

as a racemic twin did not improve the result, so the absolute structure could not be determined.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *DREADD* (Blessing, 1987). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1995). Molecular graphics: *ORTEPII* (Johnson, 1976). Software used to prepare material for publication: *SHELXL93*, local programs.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1135). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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8-Acid Derivative of the Antitumour Agent Mitozolomide

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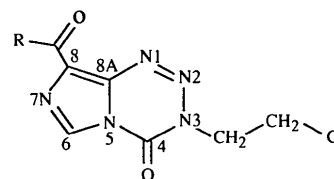
Abstract

The crystal structure of 3-(2-chloroethyl)-3,4-dihydro-4-oxoimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylic acid, C₇H₆ClN₅O₃, a derivative of the novel bicyclic

antitumour agent mitozolomide, 3-(2-chloroethyl)-3,4-dihydro-4-oxoimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carboxamide, has been determined at 293 K. The expected dimer, hydrogen bonded *via* the two carboxyl groups, does not occur. In preference, the two molecules in the asymmetric unit utilize hydrogen bonding between the carboxyl group of one and the N atom and CH in the imidazo ring of the other. These two then further interact *via* the same scheme with their centrosymmetrically related pair to produce a fully hydrogen-bonded planar tetramer.

Comment

Although in itself not a particularly active antitumour agent, the title compound (1) proved to be an important intermediate in the preparation of a range of active 8-carbamoyl derivatives of mitozolomide (2) (Horspool *et al.*, 1990). Previous attempts at preparing these directly from (2) had resulted in nucleophilic attack at O4 and the resultant destruction of the molecule. Preparation of the 8-acid and then the acid chloride had allowed nucleophilic reactions under much milder conditions without affecting the ring system.



- (1) R = OH, 8-acid derivative
 (2) R = NH₂, mitozolomide

As with mitozolomide (Lowe, Schwalbe & Stevens, 1985), the 8-acid derivative contains two molecules in the asymmetric unit.

Both chloroethyl side chains at N3 and N3P, as with the two independent molecules in (2), adopt a *gauche* conformation with the N3—C31—C32—Cl1 torsion angles being 64.9 (2) and 73.9 (3)°, respectively, for the unprimed and primed molecules. The carboxyl groups are almost coplanar with the ring system as shown by the torsion angle C8A—C8—C81—O82 and its primed equivalent being 177.5 (2) and –174.0 (2)°, respectively.

However, by far the most interesting feature is the overall hydrogen-bonding scheme. Whilst it was tempting to hypothesize a hydrogen-bonded dimer *via* the two carboxyl groups, this does not occur. Instead, the two molecules in the asymmetric unit form a hydrogen-bonded pair utilizing the carboxyl group of one and N7P and the electropositive C6P H atom of the other. This pair of molecules then further hydrogen bond to a centrosymmetrically related pair *via* the same arrangement (Table 3) to produce a fully hydrogen-bonded planar tetramer. In order to check the logic behind this hydrogen-bonding scheme, which utilizes

both the C6 and C6P H atoms, molecular orbital calculations were performed on the molecule (with the chloroethyl side chain simplified to methyl) to determine the magnitude of the charge on the C6 H atom. After optimization of geometry with *GAMESS* (Schmidt *et al.*, 1990) by *ab initio* MO calculations, using a 3-21G basis set, the Mulliken charge on the H atom was found to be 0.326 as compared with an average of 0.253 for the aliphatic side-chain H atoms and 0.420 for the acidic H atom. Thus, this H atom has the second largest positive charge, which significantly exceeds that on an aliphatic H atom. This charge is a likely contributing factor to the weak interaction observed, and thereby to tetramer formation, subject to satisfactory packing interactions.

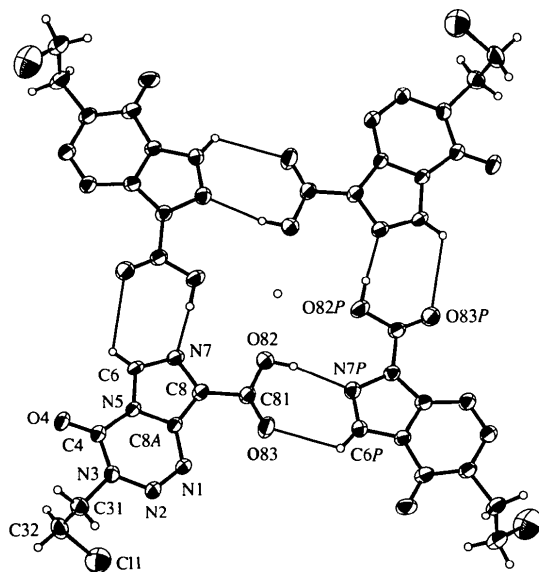


Fig. 1. ORTEP view (Johnson, 1976) of the hydrogen-bonded tetramer (1). Displacement ellipsoids are shown at the 50% probability level.

