Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Supramolecular structures of three isomeric 4-(methylphenylamino)-pyridine-3-sulfonamides

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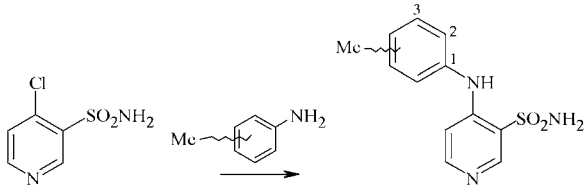
Received 25 August 2005
Accepted 6 October 2005
Online 22 October 2005

The structures of the three title isomers, namely 4-(2-methylanilino)pyridine-3-sulfonamide, (I), 4-(3-methylanilino)pyridine-3-sulfonamide, (II), and 4-(4-methylanilino)-pyridine-3-sulfonamide, (III), all $C_{12}H_{13}N_3O_2S$, differ in their hydrogen-bonding arrangements. In all three molecules, the conformation of the 4-aminopyridine-3-sulfonamide moiety is conserved by an intramolecular N—H···O hydrogen bond and a C—H···O interaction. In the supramolecular structures of all three isomers, similar $C(6)$ chains are formed *via* intermolecular N—H···N hydrogen bonds. N—H···O hydrogen bonds lead to $C(4)$ chains in (I), and to $R_2^2(8)$ centrosymmetric dimers in (II) and (III). In each isomer, the overall effect of all hydrogen bonds is to form layer structures.

Comment

Sulfonamides constitute an important class of drugs, with several types of pharmacological agents possessing, for example, antibacterial, anticarbonic anhydrase, diuretic, hypoglycaemic, antithyroid and anticancer activities. From a structural point of view, sulfonamides are interesting because of their tendency to form different hydrogen-bond systems in



the solid state by introducing various hydrogen-bond donors and acceptors as substituents into simple sulfonamide molecules. The most common hydrogen-bond motifs, widely observed in the crystal structures of simple benzenesulfonamide, are realised *via* N—H···O hydrogen bonds constituting chains or rings, *viz*. $C(4)$ and $R_2^2(8)$ (Etter *et al.*, 1990; Bernstein *et al.*, 1995). A search of the Cambridge Structural Database (CSD, Version 5.26 plus three updates; Allen, 2002) for sulfonamide structures involving $R_2^2(8)$ and $C(4)$ hydrogen-bond motifs (restricting H···O contact distances from 1.0 to 2.7 Å, organic molecules only, redeterminations omitted) identified 13 structures containing $R_2^2(8)$ dimers and 36 structures containing $C(4)$ chains. Only in the crystal structure of GUFQED (Tremayne *et al.*, 1999) are both hydrogen-bond motifs present.

We report here the syntheses and structures of three pyridinesulfonamide isomers, *i.e.* (I), (II) and (III). These pyridinesulfonamides are known as intermediates and potential impurities of the drug torasemide, which is widely used as a loop diuretic (Danilovski *et al.*, 2001).

The X-ray analyses of (I), (II) and (III) (Figs. 1–3) unambiguously confirm their *ortho*-, *meta*- and *para*-substitution patterns. The three isomers differ primarily in their benzene-

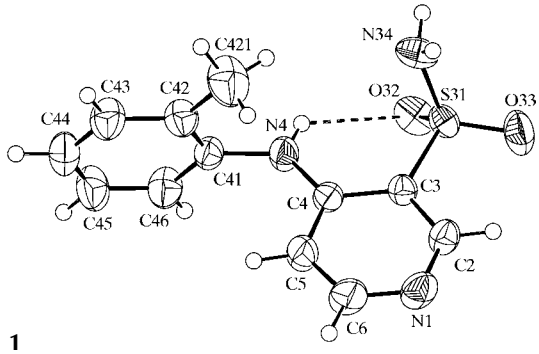


Figure 1
A view of the molecule of (I), shown with 50% probability displacement ellipsoids. The dashed line indicates the intramolecular hydrogen bond.

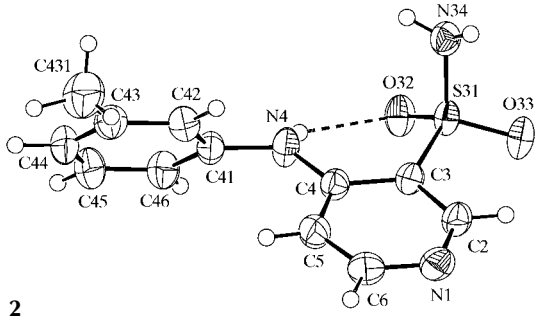


Figure 2
A view of the molecule of (II), shown with 50% probability displacement ellipsoids. The dashed line indicates the intramolecular hydrogen bond.

