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2-Amino-6-methoxy-4-(4-methylanilino)-5-nitrosopyrimidine and ethyl *N*-[4-(adamantan-1-ylamino)-2-amino-5-nitrosopyrimidin-6-yl]-3-aminopropionate: polarized electronic structures and hydrogen-bonded supramolecular assembly in one and two dimensions

Andrés F. Yépes,[a]‡ Alirio Palma,[b] Antonio Marchal,[a] Justo Cobo[a] and Christopher Glidewell[c]*

[a]Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain, [b]Laboratorio de Síntesis Orgánica, Escuela de Química, Universidad Industrial de Santander, AA 678 Bucaramanga, Colombia, and [c]School of Chemistry, University of St Andrews, Fife KY16 9ST, Scotland
Correspondence e-mail: cg@st-andrews.ac.uk

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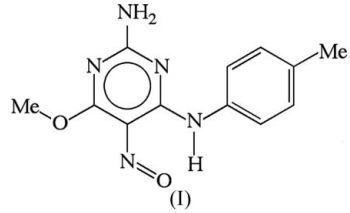
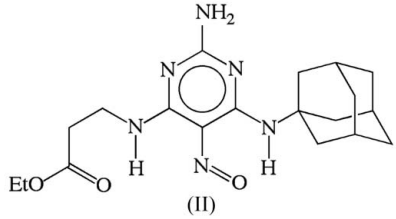
In both 2-amino-6-methoxy-4-(4-methylanilino)-5-nitrosopyrimidine, $C_{12}H_{13}N_5O_2$, (I), and ethyl *N*-[4-(1-adamantylamino)-2-amino-5-nitrosopyrimidin-6-yl]-3-aminopropionate, $C_{19}H_{28}N_6O_3$, (II), the nitrosopyrimidine unit is planar and the bond distances provide evidence for significant polarization of the electronic structures. In (II), the ethoxycarbonyl fragment of the molecule is disordered over two sets of sites with occupancies of 0.910 (4) and 0.090 (4). In the molecules of both compounds, there is an intramolecular N—H···O hydrogen bond. The molecules of (I) are linked into a chain of rings by a combination of N—H···O and C—H···O hydrogen bonds, while the molecules of (II) are linked by a two-centre N—H···N hydrogen bond and a three-centre N—H···(N,O) hydrogen bond to form sheets containing four distinct types of ring.

Comment

5-Nitrosopyrimidines constitute versatile intermediates for the design and synthesis of fused polycyclic pharmaceutical targets such as purines, pteridines and nucleoside analogues (Hurst, 1980). We report here the structures of two such nitrosopyrimidine derivatives, the title compounds (I) (Fig. 1) and (II) (Fig. 2), both prepared using nucleophilic displacement of methoxy substituents by amino units, following a recently reported procedure (Marchal *et al.*, 2010).


(I)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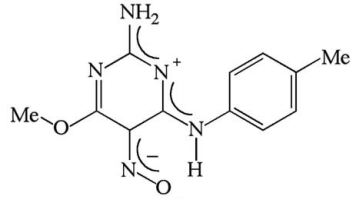
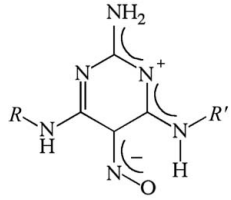
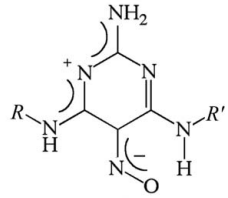

(I*a*)


(II*a*)


(II*b*)

