Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

4-Amino-6-benzyloxy-2-(methylsulfanyl)-5-nitrosopyrimidine: hydrogen-bonded dimers linked into π-stacked chains

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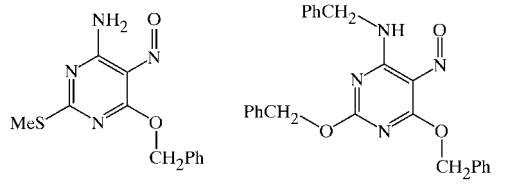
Received 22 March 2002
Accepted 28 March 2002
Online 30 April 2002

The title compound, $C_{12}H_{12}N_4O_2S$, crystallizes with $Z' = 2$ in space group $P2_1/c$. The intramolecular dimensions are consistent with a highly polarized electronic structure. Each of the independent molecules forms a centrosymmetric dimer linked by paired N—H···N hydrogen bonds, and these dimers are linked into a single type of chain by aromatic π–π-stacking interactions.

Comment

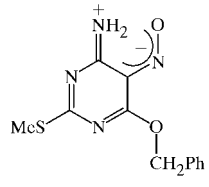
Alkoxy- and amino-substituted O^6-benzyloxy-5-nitrosopyrimidines (Marchal *et al.*, 2000, 2002; Quesada *et al.*, 2000) are important as potential, or proven, *in vitro* inhibitors of the human DNA-repair protein O^6-alkylguanine–DNA-transferase (Chae *et al.*, 1995; Quesada *et al.*, 2002). We report here the molecular and supramolecular structure of a closely related analogue, (I), containing a methylsulfanyl substituent.

The title compound, (I), crystallizes in space group $P2_1/c$ with two independent molecules in the asymmetric unit, *i.e.* with $Z' = 2$ (Fig. 1); no additional symmetry could be detected. The intramolecular dimensions of the two independent molecules are very similar (Table 1), and show a number of features typical of 5-nitrosopyrimidines (Low *et al.*, 2000; Low, Cannon *et al.*, 2001; Low, Moreno *et al.* 2001; Quesada *et al.*, 2002); in particular, there is marked fixation of the C—C and C—N bonds, with bonds C*n*2—N*n*3, C*n*4—N*n*4 and C*n*6—N*n*1 ($n = 1$ or 2) being short, despite the C*n*4—N*n*4 bond being formally a single bond in the classical representation of (I); in addition, the C—N and N—O distances in each C-nitroso

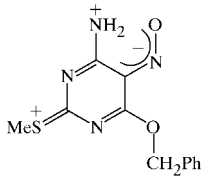


(I)

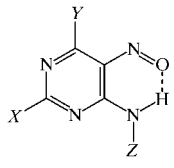
(II)



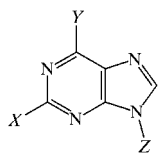
(Ia)



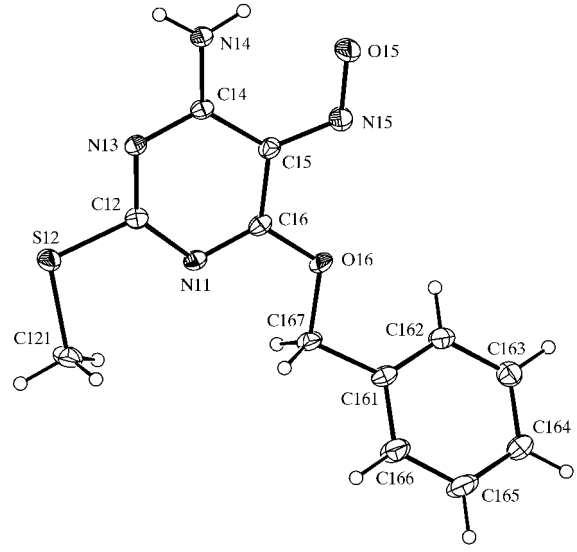
(Ib)



(III)



(IV)



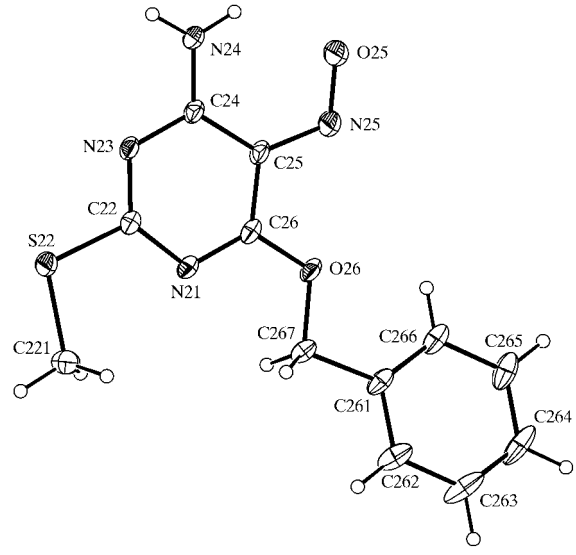


Figure 1
The two independent molecules of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

