Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

5-[Acetamido(phenyl)methyl]-5-methylimidazolidine-2,4-dione

K. SethuSankar,[a] S. Thennarasu,[b] D. Velmurugan[a]* and Moon Jib Kim[c]

[a]Department of Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai 600 025, India, [b]Organic Chemistry Division, CLRI, Chennai 600 020, India, and [c]Department of Physics, Soonchunbyang University, PO Box 97, Asan, Chungnam 336-600, South Korea
Correspondence e-mail: d_velu@yahoo.com

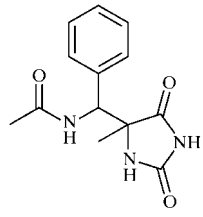
Received 8 October 2002
Accepted 21 October 2002
Online 20 November 2002

The title compound, alternatively named *N*-[(4-methyl-2,5-dioxoimidazolidin-4-yl)(phenyl)methyl]acetamide, $C_{13}H_{15}N_3O_3$, crystallizes in the centrosymmetric space group $P2_1/c$ with one molocule in the asymmetric unit. The imidazolidine-2,4-dione system is essentially planar, as evidenced by NMR studies. The dihedral angle between the planes of the imidazolidine and phenyl rings is 23.3 (1)°, while the dihedral angle between the acetamide side chain and the imidazolidine ring is 60.7 (1)°. The molecular structure and packing is stabilized by C—H···O and N—H···O interactions. Intermolecular hydrogen bonds form cyclic dimers, with graph-set descriptor $R_2^2(8)$, and a chain of $C(7)$.

Comment

1,3-Imidazolidine-2,4-dione, also known as hydantoin, is a five-membered ring structure which has been implicated in several biological activities. Allantoin is a natural hydantoin found in the uric acid excretion pathway in humans (Lehninger *et al.*, 1993). Phenytoin, the most widely used anticonvulsant drug (Woodbury, 1980; Tunnicliff, 1996; Morkunas & Miller, 1997), has two phenyl rings at the 5-position of the imidazolidine-2,4-dione system. Several 5,5-disubstituted imidazolidinediones have been identified as inhibitors (Kelly *et al.*, 1997) of metalloproteins and HIV protease (Comber *et al.*, 1992, 1997), and also act as sodium channel blockers (Brown *et al.*, 1997; Brouillette *et al.*, 1994). The enzyme inhibitory effect of imidazolidinedione has been correlated with the spatial disposition of functional groups having hydrogen-bonding ability. Hydantoins are also attractive intermediates for the synthesis of α-amino acids (Knapp, 1979; Musson *et al.*, 1980).

Aminohydantoins have been found to display antimicrobial activity (Malhotra *et al.*, 1990). DMDM hydantoin (DMDM is dimethyldimethylal) is a widely used antimicrobial agent and a preservative in cosmetics. To understand the structure–activity relationship involved in the antimicrobial activity of 5,5-disubstituted imidazolidinediones, the solution and solid-state structure of 5-[acetamido(phenyl)methyl]-5-methylimidazolidine-2,4-dione, (I), were examined. Against this background, and in order to obtain detailed information about the molecular conformations of 5,5-disubstituted imidazolidinediones in the solid state, the X-ray structure determination of (I) was carried out and the results are presented here.



(I)

Fig. 1 shows a *ZORTEP* plot (Zsolnai, 1997) of (I) with the atom-numbering scheme. The imidazolidine-2,4-dione system is planar. In a previous report (SethuSankar *et al.*, 2001), coupling between the two imino H atoms of the imidazolidinedione ring was attributed to a distorted rather than a planar conformation. However, the ^{1}H NMR spectrum of (I) shows only two singlets (7.86 and 10.58 p.p.m.) and these correspond to the amide and imino H atoms, respectively. This clearly indicates a planar conformation for the imidazolidinedione ring. Additional support was obtained from the three-dimensional structures of the five lowest-energy conformers, obtained using *MM*2 force-field calculations (Allinger, 1977). The calculated lowest-energy conformers of (I) all show a planar structure with respect to the imidazolidinedione ring. However, the orientation of the phenyl ring and the acetamide group with respect to the hydantoin ring could not be estabilished using NMR data. Spectroscopic data obtained from IR, NMR and mass spectroscopic analysis support the proposed structure.