Within the molecules of (I) and (II), the pyrimidine rings are planar. The maximum deviations of the ring atoms from the mean planes through atoms N1–C6 (Figs. 1 and 2) are 0.007 (3) Å for atom N3 in (I) and 0.026 (2) Å for atom C5 in (II). Similarly, the nitroso groups are effectively coplanar with the pyrimidine rings: atom O51 deviates from the pyrimidine mean plane by only 0.053 (2) Å in (I) and 0.001 (2) Å in (II). Indeed, in (I), the only significant deviation from planarity of the entire molecular skeleton is exhibited by the aryl ring, which makes a dihedral angle of 5.0 (2)° with the adjacent pyrimidine ring. This ring planarity in (I) and (II) may be contrasted with the nonplanarity often observed for pyrimidine rings bearing adjacent bulky substituents at the 4-, 5- and 6-positions, where such rings are often, but not always, markedly nonplanar, leading to a variety of ring conformations including boat forms (Quesada *et al.*, 2004; Low *et al.*, 2007; Trilleras *et al.*, 2007; Cobo *et al.*, 2008), twist-boat forms (Melguizo *et al.*, 2003; Quesada *et al.*, 2003; Cobo *et al.*, 2008) and a screw-boat form (Low *et al.*, 2007), as well as a range of intermediate forms.

The ethoxycarbonyl unit in (II), encompassing atoms O63, O64, C65 and C66 and the associated H atoms (Fig. 2), is disordered over two sets of atomic sites, with refined occupancies of 0.910 (4) and 0.090 (4). The difference between the two orientations corresponds to a rotation of *ca* 25° about the C62—C63 bond, while the dispositions of the ethyl groups

‡ Permanent address: Laboratorio de Síntesis Orgánica, Escuela de Química, Universidad Industrial de Santander, AA 678 Bucaramanga, Colombia.

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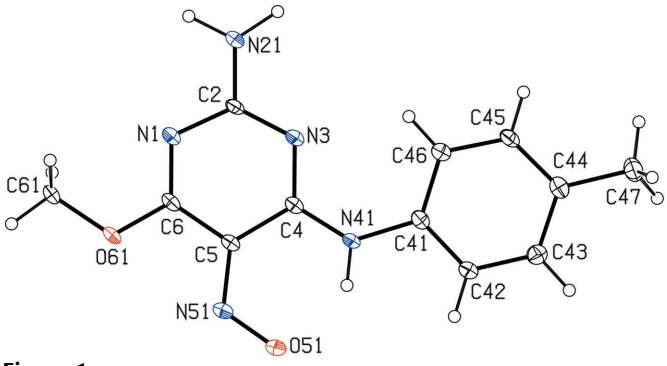

Figure 1
The molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

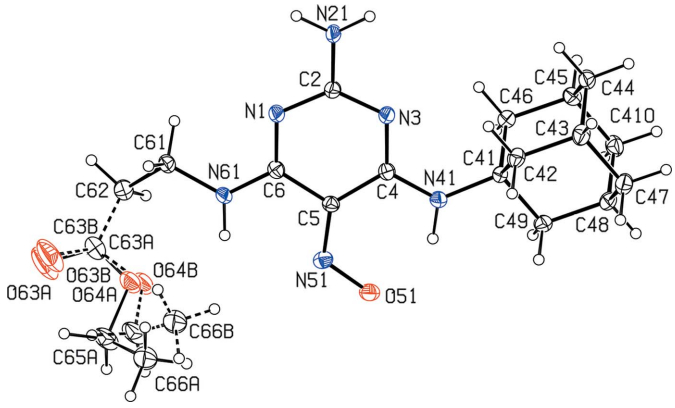

Figure 2
The molecular structure of (II), showing the atom-labelling scheme. The major and minor orientation components, denoted *A* and *B*, respectively, have refined site occupancies of 0.910 (4) and 0.090 (4). Displacement ellipsoids are drawn at the 30% probability level.

relative to the rest of the side chain also differ (Fig. 2 and Table 1).

Each compound contains an intramolecular N—H···O hydrogen bond (Table 2) having the nitroso O atoms as the acceptor in an *S*(6) motif (Bernstein *et al.*, 1995). The formation of this hydrogen bond may be linked to the planarity of the nitrosopyrimidine unit in each compound. There are also two further short intramolecular contacts in (II), both involving atom N61 (Table 2), but their *D*—H···*A* angles are far too small for them to be regarded as hydrogen bonds (Wood *et al.*, 2009). Nonetheless, the associated molecular conformation (Fig. 2) effectively prevents atom N61 from playing any role in the supramolecular assembly in (II).

