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DCMCIT, an Analogue of the Antitumour Drugs Mitozolomide and Temozolomide

P. R. LOWE AND C. H. SCHWALBE

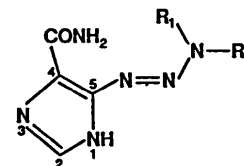*Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET, England*

Abstract

The crystal structure of 3-(2-chloroethyl)-N,N-dimethyl-4-oxo-3,4-dihydroimidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamide, (1), $C_9H_{11}ClN_6O_2$, an analogue of the novel bicyclic antitumour agents mitozolomide (2) and temozolomide (3), has been determined at 290 K. Although, as in structures (2) and (3), the imidazotetrazinone ring system is essentially planar, the substitution of the —$CONH_2$ group at C8 by a —$CON(CH_3)_2$ group in (1) negates the possibility of forming an intramolecular hydrogen bond at either N7 or N1 and thus allows rotation of this group about the C8—C81 bond by *ca* 45°.

Comment

Structure–activity studies on 8-substituted imidazotetrazinones show very good antitumour activity for both unsubstituted and a range of N-monosubstituted carboxamides (Lunt *et al.*, 1987). The proposed mode of action is that of a prodrug for two cytotoxic alkylating species: MCTIC (4) for analogues of mitozolomide and MTIC (5) for analogues of temozolomide. The model proposes that this is effected by ring opening at the weak C4—N5 bond following nucleophilic attack at the C4 atom by water molecules in the major groove of DNA (Clark, Stevens, Sansom & Schwalbe, 1990). It is further

postulated that the carboxamide substitutent may play an important role in DNA sequence recognition (Lowe, Sansom, Schwalbe, Stevens & Clark, 1992).
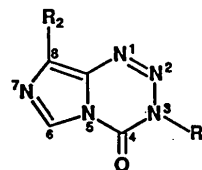
(1) R_1 = $(CH_2)_2Cl$, R_2 = $CON(CH_3)_2$ DCMCIT
(2) R_1 = $(CH_2)_2Cl$, R_2 = $CONH_2$ Mitozolomide
(3) R_1 = CH_3, R_2 = $CONH_2$ Temozolomide

(4) R_1 = H, R_2 = $(CH_2)_2Cl$ MCTIC
(5) R_1 = H, R_2 = CH_3 MTIC

The fact that the title compound differs from (2) only in that it is N-disubstituted, and yet has very impaired activity, points to the importance of the nature of the carboxamide substituent; it is proposed that DCMCIT has to undergo metabolic demethylation to become active (Lowe, Sansom, Schwalbe, Stevens & Clark, 1992).

Although, in general, the bond lengths in the planar bicyclic ring system are similar in compounds (1), (2) and (3), a difference does occur in the N1—N2, N1—C8A and C8—C8A bond lengths which are shorter, longer and shorter, respectively, by greater than 3σ in structure (1) than in structures (2) and (3), suggesting considerably less conjugation (Lowe, Schwalbe & Stevens, 1985; Lowe, Sansom, Schwalbe, Stevens & Clark, 1992). While it is tempting to attribute this largely to the coplanar nature of the carboxamide group and ring system in structures (2) and (3) compared with the observed twist in structure (1) [C8A—C8—C81—O82 46.1 (4)°] which reduces the conjugative effect between them, it is not substantiated by the C8—C81 bond length which shows little variation among the three compounds.

The C81—N82 bond length of 1.334 (3) Å suggests considerable double-bond character, which is consistent with sp^2 hybridization of the amide N atom shown by the closeness to 360° of the sum of the bond angles around the N82 atom [359.8 (4)°]. As such, conjugation appears to be restricted to the ring system and the carboxamide group separated by the rotation about the C8—C81 bond.

Since the title compound (1) is N-disubstituted, no strong hydrogen bonds exist, as demonstrated by the relatively low melting point of 389 K. However, there is a somewhat weaker interaction, namely

C6—H6···O82, with a donor–acceptor distance of 3.211 (4) Å and a donor–H–acceptor angle of 163 (3)° with a transformation from donor to acceptor of $(1 - x, \frac{1}{2} + y, 1 - z)$.

