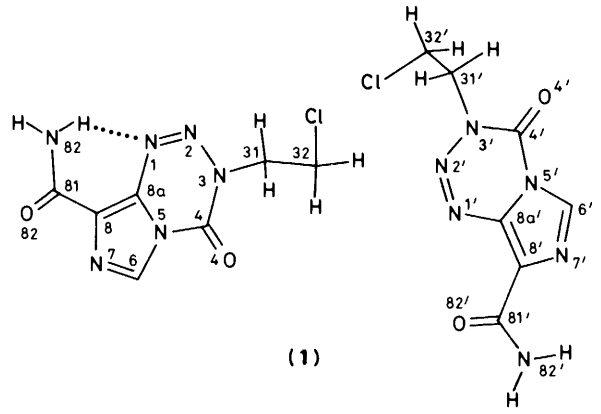
Antitumour Imidazotetrazines. Part 5.[1] Crystal and Molecular Structure of 8-Carbamoyl-3-(2-chloroethyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one (Mitozolomide)†

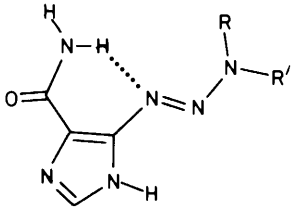
Philip R. Lowe, Carl H. Schwalbe,* and Malcolm F. G. Stevens
Department of Pharmaceutical Sciences, University of Aston in Birmingham, Birmingham B4 7ET

The structure of the novel bicyclic antitumour agent 8-carbamoyl-3-(2-chloroethyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one (Mitozolomide) has been investigated by single-crystal *X*-ray diffraction methods. The compound crystallizes in the triclinic space group $P\bar{1}$ in a cell of dimensions a = 7.003(4), b = 8.680(4), c = 16.041(9) Å, α = 93.76(5), β = 93.99(5), γ = 92.08(7)° with Z = 4. The structure was solved by direct methods and refined using full-matrix least-squares calculations, which at convergence produced a final R index of 0.052 for the 3 244 observed data. The two independent molecules per asymmetric unit are rotamers about the C(8)–C(81) and C(8)'–C(81)' bonds, the orientation of the carbamoyl group in one rotamer facilitating an intramolecular hydrogen bond of the type N–H • • • N. With the exception of the chloroethyl side chain, both molecules are approximately planar and intermolecular hydrogen bonds hold groups of four molecules together around the centre of symmetry.

The new antitumour compound 8-carbamoyl-3-(2-chloroethyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one (**1**; Mitozolomide)‡ is a derivative of a new bicyclic ring-system[2] and entered Phase I clinical trial in 1983. The potent broad-spectrum antitumour activity of (**1**) in experimental systems[2,3] is markedly superior to that of the structurally related triazene 5-(3,3-dimethyltriazen-1-yl)imidazole-4-carboxamide (**2**; DTIC),[4] which is used clinically as a single agent for the treatment of malignant melanoma,[5,6] and in combination regimes against soft tissue sarcomas[7] and Hodgkin's disease.[8] The consensus of views on the mode of action of DTIC and of the family of 1-aryl-3,3-dialkyltriazenes[9] favours the metabolic activation hypothesis and implicates the monomethyltriazene (**3**; MTIC) as the bioactive species.[10] Two related imidazoles are worthy of note: the bis(chloroethyl)triazene (**4**; BCTIC), which has potent activity against the L-1210 leukaemia in mice,[11] proved disappointing in the clinic;[12] and the monochloroethyltriazene (**5**; MCTIC) is too unstable to be a realistic clinical candidate although it demonstrates good antitumour activity in animal systems.[13] Preliminary chemical[2] evidence points to the new bicycle (**1**) being a stable pro-drug modification of MCTIC since the latter species can be isolated from solutions of (**1**) decomposing in aqueous sodium carbonate. Moreover, the biochemical effects of (**1**) in *in vivo* and *in vitro* systems closely parallel those of MCTIC.[14,15]



(**1**)



(**2**) R = R' = Me (DTIC)
(**3**) R = H, R' = Me (MTIC)
(**4**) R = R' = CH_2CH_2Cl (BCTIC)
(**5**) R = H, R' = CH_2CH_2Cl (MCTIC)