Some of the bond distances in the molecules of (I) and (II) (Table 1) are of particular interest. In (I), the four independent N—C distances in the N21/C2/N3/C4/N41 fragment all have very similar values, lying in the range 1.328 (4)–1.332 (4) Å, despite the fact that the exocyclic N—C bonds are formally single bonds while the ring bonds are formally of aromatic type. On the other hand, the N1—C6 bond is significantly shorter, and N1—C2 significantly longer, than the other N—C bonds in the molecule of (I), while the C4—C5 and C5—C6 bonds are both long for their type (Allen *et al.*, 1987). At the same time, the difference between the C5—N51 and N51—O51 distances is only 0.074 (4) 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 NO distance rarely exceeds 1.25 Å (Davis *et al.*, 1965; Bauer & Andreassen, 1972; Talberg, 1977; Schlemper *et al.*, 1986).

In combination, these observations point to significant polarization of the electronic structure of (I), with delocalized charges as in (I*a*) (see Scheme). Rather similar remarks apply to the bond lengths in (II), except that the difference between the C5—N51 and N51—O51 bond lengths is even smaller in (II), at only 0.043 (3) Å, than it is in (I), while the N1—C6 and C5—N51 bond lengths in (II) are identical within experimental uncertainty, suggesting that forms (II*a*) and (II*b*) (see Scheme) both contribute to the overall electronic structure of (II).

In (I), the supramolecular assembly is determined by two intermolecular hydrogen bonds, one each of the N—H···N and C—H···O types (Table 2). The N21—H21*A* bond plays no part in the assembly as there are no other potential acceptors within plausible hydrogen-bonding distance of atom N21. In particular, N—H···π(arene) interactions are absent from the crystal structure of (I). Atom N21 in the molecule at (*x*, *y*, *z*) forms, *via* atom H21*B*, a nearly linear hydrogen bond to atom N51 in the molecule at (*x*, *y* − 1, *z*), so generating a *C*(7) chain running parallel to the [010] direction. In addition, atom C46 at (*x*, *y*, *z*) acts as a hydrogen-bond donor to atom O51, also in the molecule at (*x*, *y* − 1, *z*), so forming a second chain motif parallel to [010], this time of *C*(8) type and modestly reinforcing the action of the N—H···N hydrogen bond. The combination of these two interactions generates a chain of $R_2^2(11)$ rings (Fig. 3). There are no C—H···π(arene) hydrogen bonds or aromatic π–π stacking interactions in the crystal structure of (I), so that the supramolecular aggregation is one-dimensional.

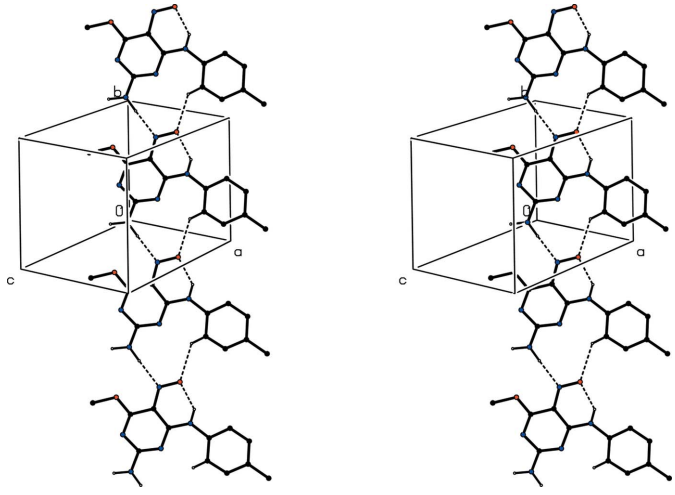

Figure 3
A stereoview of part of the crystal structure of (I), showing the formation of a chain of $R_2^2(11)$ hydrogen-bonded rings parallel to [010]. For the sake of clarity, H atoms bonded to C atoms but not involved in the motif shown have been omitted.