The chloroethyl side chain at the N3 atom adopts a *gauche* conformation with an N3—C31—C32—Cl1 torsion angle of −65.5 (3)° in structure (1), similar to those in the two independent molecules in structure (2).
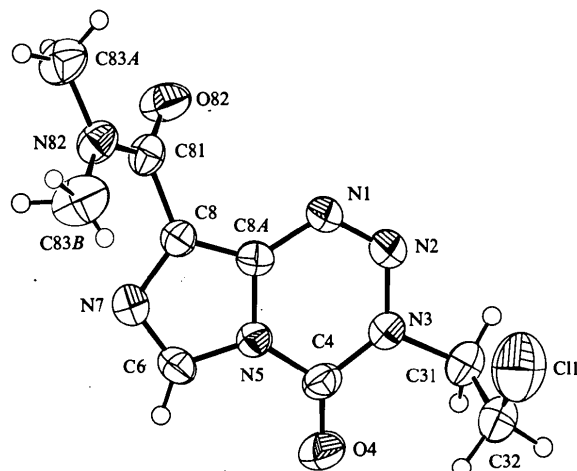

Fig. 1. *ORTEP* (Johnson, 1976) plot of DCMCIT showing the labelling of the non-H atoms. Displacement ellipsoids are shown at the 50% probability level.

Experimental

Crystal data

$C_9H_{11}ClN_6O_2$
$M_r = 270.68$
Monoclinic
$P2_1$
$a = 9.078$ (2) Å
$b = 7.518$ (5) Å
$c = 9.780$ (2) Å
$\beta = 112.71$ (1)°
$V = 615.7$ (5) Å^3
$Z = 2$
$D_x = 1.460$ Mg m^{-3}

Mo $K\alpha$ radiation
$\lambda = 0.71069$ Å
Cell parameters from 25 reflections
$\theta = 9.88–15.44°$
$\mu = 0.321$ mm^{-1}
$T = 290$ K
Lath
$0.6 \times 0.4 \times 0.2$ mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: none
2231 measured reflections
2160 independent reflections
2070 observed reflections
$[F > 3\sigma(F)]$

$R_{int} = 0.011$
$\theta_{max} = 25°$
$h = 0 \rightarrow 11$
$k = -9 \rightarrow 9$
$l = -12 \rightarrow 12$
3 standard reflections
frequency: 120 min
intensity variation: 0.7%

Refinement

Refinement on F
$R = 0.0345$

$\Delta\rho_{max} = 0.29$ e Å^{-3}
$\Delta\rho_{min} = -0.38$ e Å^{-3}

$wR = 0.0405$
$S = 0.80$
2027 reflections
206 parameters
All H-atom parameters refined
$w = 2.3316/[\sigma^2(F) + 0.00029F^2]$
$(\Delta/\sigma)_{max} = 0.017$

Extinction correction:
$F_{corr} = F[1 - (0.0001 \times \chi F^2/\sin\theta)]$
(*SHELX*76; Sheldrick, 1976)
Extinction coefficient:
$\chi = 0.0389$
Atomic scattering factors from *SHELX*76

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
Cl1	0.9867 (1)	−0.0820	1.1081 (1)	0.1030 (8)
N1	0.7654 (2)	0.0171 (3)	0.6299 (2)	0.0443 (9)
N2	0.7571 (2)	−0.0809 (3)	0.7304 (2)	0.049 (1)
N3	0.6766 (2)	−0.0213 (3)	0.8172 (2)	0.045 (1)
C4	0.6003 (3)	0.1387 (4)	0.8061 (2)	0.042 (1)
N5	0.6197 (2)	0.2446 (3)	0.6959 (2)	0.039 (1)
C6	0.5631 (3)	0.4113 (4)	0.6463 (3)	0.048 (1)
N7	0.5998 (2)	0.4561 (3)	0.5338 (2)	0.049 (1)
C8	0.6825 (2)	0.3153 (4)	0.5086 (2)	0.039 (1)
C8A	0.6960 (2)	0.1839 (3)	0.6083 (2)	0.038 (1)
C31	0.6781 (4)	−0.1478 (5)	0.9322 (3)	0.057 (2)
C32	0.7827 (4)	−0.0881 (5)	1.0841 (3)	0.069 (2)
O4	0.5275 (2)	0.1851 (3)	0.8784 (2)	0.064 (1)
C81	0.7280 (2)	0.3051 (4)	0.3780 (2)	0.041 (1)
O82	0.6869 (2)	0.1739 (3)	0.2976 (2)	0.060 (1)
N82	0.8065 (2)	0.4404 (3)	0.3491 (2)	0.050 (1)
C83A	0.8388 (4)	0.4311 (5)	0.2141 (3)	0.062 (2)
C83B	0.8744 (5)	0.5903 (5)	0.4488 (5)	0.078 (2)

Table 2. *Selected geometric parameters* (Å, °)