The original specimen of (**1**) synthesized by interaction of 5-diazoimidazole-4-carboxamide and 2-chloroethyl isocyanate in dichloromethane at 25 °C had i.r. absorptions (KBr) at 3 500 and 3 240 cm^{-1} (broad) and carbonyl bands at 1 740 and 1 680 cm^{-1}. Samples synthesised employing ethyl acetate as solvent, or obtained by crystallizing the dichloromethane product from aqueous acetone, on the other hand, differed in that NH absorptions appeared at 3 450, 3 350, and 3 230 (broad), and 3 120 cm^{-1}, with carbonyl frequencies at 1 748 and 1 673 cm^{-1}. The solution i.r. and ^1H n.m.r. spectra in $CHCl_3$ and [$^2H_6$]DMSO, respectively, of the different samples were identical. Because of the commercial and clinical interest in this compound an unequivocal proof of the structure of the product crystallized from aqueous acetone was required.

Experimental

The imidazotetrazinone (**1**) was synthesized by the interaction of 5-diazoimidazole-4-carboxamide and chloroethyl isocyanate in ethyl acetate at 30 °C in the dark (95%) yield). Well formed plate-like crystals were grown by slow evaporation at room temperature from 50% aqueous acetone.

† Contribution from the Joint Crystallography Unit, Universities of Aston and Birmingham.

‡ Formerly known as Azolastone (CCRG 81010; M&B 39565; NSC 353451).

Crystal Data.—$C_7H_7ClN_6O_2$, M = 242.5. Triclinic, a = 7.003(4), b = 8.680(4), c = 16.041(9) Å, α = 93.76(5), β = 93.99(5), γ = 92.08(7)°, V = 969.8(9) Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, λ = 0.710 69 Å), space group $P\bar{1}$, Z = 4, D_m (by flotation in CCl_4 and C_2H_5I) = 1.670 g cm^{-3}, D_x = 1.660 g cm^{-3}. Crystal dimensions: 1.2 × 0.8 × 0.35 mm, μ(Mo-K_α) = 3.44 cm^{-1}.

Data Collection and Processing.—CAD4 diffractometer, $\omega/2\theta$ mode with scan width = 1.25 + 0.35 tan θ, scan speed 1.25—6.7 deg min^{-1}, graphite-monochromated Mo-K_α radiation; 3 797 unique reflections (merging R = 0.038) measured between $2° < \theta + 25°$ for $+h$, $\pm k$, $\pm l$ giving 3 244 with $|F_o| > 3\sigma(F_o)$. No decomposition or movement of the crystal was detected during data collection and refinement.

Structure Analysis and Refinement.—The structure was solved by use of the SHELX[16] direct methods package with a subsequent calculation of structure factors and an electron-density map to determine the position of one remaining non-hydrogen atom. All hydrogen atoms were located by difference electron density synthesis. Final full-matrix least-squares refinement of co-ordinates and anisotropic thermal parameters for non-hydrogen atoms, and co-ordinates and isotropic temperature factors for hydrogen atoms, reduced $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_w = \Sigma w^{\frac{1}{2}}||F_o| - |F_c||/\Sigma w^{\frac{1}{2}}|F_o|$ to 0.052 and 0.058, respectively. In the final stages of refinement reflections were weighted according to $w = 1/[\sigma^2(F_o) + 0.0013\ F_o^2]$, where $\sigma(F_o)$ was obtained from counting statistics and an allowance for instrument instability. Refinement was terminated when no positional parameter shifted by more than 0.22 e.s.d., at which point a difference electron-density map showed no feature greater than 0.35 e Å^{-3}.

Positional and thermal parameters for all atoms have been deposited as Supplementary Publication No. SUP 56126 (3 pp.).*

Results and Discussion

The structure of (1) is confirmed. The numbering scheme is shown in the displayed formula, which is in the same orientation as the stereo view of the two molecules comprising the asymmetric unit in Figure 1. Positional parameters of the atoms are given in Table 1. The two conformationally distinct molecules are rotamers about the C(8)–C(81) ring to carboxamide bond, the one amide being intramolecularly hydrogen-bonded to N(1) of the tetrazine ring, the other not.