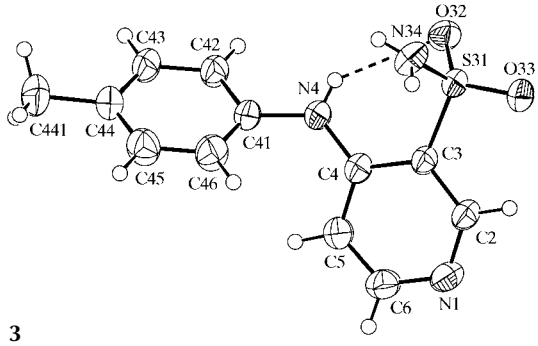


Figure 3
A view of the molecule of (III), shown with 50% probability displacement ellipsoids. The dashed line indicates the intramolecular hydrogen bond.

  DOI: 10.1107/S0108270105031902

ring orientation with respect to the pyridine ring (Fig. 4). The dihedral angles between the best planes of the pyridyl and benzene rings are 93.95 (7), 117.75 (5) and 122.40 (5)° in (I), (II) and (III), respectively. The conformation of the 4-amino-pyridine-3-sulfonamide part of the molecule is conserved by an intramolecular N4—H4···O32 hydrogen bond and a C2—H2···O33 interaction in all three isomers. The C4—C3—S31—N34 torsion angles are 65.22 (17), 77.27 (13) and 58.82 (17)° in (I), (II) and (III), respectively.

Although the same intermolecular hydrogen-bonding types (sulfonamide NH_2 groups as donors to sulfonamide O or pyridine N atoms) are observed in all three structures (Tables 1–3), their supramolecular structures are appreciably different.

In compound (I), two major chains, *viz*. $C(4)$ and $C(6)$, are formed *via* N34—H342···O33 and N34—H341···N1 hydrogen bonds, respectively. Both chains run parallel to the *b* axis and combine to form a tetramolecular $R_4^4(18)$ motif. Additional linking across these 18-membered rings is realised by weak C6—H6···O32 interactions forming a $C(7)$ chain parallel to the *a* axis. These three chains combine to form layers parallel to (001) (Fig. 5).

The observed $C(4)$ chain motif is characteristic of simple sulfonamides. The most characteristic hydrogen-bond motif of sulfonamides, the $R_2^2(8)$ ring [for a discussion of both types, see Glidewell *et al.* (2004), and references therein] is, however, not observed for (I), but only for the structures of (II) and (III).

In contrast with (I), where the $C(4)$ and $C(6)$ chains are helical, the $C(6)$ chains in compound (II) are formed by pure translation parallel to the *a* axis (Fig. 6), whereby the N34—H341···N1 hydrogen bond connects the molecules (denoted *A*, *B*, *C*, *D*, *etc*.). The second chain is built up from molecules (denoted *A*′, *B*′, *C*′, *D*′, *etc*.) related to the first chain by inversion. Centrosymmetrically related molecules *B*/*B*′, *etc*., are connected by intermolecular N4—H4···O32 hydrogen bonds to form dimers involving $R_2^2(4)$ rings. By these interactions, two antiparallel $C(6)$ chains form one ribbon through

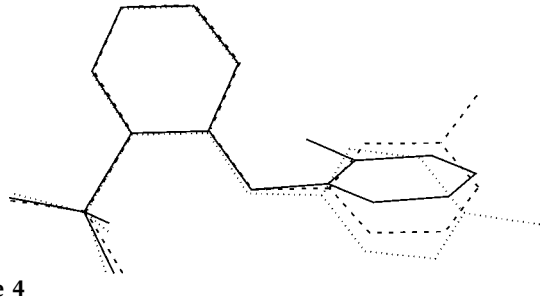


Figure 4
Superimposition of (I), (II) and (III), showing the different benzene-ring orientations. Compound (I) is shown with solid lines, (II) with dashed lines and (III) with dotted lines (*WebLab ViewerPro*; Accelrys, 2000).