Experimental

Crystal data

C₇H₆ClN₅O₃

$M_r = 243.62$

Triclinic

$P\bar{1}$

$a = 6.7420(10) \text{ \AA}$

$b = 9.005(5) \text{ \AA}$

$c = 15.932(2) \text{ \AA}$

$\alpha = 92.96(2)^\circ$

$\beta = 95.78(1)^\circ$

$\gamma = 94.45(2)^\circ$

$V = 957.7(6) \text{ \AA}^3$

$Z = 4$

$D_x = 1.690 \text{ Mg m}^{-3}$

Data collection

Enraf–Nonius CAD-4
diffractometer

Mo $K\alpha$ radiation

$\lambda = 0.71069 \text{ \AA}$

Cell parameters from 25
reflections

$\theta = 9.88\text{--}14.31^\circ$

$\mu = 0.400 \text{ mm}^{-1}$

$T = 293(2) \text{ K}$

Lath

$0.60 \times 0.35 \times 0.15 \text{ mm}$

Colourless

Crystal source: Dr K.

Horspool, Aston
University

$R_{\text{int}} = 0.0188$

$\theta_{\text{max}} = 24.97^\circ$

$\omega/2\theta$ scans

Absorption correction:

none

3660 measured reflections

3346 independent reflections

2615 observed reflections

$[I > 2\sigma(I)]$

Refinement

Refinement on F^2

$R[F^2 > 2\sigma(F^2)] = 0.0423$

$wR(F^2) = 0.1238$

$S = 1.237$

3346 reflections

339 parameters

All H-atom parameters

refined

$w = 1/[\sigma^2(F_o^2) + (0.0866P)^2]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\text{max}} = 0.001$

$h = 0 \rightarrow 8$

$k = -10 \rightarrow 10$

$l = -18 \rightarrow 18$

3 standard reflections

frequency: 120 min

intensity decay: 1.8%

$\Delta\rho_{\text{max}} = 0.406 \text{ e \AA}^{-3}$

$\Delta\rho_{\text{min}} = -0.452 \text{ e \AA}^{-3}$

Extinction correction:

SHELXL93 (Sheldrick,
1993)

Extinction coefficient:

0.0031 (22)

Atomic scattering factors

from *International Tables*

for *Crystallography* (1992,

Vol. C, Tables 4.2.6.8 and

6.1.1.4)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (\AA^2)

$$U_{\text{eq}} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*a_i\cdot a_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}
N1	−0.0369 (3)	0.4525 (2)	0.27350 (11)	0.0323 (4)
N2	−0.1820 (3)	0.3568 (2)	0.25299 (12)	0.0333 (4)
N3	−0.3347 (3)	0.3403 (2)	0.30353 (12)	0.0304 (4)
C4	−0.3552 (3)	0.4232 (2)	0.37680 (13)	0.0299 (5)
N5	−0.1901 (3)	0.5281 (2)	0.39674 (11)	0.0265 (4)
C6	−0.1437 (3)	0.6317 (2)	0.46301 (13)	0.0296 (5)
N7	0.0304 (3)	0.7043 (2)	0.45744 (11)	0.0298 (4)
C8	0.1013 (3)	0.6490 (2)	0.38567 (13)	0.0275 (5)
C8A	−0.0338 (3)	0.5395 (2)	0.34653 (12)	0.0250 (4)
C81	0.2913 (3)	0.7001 (2)	0.35351 (13)	0.0289 (5)
O82	0.3947 (3)	0.8113 (2)	0.39996 (11)	0.0419 (4)
O83	0.3401 (3)	0.6457 (2)	0.28971 (12)	0.0485 (5)
O4	−0.4914 (3)	0.4091 (2)	0.41840 (11)	0.0497 (5)
C31	−0.4973 (3)	0.2279 (3)	0.2690 (2)	0.0352 (5)
C32	−0.6628 (4)	0.2973 (3)	0.2190 (2)	0.0405 (6)
C11	−0.58168 (12)	0.37667 (9)	0.12624 (5)	0.0636 (3)
N1P	1.1906 (3)	0.9469 (2)	0.21637 (12)	0.0330 (4)
N2P	1.2532 (3)	0.8836 (2)	0.15263 (12)	0.0347 (4)
N3P	1.1355 (3)	0.7694 (2)	0.10635 (11)	0.0314 (4)
C4P	0.9499 (4)	0.7121 (2)	0.12214 (13)	0.0313 (5)
N5P	0.8899 (3)	0.7850 (2)	0.19367 (10)	0.0273 (4)
C6P	0.7185 (3)	0.7625 (2)	0.23158 (14)	0.0302 (5)
N7P	0.7201 (3)	0.8556 (2)	0.29758 (11)	0.0304 (4)
C8P	0.8980 (3)	0.9432 (2)	0.30334 (13)	0.0273 (5)
C8AP	1.0059 (3)	0.9009 (2)	0.23895 (12)	0.0264 (4)
C81P	0.9531 (3)	1.0641 (2)	0.37010 (13)	0.0303 (5)
O82P	0.8240 (3)	1.0657 (2)	0.42681 (11)	0.0421 (4)
O83P	−1.0974 (3)	1.1505 (2)	0.37044 (12)	0.0512 (5)
O4P	0.8482 (3)	0.6142 (2)	0.08067 (11)	0.0486 (5)
C31P	1.2216 (4)	0.7101 (3)	0.0322 (2)	0.0391 (6)
C32P	1.1352 (4)	0.7692 (4)	−0.0480 (2)	0.0495 (7)
C11P	1.2261 (2)	0.95820 (10)	−0.05738 (6)	0.0780 (3)