In the imidazolidine ring, the N1—C5 and C4—C5 distances and N1—C5—C4 angle are in good agreement with the literature data (SethuSankar *et al.*, 2001; Camerman & Camerman, 1971; Florencio *et al.*, 1978; Verdier *et al.*, 1977, 1979; Fujiwara & Van Der Ween, 1979; Koch *et al.*, 1975), where the observed values are in the ranges 1.45–1.48 Å, 1.51–1.55 Å and 99–101°, respectively. The angles C2—N3—C3 and O3—C2—C1 are narrower than the reported values of 125.0 (1) and 122.4 (2)° for 5-(1-acetamido-3-methylbutyl)-5-methylimidazolidine-2,4-dione monohydrate (SethuSankar *et al.*, 2001). The torsion angle C5—C3—N3—C2 describes the conformation of the side chain as (−)anticlinal about C3—N3. The dihedral angle between the least-squares plane through atoms C3, N3, C2, O3 and C1 and the imidazolidine ring is 60.7 (1)°, whereas the corresponding angle is only 4.59 (1)° in our previous report (SethuSankar *et al.*, 2001). The angle between the planes of the imidazolidine and phenyl rings is 23.3 (1)°, while the dihedral angle between the group containing the acetamide substituent and the phenyl ring is 55.9 (1)°. Atoms O2 and C3 deviate from the plane of the imidazolidine ring by 0.034 (2) and 1.202 (2) Å on one side,

 DOI: 10.1107/S0108270102019339

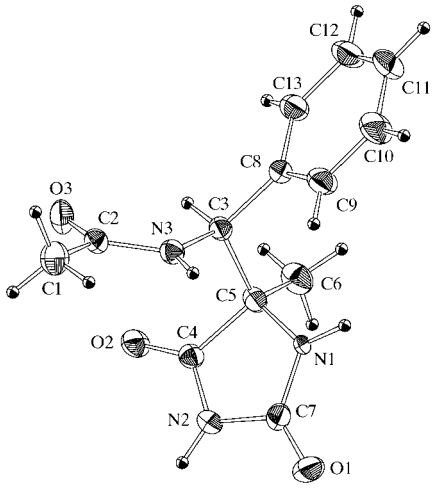


Figure 1
The molecular structure of (I), showing 35% probability displacement ellipsoids and the atom-numbering scheme. H atoms are shown as small spheres of arbitrary radii.

while atoms C6 and O1 deviate by 1.334 (2) and 0.095 (2) Å on the opposite side.

In addition to van der Waals interactions, the molecular structure and crystal packing of (I) are stabilized by C—H···O and N—H···O intermolecular hydrogen bonds. There are three N—H···O intermolecular interactions. Of these, the N2—H2···O2 interaction participates in an eight-membered cyclic dimer arrangement [N2—H2···O2^{i}—C4^{i}—N2^{i}—H2^{i}···O2—C4; symmetry code: (i) $2-x, 1-y, 1-z$], with an $R_2^2(8)$ ring descriptor (Bernstein *et al.*, 1995), while the N1—H1···O3 hydrogen bond forms a $C(7)$ chain, *viz*. H1—N1—C5—C3—N3—C2—O3 (Fig. 2).