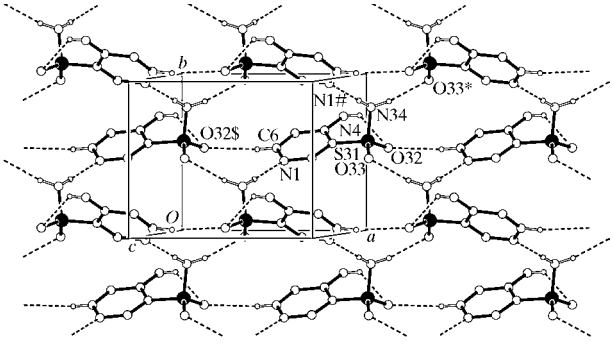


Figure 5
Part of the unit-cell packing in (I), viewed perpendicular to the *ab* plane, showing the hydrogen-bonded layer in the region around $z = \frac{1}{4}$. Dashed lines indicate hydrogen bonds. Methylphenyl C atoms, and H atoms not involved in hydrogen bonds, have been omitted for clarity. Atoms marked with an asterisk (*), hash (#) or dollar sign ($) are at the symmetry positions $(\frac{5}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z)$, $(\frac{3}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z)$ and $(x - 1, y, z)$, respectively.

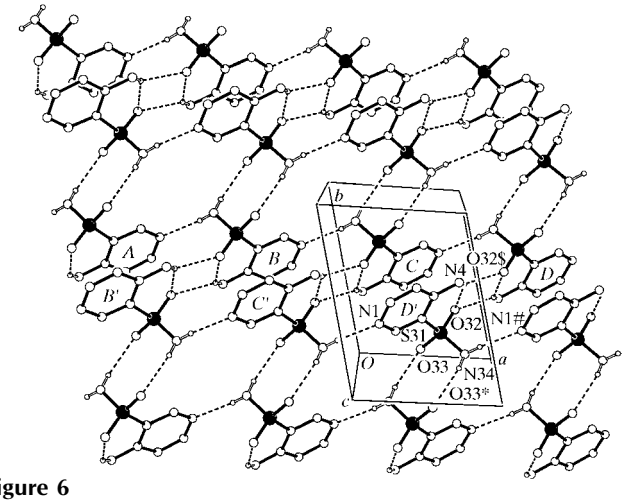


Figure 6
Part of the unit-cell packing in (II), viewed perpendicular to the *ab* plane, showing the hydrogen-bonded layer in the region around $z = \frac{1}{2}$. Dashed lines indicate hydrogen bonds. Molecules *A*, *B*′, *etc*., are as defined in the *Comment*. Methylphenyl C atoms, and H atoms not involved in hydrogen bonds, have been omitted for clarity. Atoms marked with an asterisk (*), hash (#) or dollar sign ($) are at the symmetry positions $(1 + x, y, z)$, $(2 - x, 1 - y, 1 - z)$ and $(2 - x, 1 - y, 1 - z)$, respectively.

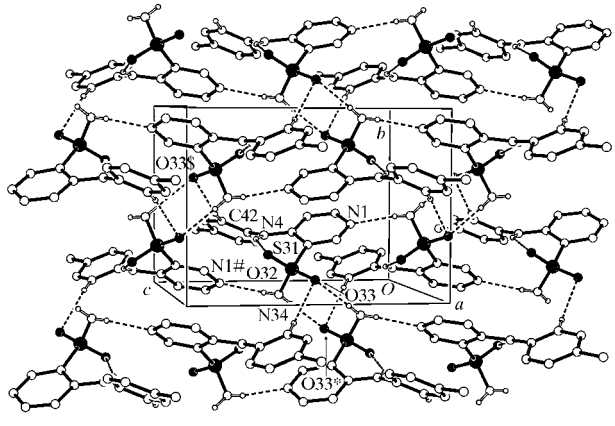


Figure 7
Part of the unit-cell packing in (III), viewed perpendicular to the *bc* plane, showing the hydrogen-bonded layer in the region around $x = 1$. Dashed lines indicate hydrogen bonds. Methylphenyl C atoms, and H atoms not involved in hydrogen bonds, have been omitted for clarity. Atoms marked with an asterisk (*), hash (#) or dollar sign ($) are at the symmetry positions $(2 - x, -y, 1 - z)$, $(x, \frac{1}{2} - y, \frac{1}{2} + z)$ and $(2 - x, \frac{1}{2} + y, \frac{3}{2} - z)$, respectively.

each unit cell. Two adjacent ribbons, related by translation in the *b* direction, are bridged by centrosymmetrically related intermolecular N34—H342···O33 hydrogen bonds, forming $R_2^2(8)$ rings. The net effect of these hydrogen-bonding arrangements is to form layers parallel to (001).