A possible explanation of the discrepancies in the solid phase i.r. spectra is that, unlike the crystals grown from aqueous acetone, the poorly crystalline material obtained from dichloromethane does not contain equal quantities of the two rotamers.

A comparison of the molecular dimensions (Tables 2 and 3) shows the two independent molecules to be generally similar except in the vicinity of the carboxamide groups. In the (primed) molecule lacking an intramolecular hydrogen bond the C(8)′–C(81)′ bond nearly bisects the exterior N(7)′–C(8)′–C(8a)′ angle. In the unprimed molecule the entire carboxamide group is laterally displaced so that angle C(8A)–C(8)–C(81) is over 10° greater than N(7)–C(8)–C(81). Space is thereby created to accommodate the N(82) and H(7) atoms involved in the intramolecular hydrogen bond to N(1) (Table 4). Other possible distortions that could make more room for these atoms do not appear: the C(8)–C(81)–N(82) angle is not enlarged and is actually smaller than C(8)′–C(81)′–N(82)′; and both carboxamide moieties remain reasonably coplanar with their imidazole rings (Tables 5 and 6), the twist angles about the C(8)–C(81) and C(8)′–C(81)′ bonds being *ca.* 8 and 6°, respectively. In DTIC[17] and its hydrochloride monohydrate,[18] where every molecule is intramolecularly hydrogen-bonded, a similar pattern is observed: a carboxamide group that is nearly coplanar with the imidazole ring, bent in-plane at the point of attachment to the ring, and with angle NCC < OCC. It is now possible to attribute the deformations which are, respectively, absent and reduced in the primed molecule, to hydrogen bonding rather than to some intrinsic property of the substituent and ring.

A possibility of some conjugation between carboxamide groups and imidazole rings is afforded by their coplanarity. The C(81)–N(82) bond distance in both unprimed and primed molecules of 1.326(4) and 1.330(3) Å, respectively, suggests

Table 1. Positional parameters (fractional co-ordinates × 10^4) with estimated standard deviations in parentheses

	x	y	z
N(1)	1 206(3)	4 413(2)	7 329(1)
N(2)	1 978(3)	3 844(2)	6 694(1)
N(3)	1 020(3)	2 687(2)	6 187(1)
C(4)	−768(3)	2 037(2)	6 287(1)
N(5)	−1 549(2)	2 715(2)	6 993(1)
C(6)	−3 258(3)	2 431(2)	7 337(1)
N(7)	−3 394(3)	3 325(2)	8 016(1)
C(8)	−1 743(3)	4 223(2)	8 133(1)
C(8a)	−576(3)	3 870(2)	7 503(1)
C(31)	2 052(3)	2 119(2)	5 469(1)
C(32)	1 398(4)	2 789(3)	4 662(1)
Cl	2 336(1)	4 721(1)	4 623(1)
O(4)	−1 567(3)	1 028(2)	5 832(1)
C(81)	−1 453(3)	5 368(2)	8 869(1)
N(82)	267(3)	6 068(3)	8 996(1)
O(82)	−2 768(3)	5 644(3)	9 306(1)
N(1)′	671(2)	1 003(2)	2 365(1)
N(2)′	2 022(2)	1 941(2)	2 629(1)
N(3)′	3 666(2)	2 061(2)	2 200(1)
C(4)′	3 995(3)	1 279(2)	1 452(1)
N(5)′	2 457(2)	262(2)	1 181(1)
C(6)′	2 194(3)	−782(2)	505(1)
N(7)′	570(3)	−1 559(2)	504(1)
C(8)′	−310(3)	−1 031(2)	1 206(1)
C(8a)′	−849(3)	109(2)	1 637(1)
C(31)′	5 143(3)	3 125(2)	2 622(1)
C(32)′	6 694(3)	2 288(3)	3 079(2)
Cl′	5 770(1)	1 299(1)	3 915(1)
O(4)′	5 420(2)	1 437(2)	1 081(1)
C(81)′	−2 181(3)	−1 630(2)	1 464(1)
N(82)′	−3 159(3)	−2 673(2)	940(1)
O(82)′	−2 717(2)	−1 180(2)	2 149(1)
H(1)	1 802(29)	997(27)	5 402(17)
H(2)	3 384(26)	2 348(23)	5 596(13)
H(3)	1 967(29)	2 220(27)	4 123(18)
H(4)	38(29)	2 746(25)	4 593(15)
H(5)	−4 200(27)	1 729(25)	7 150(16)
H(6)	545(35)	6 681(33)	9 467(24)
H(7)	1 118(35)	5 789(32)	8 671(23)
H(1)′	4 441(26)	3 786(24)	3 023(15)
H(2)′	5 716(28)	3 728(26)	2 146(16)
H(3)′	7 573(31)	3 000(29)	3 340(19)
H(4)′	7 260(28)	1 488(25)	2 688(16)
H(5)′	3 044(27)	−901(25)	124(15)
H(6)′	−2 766(30)	−2 954(27)	458(18)
H(7)′	−4 377(30)	−3 084(26)	1 106(17)

