
N(4)—C(1''')	1·465 (9)	C(5)—C(6)	1·379 (9)
N(4)—C(3)	1·457 (9)	C(5')—C(6')	1·369 (10)
N(4)—C(4a)	1·369 (8)	C(6)—C(7)	1·377 (9)
N(7)—C(7)	1·436 (9)	C(7)—C(8)	1·388 (9)
C(1')—C(1'')	1·483 (10)	C(8)—C(8a)	1·392 (9)
C(1'')—O(1''a)—C(1'''')	116·3 (7)	C(1')—C(2')—C(3')	119·1 (7)
C(2)—N(1)—C(2')	118·6 (6)	Cl—C(2''')—C(1''')	112·1 (6)
C(2)—N(1)—C(8a)	117·6 (6)	N(4)—C(3)—C(2)	110·2 (7)
C(2')—N(1)—C(8a)	122·8 (6)	C(2')—C(3')—C(4')	121·6 (7)
C(1''')—N(4)—C(3)	114·6 (6)	N(4)—C(4a)—C(5)	123·2 (6)
C(1''')—N(4)—C(4a)	123·7 (6)	N(4)—C(4a)—C(8a)	118·3 (6)
C(3)—N(4)—C(4a)	121·3 (6)	C(5)—C(4a)—C(8a)	118·6 (7)
O(7a)—N(7)—O(7b)	122·9 (7)	C(3')—C(4')—C(5')	118·9 (8)
O(7a)—N(7)—C(7)	117·5 (7)	C(4a)—C(5)—C(6)	121·5 (7)
O(7b)—N(7)—C(7)	119·6 (7)	C(4')—C(5')—C(6')	119·8 (8)
C(1'')—C(1')—C(2')	122·2 (7)	C(5)—C(6)—C(7)	119·6 (7)
C(1'')—C(1')—C(6')	118·8 (7)	C(1')—C(6')—C(5')	121·6 (7)
C(2')—C(1')—C(6')	118·9 (7)	N(7)—C(7)—C(6)	119·1 (7)
O(1''a)—C(1'')—O(1''b)	122·7 (8)	N(7)—C(7)—C(8)	120·1 (7)
O(1''a)—C(1'')—C(1')	111·1 (7)	C(6)—C(7)—C(8)	120·8 (6)
O(1''b)—C(1'')—C(1')	126·2 (8)	C(7)—C(8)—C(8a)	120·6 (7)
N(4)—C(1''')—C(2''')	113·3 (6)	N(1)—C(8a)—C(4a)	119·3 (6)
N(1)—C(2)—C(3)	109·4 (7)	N(1)—C(8a)—C(8)	121·9 (6)
N(1)—C(2')—C(1')	123·8 (7)	C(4a)—C(8a)—C(8)	118·8 (7)
N(1)—C(2')—C(3')	116·9 (7)		

confirms that the nitroaromatic mustard (2) has cyclized to the dihydroquinazoline (3), but also shows that the product is the 7-nitro derivative in contradiction to the previously proposed skeleton containing a 6-nitro substituent (Chambers & Denny, 1986). Bond distances and angles for the non-H atoms are given in Table 2.

The crystals contain discrete molecules occupying general positions. The structure adopted appears to represent a compromise between steric effects and inductive electron withdrawal by the nitro group. Each aromatic ring is planar, as are the bonds at N(1) and N(4). The two ring systems make an angle of 90·2° indicating that there is no extended conjugation between the rings, nor between N(1) and the single ring. The bonds N(1)—C(8a) 1·363 (8) and N(4)—C(4a) 1·369 Å are shorter than the corresponding bonds in those comparable compounds which contain 1,2-dinitrogen heterocycles fused to an aromatic ring; however, none of these other examples contains a nitro substituent. Several angles are distorted from ideal values, and we note in particular that the angle C(1''')—N(4)—C(4a) is 123·7 (6)° whereas C(1''')—N(4)—C(3) is 114·6 (6)°. This difference presumably allows for an otherwise very close approach between H atoms on C(1''') and C(5).

The molecules pack into the unit cell in the manner shown in Fig. 2. There are no hydrogen-

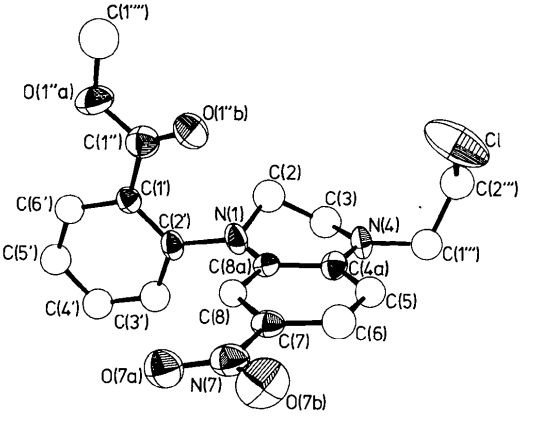


Fig. 1. Molecular geometry and atomic numbering. H atoms are numbered according to the atoms to which they are attached. Anisotropic ellipsoids represent 50% probability boundaries.

