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Sulfapyridine (polymorph III), sulfapyridine dioxane solvate, sulfapyridine tetrahydrofuran solvate and sulfapyridine piperidine solvate, all at 173 K

Jamal Pratt, Janna Hutchinson and Cheryl L. Klein Stevens*

Department of Chemistry, Xavier University of Louisiana, New Orleans, LA 70125, USA
Correspondence e-mail: cklein@xula.edu

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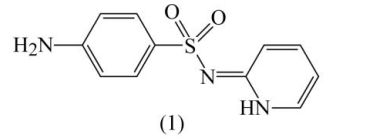
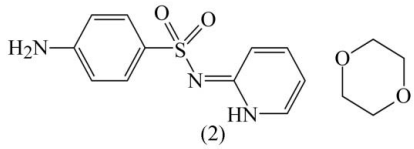
The X-ray crystal structures of solvates of sulfapyridine have been determined to be conformational polymorphs. 4-Amino-*N*-(1,2-dihydropyridin-2-ylidene)benzenesulfonamide (polymorph III), $C_{11}H_{11}N_3O_2S$, (1), 4-amino-*N*-(1,2-dihydropyridin-2-ylidene)benzenesulfonamide 1,3-dioxane monosolvate, $C_{11}H_{11}N_3O_2S{\cdot}C_4H_8O_2$, (2), and 4-amino-*N*-(1,2-dihydropyridin-2-ylidene)benzenesulfonamide tetrahydrofuran monosolvate, $C_{11}H_{11}N_3O_2S{\cdot}C_4H_8O$, (3), crystallized as the imide form, while piperidin-1-ium 4-amino-*N*-(pyridin-2-yl)benzenesulfonamidate, $C_5H_{12}N^+{\cdot}C_{11}H_{10}N_3O_2S^-$, (4), crystallized as the piperidinium salt. The tetrahydrofuran and dioxane solvent molecules in their respective structures were disordered and were refined using a disorder model. Three-dimensional hydrogen-bonding networks exist in all structures between at least one sulfone O atom and the aniline N atom.

Comment

Sulfapyridine is a member of the sulfonamide class of pharmaceuticals known for its antibacterial, antithyroid and antidiabetic properties. It was the first synthetic antibacterial agent effective against pneumonia.

Our initial interest in sulfapyridine was prompted by its ability to form conformational polymorphs, molecules that adopt different molecular conformations in different crystalline forms. The X-ray crystal structures of five polymorphs of sulfapyridine [numbered as II–VI according to a comprehensive study of polymorphism in sulfonamides by Yang & Guillory (1972)] have been reported (Bar & Bernstein, 1985; Bernstein, 1988; Gelbrich *et al.*, 2007; Basak *et al.*, 1984) in the Cambridge Structural Database (CSD; Version 5.32; Allen, 2002). The pharmaceutical industry is particularly interested in polymorphism because it can result in seemingly identical compounds having different pharmacological activity and/or bioavailability due to varying levels of thermodynamic stability, equilibrium solubilities and rates of dissolution.


(1)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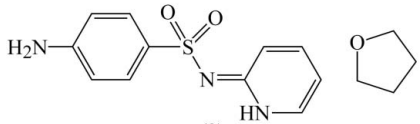
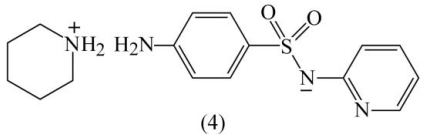

(3)


(4)

In an effort to crystallize sulfapyridine, (1), in its different polymorphic forms, we have prepared three new crystalline sulfapyridine solvates: sulfapyridine dioxane solvate, (2), sulfapyridine tetrahydrofuran solvate, (3), and sulfapyridine piperidinium salt, (4). We report here the crystal structures at 173 K along with the crystal structure of sulfapyridine (polymorph III) redetermined at 173 K. The crystal structure of a sulfapyridine tetrahydrofuran solvate with different unit-cell dimensions to those of (2) was determined previously at 150 K (Meyer *et al.*, 2000). The conformations of the sulfapyridine molecules in these solvate structures provide additional examples of conformational polymorphism.