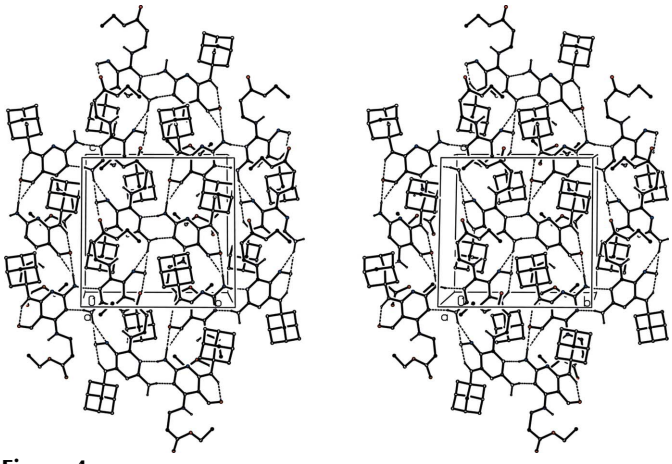

Figure 4
A stereoview of part of the crystal structure of (II), showing the formation of a hydrogen-bonded sheet parallel to (100). For the sake of clarity, only the major orientation component is included, and H atoms bonded to C atoms have all been omitted.

By contrast, the supramolecular assembly in (II) leads to a two-dimensional hydrogen-bonded structure. While both N—H bonds of the NH_2 group in (II) participate in intermolecular hydrogen bonding (Table 2), atom N61 is, as noted above, effectively prevented from participation by the adjacent substituents. Amino atom N21 in the molecule at (x, y, z) forms, *via* atom H21*B*, a nearly linear hydrogen bond to ring atom N1 in the molecule at $(-x+1, -y+1, -z+1)$, so forming a centrosymmetric $R_2^2(8)$ dimer motif centred at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$. It is convenient to consider this dimeric unit as the basic building block in the structure of (II). The $R_2^2(8)$ motif is a very common feature in the supramolecular assembly of amino-substituted pyrimidines (Rodríguez *et al.*, 2008), sometimes giving simple dimeric aggregates (Quesada *et al.*, 2004), sometimes linear tetrameric aggregates (Bowes *et al.*, 2003) and sometimes continuous chains of edge-fused rings (Low *et al.*, 2002; Glidewell *et al.*, 2003; Melguizo *et al.*, 2003; Rodríguez *et al.*, 2008).

Amino atom N21 at (x, y, z) also forms, *via* atom H21*A*, a planar three-centre N—H···(N,O) hydrogen bond to nitroso atoms N51 and O51 in the molecule at $(x, -y+\frac{1}{2}, z-\frac{1}{2})$. This interaction directly links the $R_2^2(8)$ dimer centred at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$ to the four symmetry-related dimers centred at, respectively, $(\frac{1}{2}, 0, 0)$, $(\frac{1}{2}, 1, 0)$, $(\frac{1}{2}, 0, 1)$ and $(\frac{1}{2}, 1, 1)$, thereby forming a hydrogen-bonded sheet lying parallel to (100) (Fig. 4). Within this sheet, there are four different ring types, *viz.* $S(6)$, $R_1^2(3)$, $R_2^2(8)$ and $R_6^6(30)$.

Experimental

For the synthesis of (I), 4-toluidine (2.0 mmol) was added to a suspension of 2-amino-4,6-dimethoxy-5-nitrosopyrimidine (1.00 mmol) in water (10 ml) and the mixture was stirred at ambient temperature and monitored by thin-layer chromatography (TLC) on silica gel, using dichloromethane–methanol (9:1 *v*/*v*) as eluent, until no starting material was detected. The resulting precipitate was collected by filtration, washed with water and dried in a vacuum desiccator in the presence of potassium hydroxide pellets to provide (I) as a brown solid (yield 97%, m.p. 488–490 K). Crystals of (I) suitable for single-crystal X-ray diffraction were grown by slow evaporation, at ambient temperature and exposed to air, from a solution in methanol. MS (EI, 70 eV): 259 (M^+, 88), 242 (100), 197 (25), 172 (13), 158 (15), 91 (17). HR–MS (EI), found: 259.1067; $C_{12}H_{13}N_5O_2$ requires: 259.1069.

