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Polymorph VI of sulfapyridine: interpenetrating two- and three-dimensional hydrogen-bonded nets formed from two tautomeric forms

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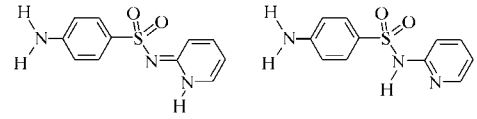
Polymorph VI of 4-amino-*N*-(2-pyridyl)benzenesulfonamide, $C_{11}H_{11}N_3O_2S$, is monoclinic (space group $P2_1/n$). The asymmetric unit contains two different tautomeric forms. The structure displays N—H···N and N—H···O hydrogen bonding. The two independent molecules form two separate two- and three-dimensional hydrogen-bonded networks which interpenetrate. The observed patterns of hydrogen bonding are analogous to those in polymorph I of sulfathiazole.

Comment

Sulfapyridine [or 4-amino-*N*-(2-pyridyl)benzenesulfonamide], was the first synthetic antibacterial agent effective against pneumonia. Its success marked the rise of the modern pharmaceutical industry. The versatile polymorphic behaviour of sulfapyridine has been studied extensively. Reimers (1941) determined the melting points of four forms. Castle & Witt (1946) identified five forms by melting point and optical characteristics. Burger *et al.* (1980) studied the thermodynamic relationships between five forms. Yang & Guillory (1972) reported the existence of six forms. Kuhnert-Brandstätter & Bachleitner-Hoffmann (1971) identified seven forms by hot-stage microscopy. It is easy to observe a multiplicity of forms, particularly by differential scanning calorimetry or by hot-stage microscopy. It is difficult to reconcile the forms identified in the literature because of the different techniques used and the absence of spectral reference data. However, comparison of the data suggests that nine forms may have been identified, which is also the number of forms noted in our own work. It is also difficult to obtain samples of sufficient purity and crystal size to obtain crystal structures. The Cambridge Structural Database (CSD, Version 1.9; Allen, 2002) contains structures of four modifications, II–V, determined by Basak *et al.* (1984), Bar & Bernstein (1985) and Bernstein (1988). Colourless crystals of form VI of sulfapyridine were obtained by pouring molten sulfapyridine into boiling toluene, as detailed below.



Sulfapyridine can adopt two tautomeric forms (see scheme above). The previously reported polymorphs II–V all contain exclusively the imide–pyridinium form. The NH_2 and NH groups provide three possible hydrogen-bond donor sites for hydrogen bonds. There are four potential acceptor sites per molecule, provided by the SO_2 and the NH_2 groups and the N atoms of either the imide (imide form) or the pyridyl ring (amide form) group. Different combinations of these donor and acceptor functions are employed in polymorphs II–V, so that different hydrogen-bonded nets are observed in these structures. However, all these modifications except polymorph III contain a (pyridine)N—H···N(imide)-bonded dimer. The dimer can adopt a centrosymmetric configuration (forms II and IV) or pseudo-twofold symmetry (form V).

The structure determination of form VI revealed the presence of two independent molecules (Fig. 1), one adopting the imide and the other the amide form. Their main conformational difference is a rotation of the pyridyl ring about the C—N bond, so that the corresponding S—N—C—N torsion angle is 167.6 (2)° for the imide and −153.7 (2)° for the amide form. The two independent molecules are involved in two distinct patterns of classical hydrogen bonding (see Table 1 for parameters). Both patterns are based on an N—H···N-