Sulfapyridine, (1) (polymorph III; Fig. 1), and the sulfapyridine molecules in sulfapyridine dioxane solvate, (2) (Fig. 2), and sulfapyridine tetrahydrofuran solvate, (3) (Fig. 3),

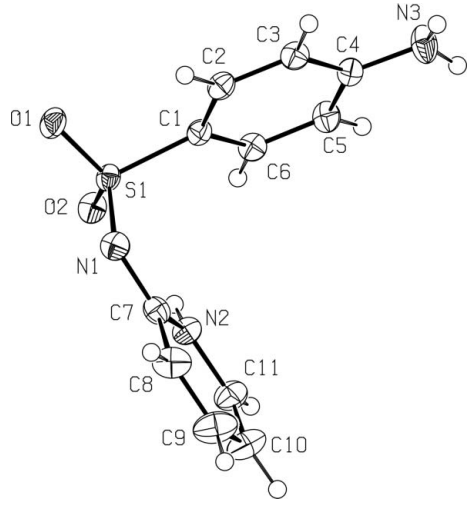


Figure 1
The molecular structure of sulfapyridine (polymorph III), (1), at 173 K. Displacement ellipsoids are drawn at the 50% probability level.

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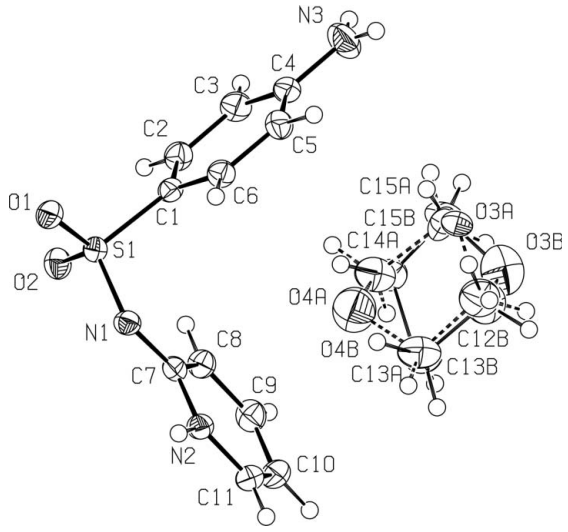

Figure 2
The molecular structure of sulfapyridine dioxane solvate, (2), at 173 K. Displacement ellipsoids are drawn at the 50% probability level.

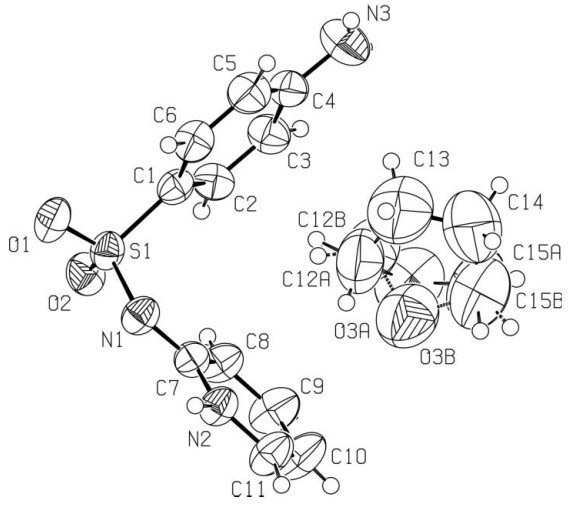

Figure 3
The molecular structure of sulfapyridine tetrahydrofuran solvate, (3), at 173 K. Displacement ellipsoids are drawn at the 50% probability level.

crystallized in the imide tautomeric form with the H atoms bonded to N2, the pyridine N atom. This seems to be the preference for sulfapyridine structures (Bar & Bernstein, 1985). Conversely, the sulfapyridine piperidine solvate, (4) (Fig. 4), crystallized in the amide tautomeric form as the piperidinium salt with the H atom located on the piperidine N atom. The conformation of the sulfapyridine molecules can be best described in terms of the angles between the three planar groups (*i.e.* the C1/S1/N1 plane, the benzene ring plane and the pyridine ring plane) and rotation around the C1—S1, S1—N1 and N1—C7 bonds. The angles between the planes are given in Table 1 and the torsion angles describing these rotations are given in Table 2. The solvated structures are generally similar to each other, although there is some rotational flexibility in the torsion angles resulting in a range of approximately 30° in the orientation of the benzene rings