  DOI: 10.1107/S0108270102005735

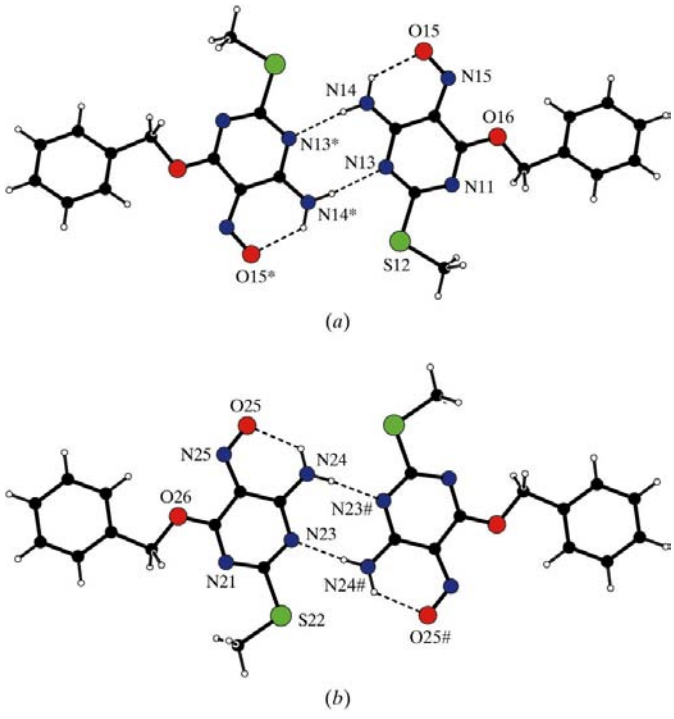


Figure 2
Part of the crystal structure of (I), showing the formation of hydrogen-bonded dimers (*a*) by molecules of type 1 and (*b*) by molecules of type 2. Atoms marked with an asterisk (*) or hash (#) are at the symmetry positions $(1-x, 1-y, 1-z)$ and $(-x, -y, 1-z)$, respectively.

fragment differ by only *ca* 0.11 Å, whereas in simple neutral compounds, where there is no possibility of significant electronic delocalization, these distances normally differ by at least 0.20 Å (Talberg, 1977; Schlemper *et al.*, 1986) and the N—O distance rarely exceeds 1.25 Å (Davis *et al.*, 1965; Bauer & Andreassen, 1972; Talberg, 1977; Schlemper *et al.*, 1986). The dimensions all point to the importance of the charge-separated form (I*a*) (see *Scheme*) as an important contributor. In this respect, the electronic structure of (I) resembles that of the 2-benzyloxy analogue, (II) (Quesada *et al.*, 2002). Although the C*n*2—S*n*2 (n = 1 or 2) distances are significantly shorter than typical C_{ar}—S distances (Allen *et al.*, 1987), there is no other support for a significant contribution from form (I*b*), although the atoms concerned in (I*b*) are almost coplanar (Table 1); the methyl–sulfur distances are entirely normal.

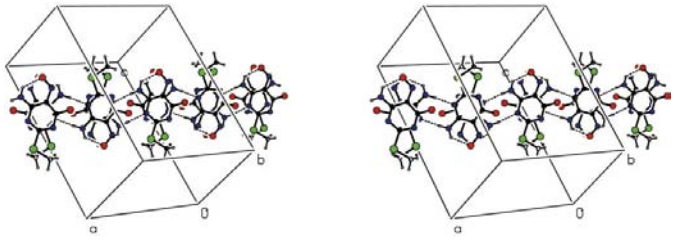


Figure 3
Stereoview of part of the structure of (I), showing a [100] chain formed by the linking of hydrogen-bonded dimers by means of π–π stacking. For the sake of clarity, the benzyl groups have been omitted.

In each of the independent molecules of (I), there is an intramolecular N—H···O hydrogen bond (Table 2) generating *S*(6) motifs; it is this motif which emphasizes the close similarity in overall molecular shape between 4-amino-5-nitrosopyrimidines, (III), and purines, (IV), which may indeed influence the biochemical activity of compounds of type (III). In addition, the molecules of each type are linked by paired N—H···N hydrogen bonds into centrosymmetric dimers (Fig. 2), in which the ring atoms N13 and N23 act as the acceptors (Table 2); molecules of type 1 (containing atom S12) form a dimer centred at $(\frac{1}{2},\frac{1}{2},\frac{1}{2})$, while molecules of type 2 (containing atom S22) form a dimer centred at $(0,\frac{1}{2},\frac{1}{2})$.

The formation of hydrogen-bonded dimers which themselves form no other hydrogen bonds is unusual in this type of pyrimidine (Quesada *et al.*, 2002); however, there are aromatic π–π-stacking interactions between the dimer units formed by (I). Within the asymmetric unit, the two pyrimidine planes make an angle of 0.57 (6)°; the centroid separation is 3.4421 (8) Å and the interplanar spacing *ca* 3.35 Å. Thus, the hydrogen-bonded dimer centred at $(\frac{1}{2},\frac{1}{2},\frac{1}{2})$ and formed by molecules of type 1 forms π–π-stacking interactions with the type 2 dimers centred at $(0,\frac{1}{2},\frac{1}{2})$ and $(1,\frac{1}{2},\frac{1}{2})$, and propagation of these interactions generates a chain running parallel to the [100] direction in which type 1 and type 2 dimers alternate (Fig. 3).