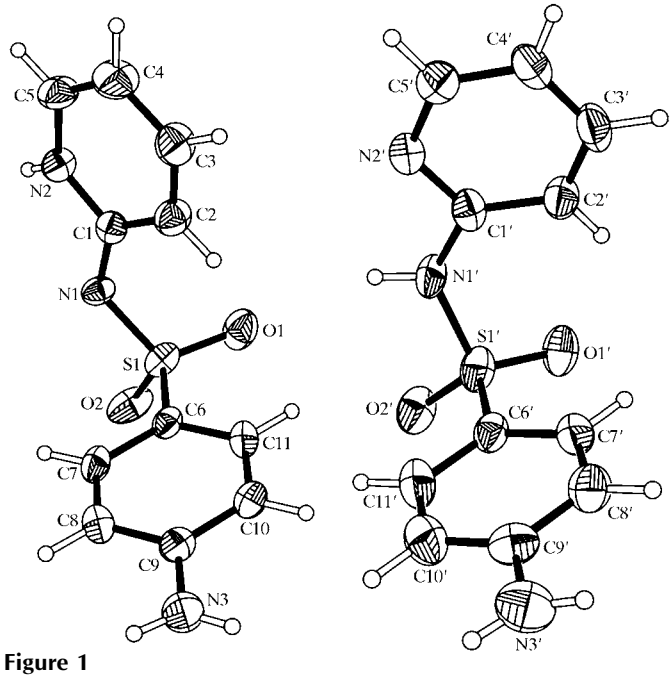


Figure 1
Molecules of the imide (left) and amide (right) forms of the title compound, showing the atomic numbering schemes. Displacement ellipsoids are drawn at the 50% probability level. The diagram does not reflect the actual mutual orientation of the two molecules in the crystal structure.

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bonded centrosymmetric dimer with a central $R_2^2(8)$ ring (Bernstein *et al.*, 1995), which was also present in forms II and IV. The geometry of the two independent dimers is similar, but the H atom bonded to N is, of course, in a different position in the two tautomers. Each dimeric unit contains an additional pair of intermolecular C—H···O contacts [imide dimer: C···O = 3.091 (4) Å and C—H···O = 128°; amide dimer: C···O = 3.314 (4) Å and C—H···O = 140°].

Furthermore, the imide molecule forms hydrogen bonds to four imide neighbours. These N—H···O interactions involve both aniline H atoms and both sulfonyl O atoms as acceptors.