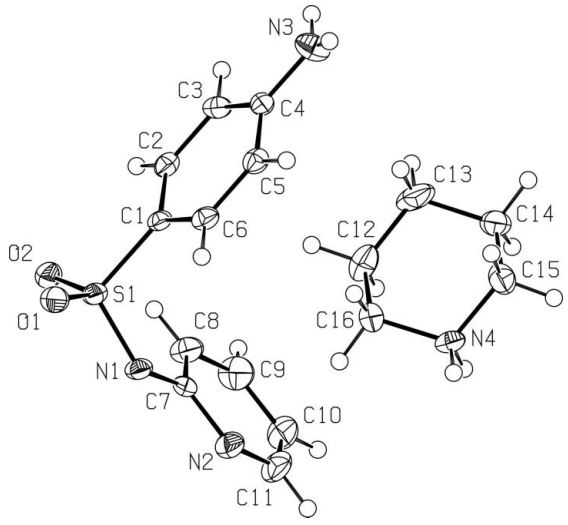

Figure 4
The molecular structure of sulfapyridine piperidinium salt, (4), at 173 K. Displacement ellipsoids are drawn at the 50% probability level.

(described by the torsion angle C2—C1—S1—N1), from 101.6 (2)° in the tetrahydrofuran solvate, (3), to 132.7 (2)° in the dioxane solvate, (2). The orientation of the pyridine rings (described by the torsion angle N2—C7—N1—S1) showed a range of approximately 12°, from 165.45 (19)° in the piperidinium salt, (4), to 176.73 (17)° in the dioxane solvate, (2). This torsion angle in (1) [10.7 (3)°] suggests that the pyridine ring plane is flipped over relative to the pyridine rings in the solvated structures. In all the imide tautomers, the orientation of the pyridine ring is stabilized by hydrogen bonding involving the pyridine N2 atom. The planes of the benzene and pyridine rings are consistently near perpendicular in all four structures, with dihedral angles ranging from 85.35 (13)° in the dioxane solvate, (2), to 89.03 (14)° in the piperidinium salt, (4). The solvent in each of the solvated structures is located between these planes, with the center of mass of the solvate approximately bisecting this dihedral angle, resulting in an approximately equal distance between the center of mass of the solvate and the centers of mass of the pyridine and benzene ring planes. The variations in the molecular structures of the sulfapyridine molecules suggest that these molecules are conformational polymorphs.

Each of the sulfapyridine solvate structures reported here crystallized with one solvent molecule per asymmetric unit. While the piperidinium cation in (4) was crystallographically well behaved, the dioxane solvent molecule in (2) and the tetrahydrofuran solvent molecule in (3) were found to be disordered and were refined with a disorder model. In both disordered models, the solvent O atoms were partially occupied above and below the best C atom plane of the solvent molecules. In the disordered dioxane molecule, the occupancies of the two conformations refined to 0.510 (4) and 0.490 (4), and in the tetrahydrofuran molecule the occupancies refined to 0.822 (9) and 0.178 (9). The displacement parameters in the tetrahydrofuran solvent molecule were unusually large, implying that the channel where it was located