In compound (III) (Fig. 7), the sulfonamide group participates in the same type of centrosymmetric N—H···O hydrogen bonds as found in (II), and there are N—H···N hydrogen-bonded chains such as were observed in both (I) and (II). The overall packing of (III) shows a network of molecules interlinked *via* classical and non-classical hydrogen bonds. The characteristic $R_2^2(8)$ hydrogen-bond motif is formed *via* N34—H342···O33 hydrogen bonds connecting two molecules into centrosymmetric dimers at (0, $\frac{1}{2}$, $\frac{1}{2}$). The dimers are further linked to each other by three additional interactions: (i) the intermolecular N34—H341···N1 hydrogen bond forms *C*(6) chains parallel to the *c* axis, (ii) N4—H4···N1 can be considered as a weak component of a three-centre hydrogen bond, and (iii) C42—H42···O33 interactions additionally stabilize the structure. The overall effect is to form layers parallel to (100).

Experimental

A mixture of 4-chloro-3-pyridinesulfonamide (36.0 g, 0.19 mol), *o*-, *m*- or *p*-toluidine (21.6 ml, 0.2 mol) and methanol (240 ml) was refluxed for 2 h, and then for a further 3.5 h after addition of additional *o*-toluidine (6.0 ml, 0.06 mol) for (I), or the mixture was stirred at 313 K for 3 h for (II) and (III), and cooled to room temperature. Water was added to the mixture and the pH was adjusted to 7 with dilute NaOH. The resulting suspension was stirred under the same conditions for an additional 1 h. Crude crystalline (I), (II) or (III) were separated by suction filtration, washed with water and dried in a vacuum oven at 333 K and 2.7 kPa for 3 h [for (I): yield 46.6 g (94.7%), m.p. 457–459 K; for (II): yield 48.0 g (96.5%), m.p. 440–442 K; for (III): yield 48.2 g (97.9%), m.p. 493–495 K]. Single crystals suitable for X-ray analysis were obtained by slow evaporation from methanol solutions for (I) and (III) and from an acetone solution for (II).

Compound (I)

Crystal data

$C_{12}H_{13}N_3O_2S$
M_r = 263.31
Monoclinic, $P2_1/n$
a = 8.5118 (7) Å
b = 7.2369 (13) Å
c = 21.181 (5) Å
β = 96.714 (15)°
V = 1295.8 (4) Å^3
Z = 4
D_x = 1.350 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 36 reflections
θ = 8.1–14.7°
μ = 0.25 mm^{-1}
T = 295 (2) K
Block, colourless
0.60 × 0.24 × 0.13 mm

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

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···O32	0.79 (3)	2.42 (2)	3.000 (2)	132 (2)
N34—H342···O33^{i}	0.91 (3)	2.10 (3)	2.990 (2)	169 (3)
N34—H341···N1^{ii}	0.86 (3)	2.00 (3)	2.875 (3)	172 (3)
C2—H2···O33	0.93	2.41	2.845 (2)	109
C6—H6···O32^{iii}	0.93	2.55	3.374 (2)	148

Symmetry codes: (i) $-x+\frac{5}{2}, y+\frac{1}{2}, -z+\frac{1}{2}$; (ii) $-x+\frac{3}{2}, y+\frac{1}{2}, -z+\frac{1}{2}$; (iii) $x-1, y, z$.

Data collection

Philips PW1100 diffractometer updated by Stoe
ω scans
7502 measured reflections
3751 independent reflections
2396 reflections with $I > 2\sigma(I)$
R_{int} = 0.001
θ_{max} = 30.0°
$h = -11 \rightarrow 11$
$k = 0 \rightarrow 10$
$l = 0 \rightarrow 29$
3 standard reflections
frequency: 90 min
intensity decay: 4.2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.127
S = 1.02
3751 reflections
175 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0592P)^2 + 0.4643P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

Compound (II)

Crystal data

$C_{12}H_{13}N_3O_2S$
M_r = 263.31
Triclinic, $P\overline{1}$
a = 6.7621 (9) Å
b = 8.6521 (13) Å
c = 11.4715 (18) Å
α = 98.523 (11)°
β = 102.398 (12)°
γ = 102.991 (9)°
V = 624.97 (16) Å^3
Z = 2
D_x = 1.399 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 40 reflections
θ = 8.2–16.4°
μ = 0.26 mm^{-1}
T = 295 (2) K
Prism, colourless
0.45 × 0.30 × 0.27 mm