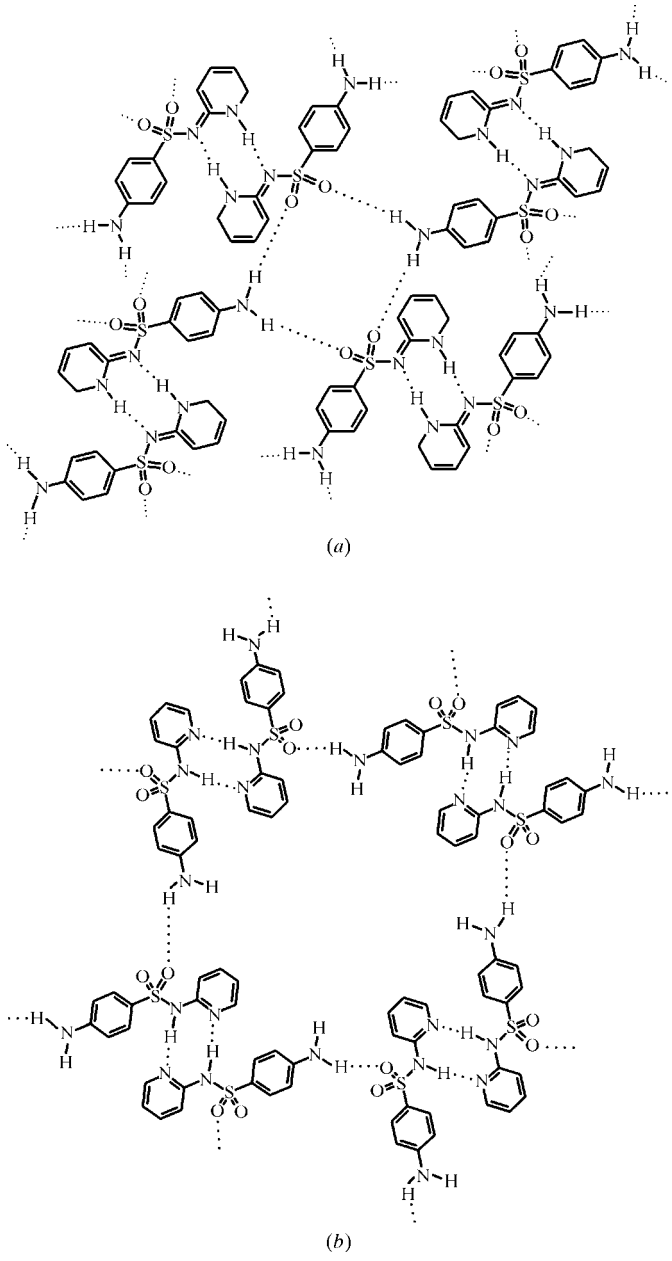

Figure 2
(*a*) The $R_4^4(12)$ ring in the three-dimensional hydrogen-bonded net of imide molecules. Four N—H···N imide/amide dimers are linked by N—H···O contacts. (*b*) The open $R_6^6(42)$ ring in the two-dimensional hydrogen-bonded net of amide molecules. Four amide/imide N—H···N-bonded dimers are linked by four N—H···O contacts.

They connect four dimeric units to give a centrosymmetric $R_4^4(12)$ ring, as shown in Fig. 2(*a*). The ring is itself just a fragment of a three-dimensional hydrogen-bonded network of imide molecules (Fig. 3). By contrast, molecules adopting the amide form are linked into a two-dimensional net. Each amide molecule forms just one pair of N—H···O contacts in addition to its dimeric bonds. Fig. 2(*b*) shows how four dimeric units are connected in a centrosymmetric $R_6^6(42)$ ring. This two-dimensional net has a simple (4,4) topology (Wells, 1977) if each dimeric unit is regarded is a single node and the four N—H···O interactions that connect to four neighbouring dimers are regarded as vertices. The two-dimensional hydrogen-bonded amide nets lie parallel to the $(10\bar{1})$ plane and interpenetrate the three-dimensional imide net (Fig. 3).

Sulfathiazole is another sulfa drug whose polymorphism has been studied extensively (Apperley *et al.*, 1999). The arrangement of hydrogen-bond donor and acceptor functions in the molecule of sulfathiazole is very similar to that found in sulfapyridine. The amide/imide N—H···N-bonded dimer that dominates the known sulfapyridine structures is observed in only one of the five structurally characterized polymorphs of sulfathiazole. A comparison between this form I of sulfathiazole ($P2_1/c$, $Z = 8$, $a = 10.554$ Å, $b = 13.220$ Å, $c = 17.050$ Å, $\beta = 108.1°$; Kruger & Gafner, 1972) and the new polymorph VI of sulfapyridine reveals a very close relationship. In fact, they are structural analogues. The main features discussed above for the sulfapyridine VI structure – the combination of hydrogen-bond donor and acceptor functions employed, the way in which the three- and two-dimensional networks are generated, and how they interpenetrate – are also present in sulfathiazole I [see also Blagden *et al.* (1998)]. There is an important difference, though, since the sulfathiazole polymorph contains just one tautomeric form of the molecule, *viz*. the imide. A comparison using the program *XPac* (Gelbrich & Hursthouse, 2005; Gelbrich, 2006) confirms that the resulting packing arrangements of molecules are also very similar. This is illustrated in Fig. 4. The molecules in these two structures pack in a similar fashion along the respective [100] (10.83 and 10.55 Å)