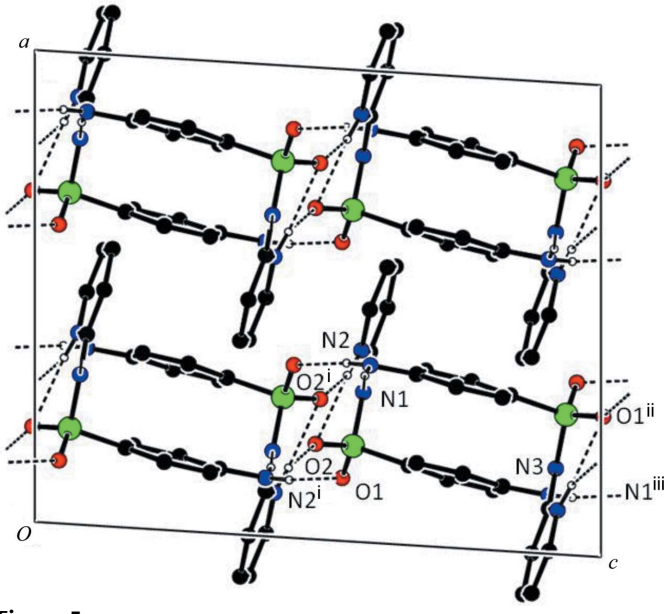

Figure 5
Packing diagram showing the hydrogen-bonding interactions in (1). H atoms not involved in these interactions have been omitted for clarity. The symmetry codes are as in Table 3.

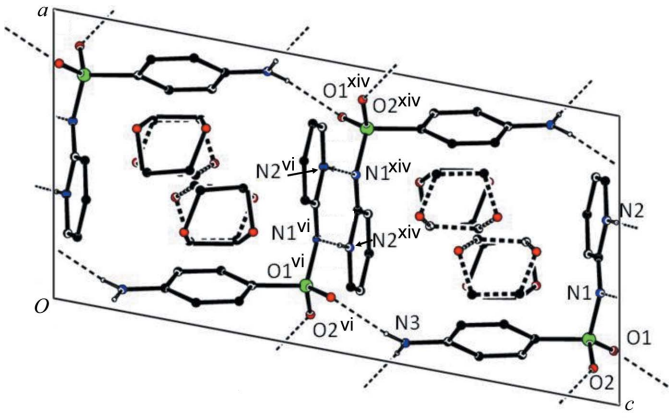

Figure 6
Packing diagram showing the hydrogen-bonding interactions in (2). H atoms not involved in these interactions have been omitted for clarity. The symmetry codes are as in Table 3; additionally, (xiv) $-x, y+\frac{1}{2}, -z+\frac{1}{2}$.

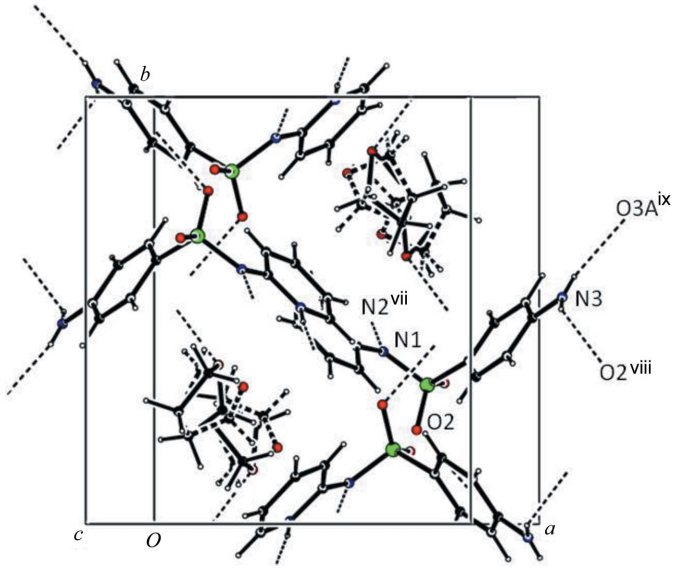

Figure 7
Packing diagram showing the hydrogen bonding interactions in (3). H atoms not involved in these interactions have been omitted for clarity. The symmetry codes are as in Table 3.