Data collection

Philips PW1100 diffractometer updated by Stoe
ω scans
6556 measured reflections
3278 independent reflections
3014 reflections with $I > 2\sigma(I)$
R_{int} = 0.001
θ_{max} = 28.9°
$h = -9 \rightarrow 8$
$k = -11 \rightarrow 11$
$l = 0 \rightarrow 15$
3 standard reflections
frequency: 90 min
intensity decay: 1.6%

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···O32	0.83 (2)	2.17 (2)	2.843 (2)	138 (2)
N4—H4···O32^{i}	0.83 (2)	2.45 (3)	3.143 (2)	142 (2)
N34—H341···N1^{ii}	0.82 (3)	2.11 (3)	2.917 (2)	168 (2)
N34—H342···O33^{iii}	0.80 (3)	2.22 (3)	2.983 (2)	159 (3)
C2—H2···O33	0.93	2.43	2.861 (2)	108

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

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

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···N1^{i}	0.79 (2)	2.71 (2)	3.222 (2)	124 (2)
N4—H4···O32	0.79 (2)	2.38 (2)	3.025 (2)	137 (2)
N34—H341···N1^{i}	0.80 (3)	2.16 (3)	2.940 (2)	166 (3)
N34—H342···O33^{ii}	0.87 (2)	2.19 (2)	3.056 (2)	172 (2)
C2—H2···O33	0.93	2.40	2.826 (3)	108
C42—H42···O33^{iii}	0.93	2.56	3.430 (3)	157

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

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.079P)^2 + 0.1589P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.045$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.130$	$\Delta\rho_{max} = 0.48$ e Å^{-3}
$S = 1.11$	$\Delta\rho_{min} = -0.32$ e Å^{-3}
3278 reflections	
176 parameters	
H atoms treated by a mixture of independent and constrained refinement	

Compound (III)

Crystal data

$C_{12}H_{13}N_3O_2S$	$D_x = 1.399$ Mg m^{-3}
$M_r = 263.31$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 39 reflections
$a = 10.7730$ (19) Å	$\theta = 8.9$–$16.7°$
$b = 9.271$ (4) Å	$\mu = 0.26$ mm^{-1}
$c = 12.5769$ (16) Å	$T = 295$ (2) K
$\beta = 95.71$ (2)°	Prism, colourless
$V = 1249.9$ (6) Å^3	0.53 × 0.20 × 0.15 mm
$Z = 4$	

Data collection

Philips PW1100 diffractometer updated by Stoe	$\theta_{max} = 29.9°$
ω scans	$h = -15 \rightarrow 15$
7224 measured reflections	$k = 0 \rightarrow 13$
3612 independent reflections	$l = 0 \rightarrow 17$
2432 reflections with $I > 2\sigma(I)$	3 standard reflections
$R_{int} = 0.001$	frequency: 90 min
	intensity decay: 5.0%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0611P)^2 + 0.3511P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.041$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.121$	$\Delta\rho_{max} = 0.32$ e Å^{-3}
$S = 1.02$	$\Delta\rho_{min} = -0.28$ e Å^{-3}
3612 reflections	Extinction correction: *SHELXL97* (Sheldrick, 1997)
176 parameters	Extinction coefficient: 0.045 (3)
H atoms treated by a mixture of independent and constrained refinement	

The sulfonamide and amine H atoms were located in difference Fourier maps and refined. The methyl H atoms were found in a difference Fourier map and subsequently refined as part of rigid rotating groups, with $U_{iso}(H) = 1.5U_{eq}(C)$. Other H atoms were placed in calculated positions and allowed to refine as riding on their parent atoms, with $U_{iso}(H) = 1.2U_{eq}(C)$.

For all three compounds, data collection: *STADI4* (Stoe & Cie, 1996); cell refinement: *STADI4*; data reduction: *X-RED* (Stoe & Cie, 1996); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Molecular graphics: *PLATON2000* (Spek, 2003) and *WebLab ViewerPro* (Accelrys, 2000) for (I); *PLATON2000* (Spek, 2003) for (II) and (III). For all compounds, software used to prepare material for publication: *SHELXL97* and *PARST96* (Nardelli, 1995).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1757). Services for accessing these data are described at the back of the journal.

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