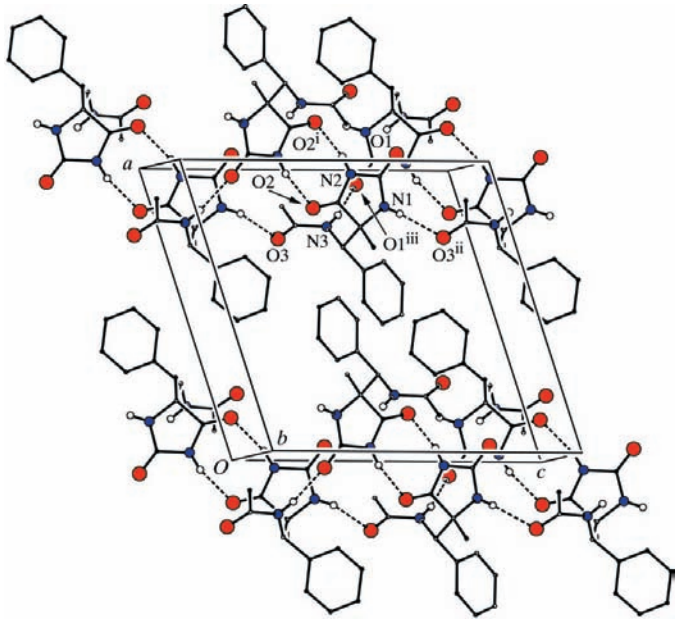


Figure 2
The crystal structure of (I), with the N—H···O hydrogen-bonding scheme shown as dashed lines. Symmetry codes are as in Table 2.

Experimental

A one-pot preparation of the title compound was achieved by treating L-phenylglycine with a mixture of acetic anhydride and pyridine, followed by a Bucherer–Bergs reaction of the acetamide ketone derivative. L-Phenylglycine (3.2 g, 20 mmol) was dissolved in a solution of acetic anhydride (15 ml) and pyridine (10 ml), and the resulting solution heated over a water bath for 3 h. After removing the solvent under reduced pressure, potassium cyanide (1.95 g, 30 mmol), commercial ammonium carbonate (4.78 g, 60 mmol) and water (100 ml) were added. The reaction mixture was subjected to ultrasonic irradiation at 318 K for 3 h and was then concentrated under reduced pressure. The colorless solid obtained was crystallized from a 3 *N* HCl–methanol (3:1) mixture to afford the title compound. Spectroscopic data obtained from IR, NMR and mass spectroscopic analysis support the proposed structure.

Crystal data

$C_{13}H_{15}N_3O_3$
$M_r = 261.28$
Monoclinic, $P2_1/c$
$a = 12.9955$ (9) Å
$b = 7.7137$ (5) Å
$c = 13.4699$ (11) Å
$\beta = 107.860$ (6)°
$V = 1285.2$ (2) Å^3
$Z = 4$
$D_x = 1.350$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 1.6$–25.0°
$\mu = 0.10$ mm^{-1}
$T = 293$ (2) K
Prism, colorless
0.35 × 0.30 × 0.30 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Non-profiled $w/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.967$, $T_{max} = 0.971$
2358 measured reflections
2249 independent reflections
1644 reflections with $I > 2\sigma(I)$
$R_{int} = 0.016$
$\theta_{max} = 25.0°$
$h = -15 \rightarrow 14$
$k = 0 \rightarrow 9$
$l = 0 \rightarrow 16$
3 standard reflections
every 100 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.042$
$wR(F^2) = 0.139$
$S = 0.97$
2249 reflections
174 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.34$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O1—C7	1.217 (2)	N2—C4	1.348 (2)
O2—C4	1.214 (2)	N2—C7	1.392 (3)
O3—C2	1.224 (2)	N3—C2	1.345 (2)
N1—C7	1.338 (3)	N3—C3	1.460 (2)
N1—C5	1.451 (2)	C4—C5	1.519 (3)
C7—N1—C5	112.7 (2)	O2—C4—N2	127.1 (2)
C2—N3—C3	122.0 (2)	O2—C4—C5	125.8 (2)
O3—C2—N3	122.4 (2)	N1—C5—C6	111.9 (2)
O3—C2—C1	121.1 (2)	N1—C5—C4	100.9 (2)
N3—C2—C1	116.5 (2)		
C2—N3—C3—C5	−113.1 (2)	N2—C4—C5—C6	114.8 (2)
C7—N1—C5—C3	122.2 (2)	N3—C3—C5—N1	−60.8 (2)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O3^{ii}	0.86	2.13	2.839 (2)	140
N2—H2···O2^{i}	0.86	2.00	2.844 (2)	167
N3—H3···O1^{iii}	0.86	2.16	3.004 (2)	167
C1—H1A···O2^{iv}	0.96	2.54	3.214 (4)	127
C1—H1B···O1^{iii}	0.96	2.51	3.388 (4)	152

Symmetry codes: (i) $2-x, 1-y, 1-z$; (ii) $x, \frac{1}{2}-y, \frac{1}{2}+z$; (iii) $2-x, y-\frac{1}{2}, \frac{3}{2}-z$; (iv) $x, y-1, z$.