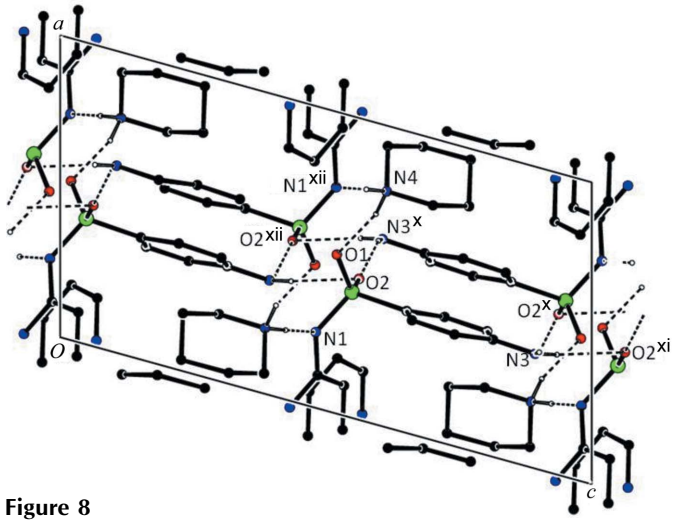

Figure 8
Packing diagram showing the hydrogen bonding interactions in (4). H atoms not involved in these interactions and some piperidinium ring atoms which lie outside the unit-cell box have been omitted for clarity. The symmetry codes are as in Table 3.

was sufficiently large to allow it significant translational flexibility. There were no hydrogen-bonding interactions involving the dioxane solvent molecule. However, there appeared to be a very weak hydrogen-bond interaction between one of the partially occupied tetrahydrofuran O atoms (O3) and the sulfapyridine molecule through aniline atom N3 (see Table 3). In the piperidinium cation, atom N4 forms a hydrogen bond to the sulfapyridine anion through amide atom N1 (see Table 3).

The packing of (1) (Fig. 5) was described previously as an interleaved herringbone motif [see polymorph III in Bar & Bernstein (1985)]. The packing in the dioxane solvate, (2) (Fig. 6), and the tetrahydrofuran solvate, (3) (Fig. 7), are similar to the packing in (1) in that the benzene and pyridine ring planes form parallel sheets. In both solvate structures, channels of solvent molecules separate the sheets. In the piperidinium salt, (4) (Fig. 8), the benzene rings in the sulfapyridine anions stack in pairs along the *a* axis, leaving solvent pockets between pairs of planes. In all three solvate structures and (1), hydrogen bonds exist between at least one sulfone O atom and the aniline N3 atom. In addition, the dioxane and tetrahydrofuran structures show a hydrogen bond between the pyridine atom N2 and the amide atom N1 in an adjacent molecule. Hydrogen-bonding interactions are listed in Table 3.

Experimental

All the sulfapyridine crystals were prepared by slow evaporation from a saturated solution of sulfapyridine and solvent [ethanol for (I),

dioxane for (II), tetrahydrofuran for (III), and piperidine for (IV)]. Mixtures were allowed to stand at room temperature for a few days after mixing. Single crystals were collected by evaporation of the mixtures and were allowed to air dry.

Compound (I)

Crystal data

$C_{11}H_{11}N_3O_2S$
M_r = 249.29
Monoclinic, $C2/c$
a = 12.7350 (16) Å
b = 11.6945 (15) Å
c = 15.3357 (18) Å
β = 93.546 (3)°
V = 2279.6 (5) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.28 mm^{-1}
T = 173 K
0.75 × 0.70 × 0.35 mm

Data collection

Bruker SMART X2S diffractometer
Absorption correction: empirical (using intensity measurements) (*SADABS*; Sheldrick, 2004)
T_{min} = 0.819, T_{max} = 0.909
6574 measured reflections
1987 independent reflections
1743 reflections with $I > 2\sigma(I)$
R_{int} = 0.043

Refinement

$R[F^2 > 4\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.096
S = 1.05
1987 reflections
166 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = −0.40 e Å^{-3}

Compound (II)

Crystal data

$C_{11}H_{11}N_3O_2S\cdot C_4H_8O_2$
M_r = 337.39
Monoclinic, $P2_1/c$
a = 9.0258 (10) Å
b = 9.9264 (12) Å
c = 17.988 (2) Å
β = 100.720 (3)°
V = 1583.5 (3) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.23 mm^{-1}
T = 173 K
0.75 × 0.63 × 0.38 mm