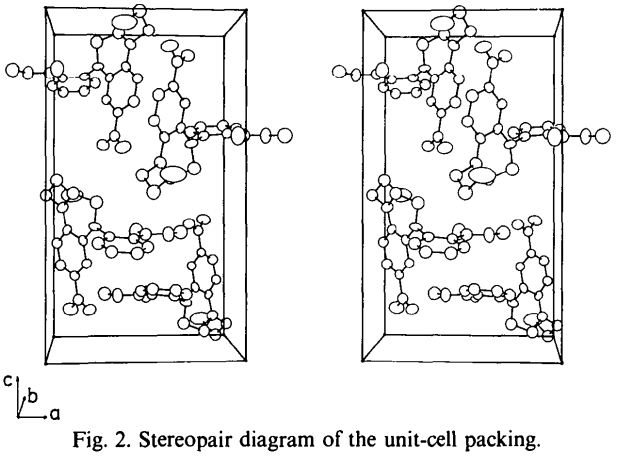


Fig. 2. Stereopair diagram of the unit-cell packing.

bonding interactions. The packing is spatially efficient, since there are five intermolecular contacts within the range 3·30–3·39 Å.

References

CHAMBERS, D. & DENNY, W. A. (1986). *J. Chem. Soc. Perkin Trans.* 1, pp. 1055–1060. (Note the acid 18a in this paper is incorrectly named as a 6-, and not a 7-nitroquinoxaline.)

DENNY, W. A. & WILSON, W. R. (1986). *J. Med. Chem.* **29**, 879–887.

Enraf–Nonius (1981). *Structure Determination Package* . Enraf–Nonius, Delft, The Netherlands.

International Tables for X-ray Crystallography (1974). Vol. IV, pp. 99, 149. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

SHELDRICK, G. M. (1986). *SHELXS86*. Program for crystal structure determination. Univ. of Göttingen, Federal Republic of Germany.

Acta Cryst. (1989). C**45**, 1944–1948

Structure of *cyclo*(-L-Prolylglycyl-)$_2$ Trihydrate

BY G. SHOHAM

Department of Inorganic and Analytical Chemistry, The Hebrew University of Jerusalem, Jerusalem, 94013 Israel

S. K. BURLEY

Gibbs Chemical Laboratory, Department of Chemistry, Harvard University, Cambridge, MA 02138, *USA and Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA* 02115, *USA*

AND W. N. LIPSCOMB*

Gibbs Chemical Laboratory, Department of Chemistry, Harvard University, Cambridge, MA 02138, *USA*

(*Received* 23 *December* 1988; *accepted* 31 *March* 1989)

Abstract. $(C_{14}H_{20}N_4O_4)_2.3H_2O$, $M_r = 670{\cdot}721$, monoclinic, $P2_1$, $a = 7{\cdot}353$ (2), $b = 21{\cdot}921$ (7), $c = 9{\cdot}878$ (2) Å, $\beta = 96{\cdot}77$ (2)°, $V = 1581{\cdot}1$ (1) Å^3, $Z = 2$, $D_x = 1{\cdot}409$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 8{\cdot}22$ cm^{-1}, $F(000) = 716$, $T = 293$ K, $R = 0{\cdot}034$ for 2456 unique observed reflections. The two independent copies of the tetrapeptide found in the asymmetric unit have similar structures, which are both consistent with the results of NMR studies of *cyclo*-(-L-Pro-Gly-)$_2$ in solution. The structures are asymmetric and have a *trans–cis–trans–cis* peptide backbone, in which the two L-Pro-Gly peptide bonds are *trans* and the two Gly-L-Pro peptide bonds are *cis*. A detailed comparison with other cyclic tetrapeptides is given, and a brief comparison with the results of single-crystal X-ray structures of other cyclic oligopeptides containing L-proline alternating with glycine is presented.

Introduction. The amino acids L-proline and glycine are known to play central roles in determining protein secondary structure, and there has been considerable interest in oligopeptides bearing these two residues. Of particular note are cyclic peptides composed of L-proline alternating with glycine, and single-crystal structures of *c*(*cyclo*)(-L-Pro-Gly-) (Von Dreele, 1975). *c*(-L-Pro-Gly-)$_3$ (Kartha, Varughese & Aimoto, 1982) and *c*(-L-Pro-Gly-)$_4$ (Chiu, Brown & Lipscomb, 1977) have been described. We report here a crystal structure containing the cyclic tetrapeptide *c*(-L-Pro-Gly-)$_2$ in two crystallographically independent environments. Both molecules resemble the conformation detected in solution by NMR (Deber, Fossel & Blout, 1974). The structural parameters are compared with those obtained from studies of other cyclic tetrapeptides, and of cyclic hexa- and octapeptides that are composed of L-proline alternating with glycine.

Experimental. Asymmetric crystal from slow evaporation from an equivolume solution of H_2O and dioxane, 0·5 × 0·5 × 1·0 mm, Nicolet $P2_1$ diffractometer, graphite monochromator, Cu $K\alpha$ radiation, $\theta/2\theta$ method, $\sin\theta/\lambda < 0{\cdot}56169$ Å^{-1}, lattice parameters determined from 2θ values of 50 reflections (25 Friedel pairs) with $30 < 2\theta < 50°$, empirical absorption correction (range 1·00 to 0·78) (North, Phillips & Mathews, 1968), h −8 to 8, k 0 to 24, l 0 to 11,

* Address correspondence to this author.

0108-2701/89/121944-05$03.00