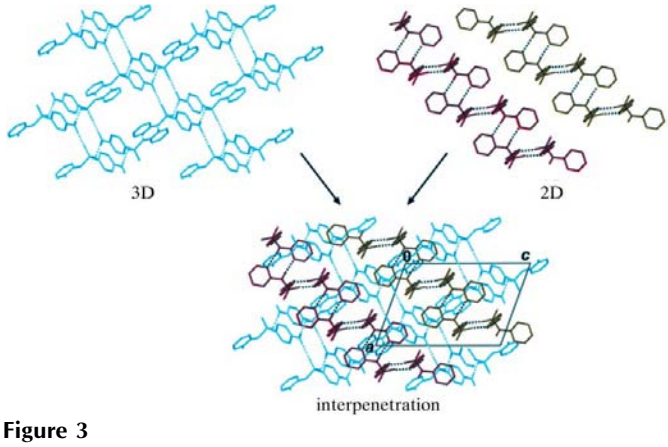

Figure 3
The crystal packing of sulfapyridine VI viewed along the *b* axis. Top left: the three-dimensional net of hydrogen-bonded imide molecules. Top right: the two two-dimensional parallel nets of amide molecules. Bottom: the interpenetration of two- and three-dimensional nets.

and [010] (14.93 and 13.22 Å) directions. Their packing parallel to the *c* axis in sulfapyridine VI is the same as that along the diagonal of the *ac* plane in sulfathiazole I (15.49 and 17.04 Å). Note that the corresponding $P2_1/c$ to $P2_1/n$ transformation of the original cell of sulfathiazole I with $T = (100\ 0\bar{1}0\ \bar{1}0\bar{1})$ leaves the length of the *c* axis and the β angle almost unchanged (the dimensions of the transformed $P2_1/n$ cell are $a = 10.554$ Å, $b = 13.220$ Å, $c = 17.045$ Å, $\beta = 108.0°$). The fact that sulfathiazole I is the stable polymorph between 389 K and the melting point at 475 K, whilst the isostructural sulfapyridine VI has no range of stability and is converted into the stable form within a few days storage, shows how sensitive stability is to small structural changes. Grzesiak *et al.* (2003) noted that the CSD contains six different structures of ROY {5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile; see also Chen *et al.* (2005)} and five of sulfathiazole. Sulfapyridine now joins sulfathiazole as an example of a compound with five known structures.

The hydrogen-bond donor function associated with aniline atom H4N′ of the amide molecule is not used in any of the interactions discussed above for sulfapyridine form VI. The closest intermolecular contact of H4N′ exists to atom O1($-x+1, -y+2, -z$) of an imide molecule [N···O = 3.384 (4) Å, H···O = 2.72 (3) Å and N—H···O = 134.3 (3)°].

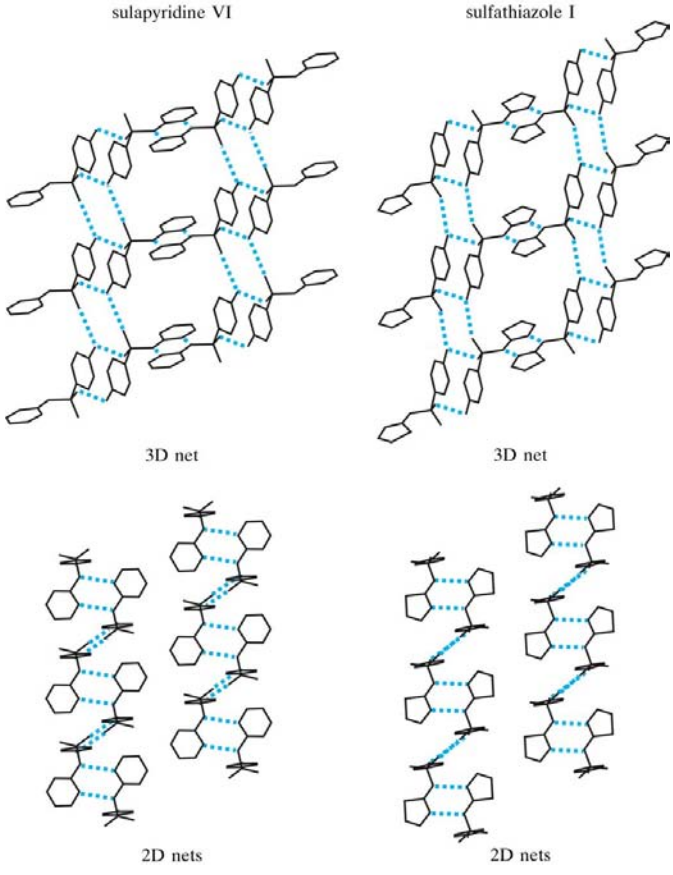

Figure 4
A comparison of the packing of molecules in polymorph VI of sulfapyridine and polymorph I of sulfathiazole. Alignment of one three-dimensional (top) and two two-dimensional (bottom) nets (both structures are viewed parallel to the *b* axis).