N1—N2	1.254 (3)	C8A—N1	1.382 (3)
N2—N3	1.391 (3)	C8—C81	1.487 (3)
N3—C4	1.371 (3)	C81—O82	1.226 (3)
C4—N5	1.405 (3)	C81—N82	1.334 (3)
C4—O4	1.191 (3)	N82—C83A	1.460 (3)
N5—C6	1.370 (3)	N82—C83B	1.462 (4)
N5—C8A	1.372 (3)	N3—C31	1.469 (3)
C6—N7	1.311 (3)	C31—C32	1.490 (4)
N7—C8	1.374 (3)	C32—Cl1	1.775 (4)
C8—C8A	1.360 (3)		
C83A—N82—C81	117.7 (2)	C83B—N82—C83A	117.4 (2)
C83B—N82—C81	124.7 (2)		
N3—C31—C32—Cl1	−65.5 (3)	C8A—C8—C81—O82	46.1 (4)

All non-H atoms in the structure were found by direct methods. Subsequent isotropic refinement and difference electron-density synthesis located all the H atoms. Final full-matrix least-squares refinement of coordinates and anisotropic displacement parameters for non-H atoms, and coordinates and isotropic temperature factors for H atoms, reduced R to 0.0345. Cell refinement: *CAD-4 Software* (Enraf–Nonius, 1989). Data reduction: *DATRED* (Brookhaven National Laboratory & Birmingham University, 1986). Program used to solve structure: *MULTAN*80 (Main *et al.*, 1980). Program used to refine structure: *SHELX*76 (Sheldrick, 1976). Software used for geometry calculations: *SHELX*76 and *CALC* (Gould & Taylor, 1983).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry, including H-atom geometry, have been deposited with the IUCr (Reference: LI1090). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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1,2-Bis(methoxycarbonyl)-3-phenyl-guanidine

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Abstract

The structure of 1,2-bis(methoxycarbonyl)-3-phenylguanidine, $C_{11}H_{13}N_3O_4$, is stabilized into a planar configuration by two intramolecular hydrogen bonds.

Comment

There is a scarcity of structural information for guanidine compounds, even though they have been shown to be mutagens and carcinogens (Gichner & Veleminsky,

1982) and are used for the acceleration of the curing of rubber (Brown & Gash, 1984). A search of the chemical literature confirmed the novelty of the title compound (I). The determination of the structure of (I) was undertaken to provide conclusive evidence for the existence of the very stable intramolecular hydrogen-bonded bis(methoxycarbonyl)guanidine system.

(I)
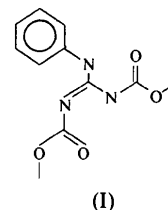
The guanidine moiety is planar, the sum of the three bond angles around C4 being 360.0°. The bond angles and distances for the guanidine moiety are consistent with the mean values calculated from the Cambridge Structural Database (Krygowski & Wozniak, 1991). The rest of the compound is stabilized into an almost flat conformation by two intramolecular hydrogen bonds; this has also been observed in similar guanidine compounds (Nordenson & Hvoslef, 1981). The r.m.s. deviation of the atoms of the phenyl ring and the atoms involved in hydrogen bonding from the least-squares plane through them is 0.025 Å. Atoms C9 and O3 also lie in this plane. The sums of the three bond angles for the non-H atoms of the six-membered rings in which hydrogen bonding is present (O1, C1, N1, C4, N3, H1 and O2, C5, N2, C4, N1, H) are 370.1 and 372.5°, respectively. The lack of a regular hexagon is probably caused by the presence of the hetero atoms
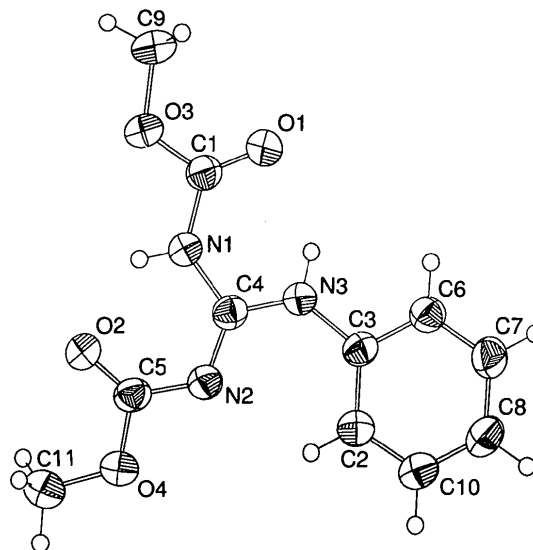

Fig. 1. *ORTEP* (Johnson, 1965) drawing of the title compound. Displacement ellipsoids are drawn at the 50% probability level.