Data collection

Bruker SMART X2S diffractometer
Absorption correction: empirical (using intensity measurements) (*SADABS*; Sheldrick, 2004)
T_{min} = 0.847, T_{max} = 0.918
13599 measured reflections
2778 independent reflections
2488 reflections with $I > 2\sigma(I)$
R_{int} = 0.028

Refinement

$R[F^2 > 4\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.157
S = 1.08
2778 reflections
268 parameters
377 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.59 e Å^{-3}
$\Delta\rho_{min}$ = −0.56 e Å^{-3}

Compound (III)

Crystal data

$C_{11}H_{11}N_3O_2S\cdot C_4H_8O$
M_r = 321.39
Monoclinic, $P2_1/c$
a = 11.212 (2) Å
b = 12.449 (2) Å
c = 11.6209 (19) Å
β = 99.888 (5)°
V = 1597.8 (5) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.22 mm^{-1}
T = 173 K
1.00 × 0.65 × 0.50 mm

Table 1
Dihedral angles (°).

Planes	(1)	(2)	(3)	(4)
Phenyl and pyridine	86.37 (9)	85.35 (13)	87.13 (19)	89.01 (9)
Phenyl and C1/S1/N1	75.14 (7)	48.76 (12)	76.67 (18)	64.24 (12)
Pyridine and C1/S1/N1	76.25 (7)	63.88 (12)	70.37 (11)	74.45 (10)

Table 2
Torsion angles (°).

	(1)	(2)	(3)	(4)
N2—C7—N1—S1	−10.6 (3)	176.74 (17)	173.50 (18)	165.5 (2)
C8—C7—N1—S1	169.32 (15)	−2.0 (4)	−6.2 (4)	−14.9 (4)
C6—C1—S1—N1	101.98 (16)	−50.4 (2)	−76.3 (2)	−64.1 (2)
C2—C1—S1—N1	−72.44 (15)	132.7 (2)	101.6 (2)	115.7 (2)
O1—S1—N1—C7	173.78 (14)	−178.20 (18)	177.3 (2)	179.8 (2)
C1—S1—N1—C7	−71.48 (16)	−63.3 (2)	−67.8 (2)	−66.4 (2)
O2—S1—N1—C7	45.93 (17)	55.4 (2)	49.6 (2)	52.7 (2)

Data collection

Bruker SMART X2S diffractometer
Absorption correction: empirical (using intensity measurements) (*SADABS*; Sheldrick, 2004)
T_{min} = 0.811, T_{max} = 0.899
7648 measured reflections
2809 independent reflections
2232 reflections with $I > 2\sigma(I)$
R_{int} = 0.046

Refinement

$R[F^2 > 4\sigma(F^2)]$ = 0.053
$wR(F^2)$ = 0.163
S = 1.08
2809 reflections
271 parameters
273 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.48 e Å^{-3}
$\Delta\rho_{min}$ = −0.39 e Å^{-3}

Compound (IV)

Crystal data

$C_5H_{12}N^+\cdot C_{11}H_{10}N_3O_2S^-$
M_r = 334.44
Monoclinic, $P2_1/c$
a = 8.6639 (16) Å
b = 12.586 (2) Å
c = 15.833 (3) Å
β = 105.447 (6)°
V = 1664.1 (5) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.21 mm^{-1}
T = 173 K
0.27 × 0.25 × 0.14 mm

Data collection

Bruker SMART X2S diffractometer
Absorption correction: empirical (using intensity measurements) (*SADABS*; Sheldrick, 2004)
T_{min} = 0.946, T_{max} = 0.971
7118 measured reflections
1922 independent reflections
1482 reflections with $I > 2\sigma(I)$
R_{int} = 0.068
θ_{max} = 21.6°

Refinement

$R[F^2 > 4\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.090
S = 1.02
1922 reflections
216 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

H atoms were located in difference maps except in the disordered dioxane and tetrahydrofuran solvent molecules where they were