* For details of the Supplementary Publications Scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1985, Issue 1, Section 4.0. Structure factors are available from the editorial office on request.

Table 2. Bond distances of the two molecules in the asymmetric unit (unprimed and primed) with estimated standard deviations in parentheses

Bond	Unprimed (Å)	Primed (Å)
N(1)–N(2)	1.266(3)	1.257(3)
N(2)–N(3)	1.374(3)	1.386(3)
N(3)–C(31)	1.469(3)	1.460(3)
C(31)–C(32)	1.503(3)	1.504(3)
C(32)–Cl	1.785(3)	1.785(3)
N(3)–C(4)	1.378(3)	1.377(3)
C(4)–O(4)	1.198(3)	1.205(3)
C(4)–N(5)	1.396(3)	1.394(3)
N(5)–C(6)	1.373(3)	1.364(3)
C(6)–N(7)	1.306(3)	1.300(3)
N(7)–C(8)	1.365(3)	1.381(3)
C(8)–C(8a)	1.369(3)	1.374(3)
C(8a)–N(5)	1.379(3)	1.391(3)
C(8)–C(81)	1.490(3)	1.487(3)
C(81)–O(82)	1.216(3)	1.229(3)
C(81)–N(82)	1.326(4)	1.330(3)
C(8a)–N(1)	1.371(3)	1.374(3)
C(31)–H(1)	0.98(2)	1.00(2)
C(31)–H(2)	0.95(2)	1.05(2)
C(32)–H(3)	1.08(3)	0.92(2)
C(32)–H(4)	0.95(2)	1.02(2)
C(6)–H(5)	0.90(2)	0.89(2)
N(82)–H(6)	0.90(3)	0.86(3)
N(82)–H(7)	0.85(3)	0.97(3)

Table 3. Important interatomic angles for the two molecules in the asymmetric unit (unprimed and primed) with estimated standard deviations in parentheses

Atoms	Bond angle (unprimed) (°)	Bond angle (primed) (°)
C(8a)–N(1)–N(2)	119.7(2)	118.6(2)
N(1)–N(2)–N(3)	119.6(2)	120.7(2)
N(2)–N(3)–C(4)	126.8(2)	126.4(2)
N(2)–N(3)–C(31)	114.8(2)	113.6(2)
C(31)–N(3)–C(4)	118.4(2)	120.0(2)
N(3)–C(4)–N(5)	111.0(2)	110.8(2)
N(3)–C(4)–O(4)	125.2(2)	125.0(2)
O(4)–C(4)–N(5)	123.8(2)	124.2(2)
C(4)–N(5)–C(8a)	122.0(2)	122.1(2)
C(4)–N(5)–C(6)	131.4(2)	131.2(2)
C(6)–N(5)–C(8a)	106.6(2)	106.7(2)
N(5)–C(6)–N(7)	110.9(2)	111.4(2)
C(6)–N(7)–C(8)	106.9(2)	107.2(2)
N(7)–C(8)–C(8a)	109.8(2)	108.8(2)
N(7)–C(8)–C(81)	119.9(2)	125.5(2)
C(8a)–C(8)–C(81)	130.4(2)	125.7(2)
C(8)–C(81)–O(82)	120.2(2)	119.2(2)
C(8)–C(81)–N(82)	116.4(2)	117.2(2)
O(82)–C(81)–N(82)	123.4(2)	123.6(2)
C(8)–C(8a)–N(5)	105.8(2)	105.9(2)
N(1)–C(8a)–N(5)	120.9(2)	121.3(2)
N(1)–C(8a)–C(8)	133.2(2)	132.8(2)
C(81)–N(82)–H(6)	119(2)	122(2)
C(81)–N(82)–H(7)	118(2)	118(2)
H(6)–N(82)–H(7)	122(3)	120(3)