For the preparation of (II), a solution containing 6-[(adamantan-1-yl)amino]-2-amino-5-nitrosopyrimidine (0.2 mmol), β-alanine ethyl ester hydrochloride (0.4 mmol) and diisopropylethylamine (2.0 mmol) in dimethylformamide (1 ml) was heated at 363 K. The reaction was monitored by TLC on silica gel, using dichloromethane–methanol (9:1 *v*/*v*) as eluent, until no starting material was detected. The solution was cooled to ambient temperature and water (20 ml) was added dropwise under continuous stirring until a fine solid appeared as a suspension. This red solid, (II), was collected by filtration, washed with water and dried in a vacuum desiccator in the presence of potassium hydroxide pellets (yield 88%, m.p. 418–420 K). Crystals of (II) suitable for single-crystal X-ray diffraction were grown by slow evaporation, at ambient temperature and exposed to air, from a solution in acetonitrile. MS (EI, 70 eV): 388 (M^+, 34), 371 (13), 343 (15), 301 (19), 273 (25), 135 (100). HR–MS (EI), found: 388.2223; $C_{19}H_{28}N_6O_3$ requires: 388.2226.

Compound (I)

Crystal data

$C_{12}H_{13}N_5O_2$
$M_r = 259.27$
Triclinic, $P\overline{1}$
$a = 6.975$ (2) Å
$b = 7.4704$ (10) Å
$c = 12.161$ (4) Å
$\alpha = 102.90$ (2)°
$\beta = 92.64$ (3)°
$\gamma = 101.144$ (19)°
$V = 603.4$ (3) Å^3
$Z = 2$
Mo $K\alpha$ radiation
$\mu = 0.10$ mm^{-1}
$T = 120$ K
0.31 × 0.17 × 0.14 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{min} = 0.960$, $T_{max} = 0.986$
12902 measured reflections
2249 independent reflections
1607 reflections with $I > 2\sigma(I)$
$R_{int} = 0.079$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.067$
$wR(F^2) = 0.203$
$S = 1.07$
2249 reflections
174 parameters
H-atom parameters constrained
$\Delta\rho_{max} = 0.37$ e Å^{-3}
$\Delta\rho_{min} = -0.36$ e Å^{-3}

Compound (II)

Crystal data

$C_{19}H_{28}N_6O_3$
$M_r = 388.47$
Monoclinic, $P2_1/c$
$a = 11.6250$ (12) Å
$b = 13.2225$ (11) Å
$c = 13.0172$ (13) Å
$\beta = 101.920$ (8)°
$V = 1957.7$ (3) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.09$ mm^{-1}
$T = 120$ K
0.40 × 0.16 × 0.16 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{min} = 0.946$, $T_{max} = 0.986$
25767 measured reflections
3639 independent reflections
2325 reflections with $I > 2\sigma(I)$
$R_{int} = 0.069$

Table 1
Selected bond distances (Å) and torsion angles (°) for (I) and (II).