Experimental

Isoamyl nitrite (1.65 ml, 12 mmol) was added to a solution of 4-amino-6-benzyloxy-2-(methylsulfanyl)pyrimidine (2.47 g, 10 mmol) in dimethyl sulfoxide (DMSO, 25 ml). The reaction mixture was stirred at room temperature and monitored by thin-layer chromatography (eluant CH_2Cl_2/MeOH, 9:1 *v*/*v*) until the starting pyrimidine was no longer detected (24 h). Addition of water (50 ml) precipitated product (I). The product was filtered off, washed with water and dried, and then recrystallized from acetonitrile–dimethyl sulfoxide (5:1, *v*/*v*) (yield 2.10 g, 76%; m.p. 420 K). ^{1}H NMR (DMSO-d_6) δ: 10.02 (*bs*, 1H, NH_2), 8.80 (*bs*, 1H, NH_2), 7.55–7.58 (*m*, 2H), 7.40–7.46 (*m*, 5H), 5.70 (*s*, 2H, CH_2O), 2.57 p.p.m. (*s*, 3H, CH_3S); ^{13}C NMR (DMSO-d_6) δ: 177.8, 168.5, 145.7, 140.2, 135.9, 128.6, 128.5, 128.4, 69.1, 14.1 p.p.m. Crystals of (I) suitable for single-crystal X-ray diffraction analysis were selected directly from the analytical sample.

Crystal data

$C_{12}H_{12}N_4O_2S$
M_r = 276.32
Monoclinic, $P2_1/c$
a = 15.6152 (10) Å
b = 9.1842 (6) Å
c = 17.7920 (11) Å
β = 90.830 (2)°
V = 2551.3 (3) Å^3
Z = 8
D_x = 1.439 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 6223 reflections
θ = 1.3–29.0°
μ = 0.26 mm^{-1}
T = 120 (2) K
Block, colourless
0.50 × 0.35 × 0.20 mm

Data collection

Bruker SMART1000 CCD diffractometer
φ scans, and ω scans with κ offsets
Absorption correction: multi-scan (*SADABS*; Bruker, 1997)
T_{min} = 0.882, T_{max} = 0.950
24 010 measured reflections
6223 independent reflections
4840 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 29.0°
$h = -20 \rightarrow 20$
$k = -12 \rightarrow 12$
$l = -23 \rightarrow 23$
Intensity decay: negligible

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.058P)^2 + 0.327P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.037$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.101$	$\Delta\rho_{max} = 0.35$ e Å^{-3}
$S = 1.05$	$\Delta\rho_{min} = -0.25$ e Å^{-3}
6223 reflections	
345 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

N11—C12	1.347 (2)	N21—C22	1.351 (2)
C12—N13	1.336 (2)	C22—N23	1.329 (2)
N13—C14	1.351 (2)	N23—C24	1.354 (2)
C14—C15	1.438 (2)	C24—C25	1.434 (2)
C15—C16	1.421 (2)	C25—C26	1.417 (2)
C16—N11	1.321 (2)	C26—N21	1.323 (2)
C12—S12	1.740 (2)	C22—S22	1.741 (2)
S12—C121	1.799 (2)	S22—C221	1.789 (2)
C14—N14	1.327 (2)	C24—N24	1.321 (2)
C15—N15	1.376 (2)	C25—N25	1.374 (2)
N15—O15	1.262 (2)	N25—O25	1.259 (2)
C16—O16	1.335 (2)	C26—O26	1.329 (2)
C121—S12—C12—N13	−177.1 (1)	C221—S22—C22—N23	−178.0 (1)
O15—N15—C15—C16	178.5 (1)	O25—N25—C25—C26	178.3 (1)

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

D—H···A	D—H	H···A	D···A	D—H···A
N14—H14A···N13^{i}	0.88	2.20	3.073 (2)	171
N14—H14B···O15	0.88	2.04	2.661 (2)	127
N24—H24A···N23^{ii}	0.88	2.12	2.985 (2)	168
N24—H24B···O25	0.88	2.03	2.655 (2)	127

Symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $-x, 1-y, 1-z$.

H atoms were treated as riding, with C—H distances in the range 0.95–0.99 Å and N—H distances of 0.88 Å.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SHELXTL* (Bruker, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2002); software used to prepare material for publication: *SHELXL*97 and *PRPKAPPA* (Ferguson, 1999).

X-ray data were collected at the EPSRC X-ray Crystallographic Service, University of Southampton, England, using a Bruker SMART1000 CCD diffractometer. The authors thank the staff for all their help and advice. JNL thanks NCR Self-Service Dundee for grants which have provided computing facilities for this work.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1564). Services for accessing these data are described at the back of the journal.

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