Table 4. Hydrogen bond contact distances and angles

Hydrogen bond[a]	Angle at H(°)	N···O distance (Å)
$N(82)_I$–H(7)···$N(1)_I$	137	3.075
$N(82)_I$–H(6)···$N(7)'_{II}$	166	3.063
$N(82)'_{II}$–H(6)′···$O(82)_I$	156	2.951
$N(82)'_{III}$–H(7)′···$N(7)_I$	153	3.089

[a] I, II, and III, refer to the symmetry operations x, y, z; $x, 1 + y, 1 + z$; $-1 - x, -y, 1 - z$.

Table 5. Deviations of non-hydrogen atoms from the least-squares plane through the imidazotetrazine ring system.[a] (The two molecules in the asymmetric unit are treated separately. Atoms used in the plane calculation are marked with an asterisk)

Atom	Deviation unprimed (Å)	Deviation primed (Å)
*N(1)	−0.004(3)	−0.017(3)
*N(2)	0.002(3)	−0.002(3)
*N(3)	0.007(3)	0.035(3)
*C(4)	0.003(3)	−0.004(3)
*N(5)	−0.010(3)	−0.029(3)
*C(6)	−0.003(3)	−0.009(3)
*N(7)	0.005(3)	0.017(3)
*C(8)	0.008(3)	0.019(3)
*C(8a)	−0.007(3)	−0.010(3)
C(31)	0.011(3)	0.142(3)
C(32)	−1.346(3)	1.547(3)
Cl	−2.355(2)	2.646(2)
O(4)	0.006(3)	−0.006(3)
C(81)	0.030(3)	0.080(3)
O(82)	−0.126(3)	0.220(3)
N(82)	0.188(3)	0.019(3)

[a] The equations of the planes are:

Unprimed $0.422X - 0.705Y + 0.571Z + 4.221 = 0$

Primed $0.433X - 0.721Y + 0.541Z + 1.611 = 0$

where X, Y, and Z are orthogonal co-ordinates in Å along a^*, cxa^*, and c.

Table 6. Important torsion angles

Atoms	Angle unprimed (°)	Angle primed (°)
N(7)–C(8)–C(81)–N(82)	172.4	−5.8
N(7)–C(8)–C(81)–O(82)	−9.2	172.2
C(8a)–C(8)–C(81)–O(82)	170.9	−6.0
C(8a)–C(8)–C(81)–N(82)	−7.5	176.0
N(3)–C(31)–C(32)–Cl	76.8	−64.9
N(2)–N(3)–C(31)–C(32)	−99.6	101.0

considerable double bond character consistent with sp^2 hybridisation of the amide nitrogen atom in each case. This is further demonstrated by the nearness to 360° of the sums of the bond angles around N(82) and N(82)′.

Some differences between rotamers are apparent in the heterocyclic system, where the N(7)–C(8) bond at 1.365(3) Å shows more double-bond character than N(7)′–C(8)′ [1.381(3) Å]. Other differences >0.01 Å affect C(8a)–N(5) and N(2)–N(3). Among the formally double bonds in both molecules, the N(1)–N(2) distances [1.266(3) Å unprimed, 1.257(3) Å primed] and the C(6)–N(7) [1.306(3) Å unprimed, 1.300(3) Å primed] show true double-bond character, whilst the C(8)–C(8a) bonds [1.369(3) Å unprimed, 1.374(3) Å primed] are compatible with a partial double bond suggesting some delocalisation.