The shortest intermolecular contacts of atom O1′, which is not engaged in classical hydrogen bonding, are C3′—H3′···O1′($-x+1, -y+1, -z$) and C7—H7···O1′($-x+\frac{3}{2}, y+\frac{1}{2}, -z+\frac{1}{2}$) [C···O = 3.333 (4) and 3.386 (4) Å, and C—H···O = 129 and 127°].

Experimental

Sulfapyridine (1 g) was melted at 468 K in a boiling tube under nitrogen, kept at that temperature for 5 min to destroy any remnant clusters of the stable polymorph and poured carefully into 30 ml of boiling toluene. This caused considerable turbulence and resulted in a few solidified globules of sulfapyridine plus some crystal flakes. The formation of these crystals was probably due to crystallization from solution under the influence of the many seeds arising from the solidification and dispersion. The reasons why this procedure gives the imide/amide polymorph, the structure of which is reported here, has been discussed by Threlfall (2003). This polymorph can be identified with polymorph III of the pharmaceutical literature described by Burger *et al.* (1980) and others. Polymorph III of the CSD is the stable sulfapyridine polymorph I of the pharmaceutical literature, which has been so described for almost 70 years. Only small and imperfectly formed crystals could be obtained, and the high merging *R* factor of the collected data set may be ascribed to the large number of weak reflections and the generally high anisotropic mosaicity.

Crystal data

$C_{11}H_{11}N_3O_2S$
$M_r = 249.29$
Monoclinic, $P2_1/n$
$a = 10.827$ (2) Å
$b = 14.932$ (3) Å
$c = 15.486$ (3) Å
$\beta = 110.07$ (3)°
$V = 2351.6$ (9) Å^3
$Z = 8$
Mo $K\alpha$ radiation
$\mu = 0.27$ mm^{-1}
$T = 120$ (2) K
0.25 × 0.20 × 0.15 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{min} = 0.903$, $T_{max} = 0.956$
23782 measured reflections
4717 independent reflections
2572 reflections with $I > 2\sigma(I)$
$R_{int} = 0.140$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.055$
$wR(F^2) = 0.130$
$S = 0.90$
4717 reflections
327 parameters
4 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.26$ e Å^{-3}
$\Delta\rho_{min} = -0.35$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2N···N1^{i}	0.84 (3)	2.09 (3)	2.929 (4)	178 (3)
N3—H3N···O2^{ii}	0.85 (2)	2.17 (2)	3.013 (3)	171 (3)
N3—H4N···O1^{iii}	0.89 (2)	2.04 (2)	2.927 (4)	173 (3)
N1′—H1N′···N2′^{iv}	0.87 (4)	2.06 (4)	2.932 (4)	175 (3)
N3′—H3N′···O2′^{v}	0.84 (2)	2.46 (3)	3.186 (4)	145 (3)

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

All H atoms were located in difference maps. The positions of the H atoms attached to nitrogen were refined using a DFIX restraint [N—H = 0.88 (3) Å]. All other H atoms were treated as riding, with

C—H distances of 0.95 Å. The U_{iso}(H) values were set at 1.2 times U_{eq} of the parent atom, except for those of imide and amide H atoms H2N and H1N′, which were refined freely.

Data collection: *COLLECT* (Hooft, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT*; data reduction: *DENZO* and *COLLECT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* (Bruker, 1998) and *Mercury* (Bruno *et al.*, 2002); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ3060). Services for accessing these data are described at the back of the journal.

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