All the H atoms were fixed geometrically and allowed to ride on their parent atoms, with C—H distances in the range 0.86–0.96 Å, and $U_{iso} = 1.5_{eq}$(C) for methyl H atoms and $1.2U_{eq}$(C) for the other H atoms.

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *XCAD*4 (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ZORTEP* (Zsolnai, 1997) and *PLATON* (Spek, 2000); software used to prepare material for publication: *SHELXL*97 and *PARST* (Nardelli, 1995).

KSS thanks the University Grants Commission (UGC), India, for the award of an FIP fellowship for the period 2001–2002. DV thanks the Department of Science and Technology (DST), India, for a major project.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1581). Services for accessing these data are described at the back of the journal.

References

Allinger, N. L. (1977). *J. Am. Chem. Soc.* **99**, 8127–8134.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Brown, M. L., Brown, G. B. & Brouillette, W. J. (1997). *J. Med. Chem.* **40**, 602–607.
Brouillette, W. J., Jestkov, V. P., Brown, M. L., Shamin Akhtar, M., DeLorey, T. M. & Brown, G. B. (1994). *J. Med. Chem.* **37**, 3289–3293.
Camerman, A. & Camerman, N. (1971). *Acta Cryst.* B**27**, 2205–2211.
Comber, R. N., Reynolds, R. C. & Buckheit, R. W. (1997). US Patent 5767140/1998; *Chem. Abstr.* (1997), **126**, 6496h.
Comber, R. N., Reynolds, R. C., Friedrich, J. D., Manguikian, R. A., Buckheit, R. W. Jr, Truss, J. W., Shannon, W. M. & Secrist, J. A. III (1992). *J. Med. Chem.* **35**, 3567–3572.
Enraf–Nonius (1994). *CAD*-4 *EXPRESS*. Version 5.0/1.2. Enraf–Nonius, Delft, The Netherlands.
Florencio, F., Verdier, P. S. & Blanco, S. G. (1978). *Acta Cryst.* B**34**, 1317–1321.
Fujiwara, H. & Van Der Ween, J. M. (1979). *J. Chem. Soc. Perkin Trans.* 2, pp. 659–663.
Harms, K. & Wocadlo, S. (1995). *XCAD*4. University of Marburg, Germany.
Kelly, T. A., Bormann, B. J., Fyre, L. L. & Wu, J.-P. (1997). US Patent 40011; *Chem. Abstr.* (1997), **129**, 260456g.
Knapp, F. F. (1979). *J. Org. Chem.* **44**, 1007–1009.
Koch, M. H., Germain, G., Declerq, J. P. & Dusausoy, Y. (1975). *Acta Cryst.* B**31**, 2547–2549.
Lehninger, A. L., Nelson, D. L. & Cox, M. M. (1993). *Principles of Biochemistry*, 2nd ed. Delhi, India: CBS Publishers and Distributors.
Malhotra, B., Dwivedi, A. K., Hora, V. & Hora, I. M. (1990). *J. Indian Chem. Soc.* **67**, 74–76.
Morkunas, A. R. & Miller, M. B. (1997). *Crit. Care Clinics*, **13**, 727–739.
Musson, D. G., Karashima, D., Rubiero, H., Melmon, K. L., Cheng, A. & Castagnoli, A. (1980). *J. Med. Chem.* **23**, 1318–1323.
Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
SethuSankar, K., Thennarasu, S., Velmurugan, D., Shanmuga Sundara Raj, S., Fun, H.-K. & Perumal, P. T. (2001). *Acta Cryst.* E**57**, o377–o379.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (2000). *PLATON*2000. University of Utrecht, The Netherlands.
Tunnicliff, G. (1996). *Gen. Pharmacol*, **27**, 1091–1097.
Verdier, P. S., Florencio, F. & Garcia-Blanco, S. (1977). *Acta Cryst.* B**33**, 3381–3385.
Verdier, P. S., Florencio, F. & Garcia-Blanco, S. (1979). *Acta Cryst.* B**35**, 216–217.
Woodbury, D. M. (1980). *Adv. Neurol.* **27**, 447–471.
Zsolnai, L. (1997). *ZORTEP*. University of Heidelberg, Germany.