	(I)	(II)
N1—C2	1.382 (4)	1.370 (3)
C2—N3	1.332 (4)	1.347 (3)
N3—C4	1.331 (4)	1.335 (3)
C4—C5	1.460 (4)	1.457 (4)
C5—C6	1.424 (4)	1.452 (4)
C6—N1	1.303 (4)	1.331 (3)
C2—N21	1.328 (4)	1.331 (3)
C4—N41	1.332 (4)	1.332 (3)
C5—N51	1.347 (4)	1.333 (3)
N51—O51	1.273 (3)	1.290 (3)
C6—O61	1.336 (3)	
C6—N61		1.373 (3)
C4—C5—N51—O51	0.4 (5)	0.4 (4)
C4—N41—C41—C42	−173.0 (3)	64.7 (3)
C4—N41—C41—C46		−58.2 (3)
C4—N41—C41—C49		−176.6 (2)
C5—C6—O61—C61	−175.7 (3)	
C5—C6—N61—C61		−171.0 (2)
C6—N61—C61—C62		149.6 (2)
N61—C61—C62—C63*A*		75.0 (3)
C61—C62—C63*A*—O64*A*		−32.0 (4)
C62—C63*A*—O64*A*—C65*A*		177.(3)
C63*A*—O64*A*—C65*A*—C66*A*		−162.7 (3)
N61—C61—C62—C63*B*		75.0 (3)
C61—C62—C63*B*—O64*B*		−57.0 (10)
C62—C63*B*—O64*B*—C65*B*		153.5 (19)
C63*A*—O64*B*—C65*B*—C66*B*		−116 (3)

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.059$	7 restraints
$wR(F^2) = 0.154$	H-atom parameters constrained
$S = 1.02$	$\Delta\rho_{max} = 0.31$ e Å^{-3}
3639 reflections	$\Delta\rho_{min} = -0.31$ e Å^{-3}
268 parameters	

It was apparent from an early stage in the refinement of (II) that the ester group was disordered. This unit was subsequently modelled using two sets of atomic sites, denoted *A* and *B* for the major and minor orientation components, respectively (Fig. 2), such that the two components differ by their orientation about the C62—C63 bond. The directly bonded interatomic distances and the one-angle nonbonded distances in the minor components were restrained to be equal to the corresponding distances in the major component, subject to s.u. values of 0.005 and 0.01 Å, respectively. The anisotropic displacement parameter components for pairs of partially occupied atomic sites occupying similar regions of space were constrained to be equal. Subject to these conditions, the site-occupancy factors refined to 0.910 (4) and 0.090 (4), respectively. All H atoms were located in difference maps, apart from those in the minor orientation component of (II), which were added in calculated positions. H atoms bonded to C atoms were then treated as riding in geometrically idealized positions, with C—H = 0.95 (aromatic), 0.98 (CH_3), 0.99 (CH_2) or 1.00 Å (aliphatic C—H), and with $U_{iso}(H) = kU_{eq}(C)$, where $k = 1.5$ for the methyl groups, which were permitted to rotate but not to tilt, and 1.2 for all other C-bound H atoms. H atoms bonded to N atoms were permitted to ride at the positions located in the difference maps, with $U_{iso}(H) = 1.2U_{eq}(N)$, giving ranges of N—H distances of 0.88–1.02 Å for (I) and 0.91–0.96 Å for (II) (Table 2).

For both compounds, data collection: *COLLECT* (Nonius, 1999); cell refinement: *DIRAX*/*LSQ* (Duisenberg *et al.*, 2000); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97* and *PLATON*.

Table 2
Hydrogen bonds and short intramolecular contacts (Å, °) for (I) and (II).

	D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
(I)	N21—N21B···N51^{i}	1.01	1.98	2.990 (4)	177
	N41—H41···O51	0.88	1.87	2.584 (3)	137
	C46—H46···O51^{i}	0.95	2.42	3.143 (4)	133
(II)	N21—H21*A*···O51^{ii}	0.95	2.13	3.081 (3)	178
	N21—H21*A*···N51^{ii}	0.95	2.26	3.104 (3)	147
	N21—H21*B*···N1^{iii}	0.96	2.17	3.121 (3)	170
	N41—H41···O51	0.94	1.88	2.663 (3)	139
	N61—H61···O64*A*	0.91	2.36	2.843 (3)	113
	N61—H61···O64*B*	0.91	2.13	2.71 (2)	120
	N61—H61···N51	0.91	2.26	2.653 (3)	105

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

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3170). Services for accessing these data are described at the back of the journal.

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