Depending on reaction conditions the title compound may decompose in two ways.[2] At elevated temperatures in organic solvents the dominant reaction is fragmentation in which the C(4)–N(5) and N(2)–N(3) bonds cleave. Application of the formula used by Hjortås[19] to obtain π bond orders from bond distances, yields orders of 0.35 and 0.41 for these bonds averaged over the two independent molecules of the title compound. These are the weakest and presumably most labile ring bonds in the entire molecule, but in view of their significant multiple-bond character it is understandable that input of heat is required to rupture them.

The alternative decomposition process takes place in aqueous media and involves attack by water at C(4) followed by ring opening. The C(4)–O(4) bond is short and strong, but the π

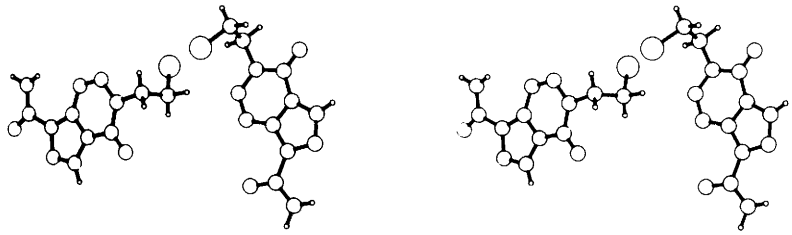


Figure 1. Stereoview of the two molecules comprising the asymmetric unit of the structure of 8-carbamoyl-3-(2-chloroethyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one

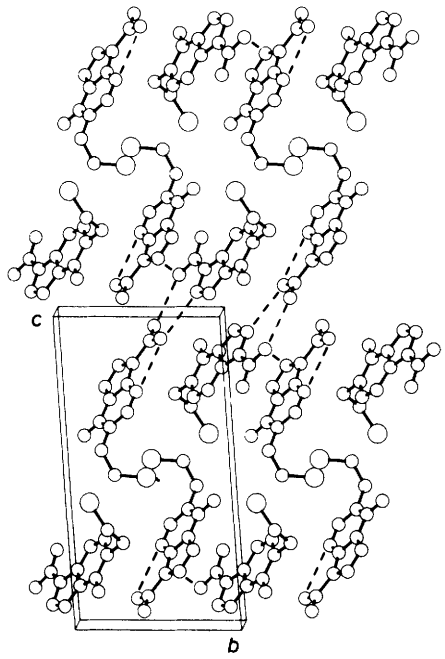


Figure 2. Molecular packing and hydrogen bonding for 8-carbamoyl-3-(2-chloroethyl)imidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one

bond orders for C(4)–N(3) and C(4)–N(5) (0.45 and 0.35) are weaker than corresponding values in urea[20] (0.66 each). Presumably less electron density is being transferred from adjacent atoms to the C(4)–O(4) system here than in urea, and nucleophilic attack by water may be facilitated.

Deviations in Å from the least-squares plane through the nine atoms of the bicyclic systems in the two molecules (Table 5) show the imidazotetrazine moieties to be substantially planar, albeit that N(1)′, N(3)′, N(5)′, and N(7)′ show significantly greater deviations ($>5\sigma$) than in the unprimed molecule. The chloroethyl groups are both of similar geometry, but as can be seen from the least-squares planes calculations and torsion angles are approximate opposites with respect to their tetrazine rings.

The molecular packing and hydrogen bonding are shown in Figure 2 and the contact distances and symmetry operations given in Table 4. Groups of four molecules hydrogen bond around a centre of symmetry facilitated by a 'base pairing' interaction of the type N(82)–H(6)···· N(7)′ (3.063 Å) and N(82)′–H(6)′···· O(82) (2.951 Å). The intramolecular hydrogen bond N(82)–H(7)···· N(1) (3.075 Å) maintains the coplanarity of the carboxamide group with the ring-system of the unprimed molecule. This feature is also found in the crystal structure of DTIC[17] and its hydrochloride (hydrate) salt[18] and ensures a reasonably planar 'base pair.' The interaction between the two sets of bases is then completed by an N(82)′–H(7)′···· N(7) contact (3.089 Å) to produce a group of four.

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