Table 3
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
(I)				
N2—H1···O2	0.86 (2)	2.19 (2)	2.847 (2)	132 (2)
N2—H1···O2^{i}	0.86 (2)	2.15 (2)	2.874 (2)	140 (2)
N3—H1A···O1^{ii}	0.87 (2)	2.12 (2)	2.985 (2)	172 (2)
N3—H1B···N1^{iii}	0.84 (2)	2.23 (2)	3.050 (2)	168 (2)
(II)				
N2—H2*A*···N1^{iv}	0.95 (3)	1.98 (3)	2.930 (3)	178 (3)
N3—H3*A*···O2^{v}	0.88	2.26	3.104 (3)	162
N3—H3*B*···O1^{vi}	0.88	2.22	3.071 (3)	162
(III)				
N2—H2*A*···N1^{vii}	0.97 (3)	1.92 (3)	2.892 (3)	173 (2)
N3—H3*A*···O3*A*^{viii}	0.82 (5)	2.43 (5)	3.103 (7)	140 (4)
N3—H3*B*···O2^{ix}	0.77 (4)	2.37 (4)	3.023 (4)	143 (4)
(IV)				
N3—H3*A*···O2^{x}	0.83 (3)	2.35 (3)	3.169 (4)	172 (2)
N3—H3*B*···O2^{xi}	0.79 (3)	2.34 (3)	3.071 (4)	155 (3)
N4—H4*A*···N1^{xii}	0.92	1.84	2.746 (3)	168
N4—H4*B*···O1^{xiii}	0.92	2.00	2.904 (3)	165

Symmetry codes: (i) $-x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (ii) $x, -y, z+\frac{1}{2}$; (iii) $-x+\frac{1}{2}, y+\frac{1}{2}, -z+\frac{3}{2}$; (iv) $-x+1, -y+1, -z+2$; (v) $x, -y+\frac{1}{2}, z-\frac{1}{2}$; (vi) $-x, y-\frac{1}{2}, -z+\frac{3}{2}$; (vii) $-x+1, -y+1, -z$; (viii) $-x+2, y+1, -z+1$; (ix) $-x+2, y+\frac{1}{2}, -z+\frac{1}{2}$; (*x*) $x, -y+\frac{3}{2}, z+\frac{1}{2}$; (xi) $-x+1, y+\frac{1}{2}, -z+\frac{3}{2}$; (xii) $-x, -y+2, -z+1$; (xiii) $x-1, y, z$.

calculated. The dioxane and tetrahydrofuran solvent molecules were refined with a disorder model. In this model, the disordered pair in each structure was divided into parts 1 and 2, with constraints applied such that the sum of the occupancies was 1.0 and bond lengths of similar bond types were equal and within a defined tolerance, *i.e.* Csp^3—Csp^3 and Csp^3—Osp^3 bonds were constrained to be equal within a tolerance of 0.002 Å. H atoms bonded to N atoms likely to be involved in hydrogen-bonding interactions were allowed to refine independently assuming they converged to chemically reasonable values. In sulfapyridine, H atoms bonded to N1 and N3 were allowed to refine independently. In the dioxane solvent molecule, only the H atom on N2 was allowed to refine independently (H3*A* and H3*B* bonded to N3 did not converge during refinement to chemically reasonable values). In the piperidinium cation, the H atoms on N3 were allowed to refine independently. In the tetrahydrofuran solvent molecule, all atoms were allowed to refine independently, except those of the tetrahydrofuran ring. All other H atoms were treated as riding, with C—H distances of 0.95 Å and N—H distances of 0.88 Å. The U_{iso}(H) values of the riding atoms were set at 1.2 times the U_{eq} values of the parent atom. The resolution of the data collected for the piperidinium salt is lower than that of the data collected for the other crystals in this series. This is due to the weak scattering at high θ angle. The Bruker SMART X2S software does not allow the user to modify the scan rate. However, even with the data collected at the faster scan rate, the quality of the final refined structure is comparable in quality to the other sulfapyridine structures in this series.

For all compounds, data collection: *APEX2* (Bruker, 2008); cell refinement: *SAINT* (Bruker, 2008); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXTL* (Sheldrick, 2008).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: QS3006). Services for accessing these data are described at the back of the journal.

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