Table 2. Selected geometric parameters (\AA , $^\circ$)

N1—N2	1.258 (3)	N1P—N2P	1.264 (3)
N1—C8A	1.366 (3)	N1P—C8AP	1.370 (3)
N2—N3	1.373 (3)	N2P—N3P	1.381 (3)
N3—C4	1.378 (3)	N3P—C4P	1.368 (3)
N3—C31	1.475 (3)	N3P—C31P	1.462 (3)
C4—O4	1.188 (3)	C4P—O4P	1.199 (3)
C4—N5	1.402 (3)	C4P—N5P	1.396 (3)
N5—C6	1.368 (3)	N5P—C6P	1.363 (3)
N5—C8A	1.386 (3)	N5P—C8AP	1.380 (3)

C6—N7	1.312 (3)	C6P—N7P	1.309 (3)
N7—C8	1.369 (3)	N7P—C8P	1.375 (3)
C8—C8A	1.369 (3)	C8P—C8AP	1.371 (3)
C8—C81	1.476 (3)	C8P—C81P	1.481 (3)
C81—O83	1.193 (3)	C81P—O83P	1.197 (3)
C81—O82	1.321 (3)	C81P—O82P	1.317 (3)
C31—C32	1.501 (4)	C31P—C32P	1.492 (4)
C32—C11	1.790 (3)	C32P—C11P	1.782 (3)
C8A—C8—C81—O82		177.5 (2)	
N3—C31—C32—C11		64.9 (2)	
C8AP—C8P—C81P—O82P		-174.0 (2)	
N3P—C31P—C32P—C11P		73.9 (3)	

Table 3. Hydrogen-bonding geometry (Å, °)

D—H...A	D...A
O82—H82...N7P	2.879 (3)
C6P—H6P...O83	2.938 (3)
O82P—H82P...N7 ¹	2.753 (3)
C6—H6...O83P ¹	3.191 (3)

Symmetry code: (i) 1 - x, 2 - y, 1 - z.

Data collection: *CAD-4 Software* (Enraf-Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *DATRED* (Brookhaven National Laboratory & Birmingham University, 1986). Program(s) used to solve structure: *MULTAN80* (Main *et al.*, 1980). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ORTEPII* (Johnson, 1976). Software used to prepare material for publication: *SHELXL93*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: HA1135). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Heptahydrated Monosodium Salt of 6-Amino-5-(2-carboxyphenyl)azouracil

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Abstract

The bulky organic molecule in the title compound, sodium 2-[6-amino-2,4(3*H*,5*H*)-dioxypyrimidin-5-ylazo]benzoate heptahydrate, Na⁺.C₁₁H₈N₅O₄.7H₂O, exists as a monovalent anion with negatively charged carboxylate and uracil groups and a protonated azo group. An intramolecular bifurcated hydrogen bond contributes to the approximate planarity of the anion.

Comment

The dinuclear copper(II) complex [Cu(μ-HL¹)Cu(H₂O)₂-(CH₃CH₂OH)](ClO₄)₃ [H₂L¹ = α,ω-bis(1,3-dimethyl-5-nitrosouracil-6-ylamino)propane], which contains *syn-syn* oximate bridging groups, has been found to form mixed-bridged trinuclear complexes such as [(μ-L){Cu(μ-L)Cu(H₂O)Cu(μ-L)}](ClO₄)₂.4.88H₂O (Colacio, Dominguez-Vera, Escuer, Klinga, Kivekäs & Romerosa, 1995). In an attempt to obtain an analogous trinuclear complex containing a hydroxide ion instead of the chloride bridging ion, we obtained, surprisingly, a hydrated monosodium salt of 6-amino-5-(2-carboxyphenyl)azouracil (H₂L). We have recently prepared other non-coordinated phenylazouracil derivatives: the cations 6-amino-1,3-dimethyl-5-(phenylazonio)uracil (Kivekäs, Colacio, Ruiz, López-González & León, 1989), 6-amino-1,3-dimethyl-5-(2-ethylphenylazonio)uracil (Kivekäs, Sundberg, Ruiz & Colacio, 1991; Kivekäs, Ruiz & Colacio, 1994) and 6-amino-1,3-dimethyl-5-(2-carboxyphenylazonio)uracil (Sundberg, Kivekäs, Ruiz, Moreno & Colacio, 1992). In these structures, the bulky non-coordinated molecules exist as monovalent cations, the N8 atom of the azo group being protonated. In the metal complexes, the phenylazouracil and analogous barbituric acid derivatives coordinate as anionic ligands and the N8 atom of the neutral azo group is coordinated to the metal (Colacio, Dominguez-Vera, Kivekäs, Moreno &