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Structure of Sulphamethazine [4-Amino-*N*-(4,6-dimethyl-2-pyrimidinyl)benzenesulphonamide], $C_{12}H_{14}N_4O_2S$

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Abstract. $M_r = 278{\cdot}33$, monoclinic, space group $P2_1/a$, $a = 7{\cdot}427$ (2), $b = 18{\cdot}986$ (11), $c = 9{\cdot}323$ (4) Å, $\beta = 99{\cdot}09$ (2)°, $V = 1298$ (1) Å^3, $Z = 4$, $D_m = 1{\cdot}430$, $D_x = 1{\cdot}424$ Mg m^{-3}, λ (Mo $K\alpha$) = 0·7107 Å, $\mu = 0{\cdot}253$ mm^{-1}, $F(000) = 584$, $T = 297$ K. Final $R = 0{\cdot}045$ using 1766 observed reflections. The structure is compared with those of other similar sulphonamides. In packing, the molecules form dimers through pairs of N—H···N hydrogen bonds and these dimers are linked together through N—H···N and N—H···O hydrogen bonds. The pyrimidine and the phenyl rings are observed to stack independently.

Introduction. Sulphamethazine is one of the constituents of the 'triple sulpha' drug combination containing, in addition, sulphadiazine (4-amino-*N*-2-pyrimidinylbenzenesulphonamide) and sulphamerazine [4-amino-*N*-(4-methyl-2-pyrimidinyl)-benzenesulphonamide]. All these three drugs have sulphonamide linkages at the 2-position of the pyrimidine ring which, together with drugs having sulphonamide linkages at the 4-position, have been shown to produce clinically active compounds (Nitya Anand, 1979). Sulphamethazine, a derivative of sulphadiazine with methylation at the 4- and 6-positions of the pyrimidine ring, has diminished activity *in vitro* and *in vivo* compared to the other two constituents of 'triple sulpha', and is excreted less rapidly and, therefore, has greater tolerance and clinical advantages.

X-ray crystallographic analyses of these drugs were undertaken as a part of a research programme to study the effect of substituents on the molecular geometry and conformation of the sulphonamides with the ultimate aim of understanding their biological activity. The crystal structure of sulphamethazine is presented here.

Experimental. Transparent lath-shaped crystals (from acetone), density by flotation (benzene–bromoform), 0·25 × 0·20 × 0·12 mm, symmetry from oscillation and Weissenberg photographs, absences: $0k0$, k odd and $h0l$, h odd, Enraf–Nonius CAD-4 diffractometer, graphite-monochromatized Mo $K\alpha$, accurate cell parameters from 25 high-angle reflections, 2269 unique reflections ($h = -8$ to 8, $k = 0$ to 22, $l = 0$ to 11; $2 \le \theta \le 25°$), 1766 with $I \ge 3\sigma(I)$, corrected for Lp, absorption ingnored, intensity variation < 2%; direct method (*MULTAN*, Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), anisotropic full matrix based on F (*ORFLS*, Busing, Martin & Levy, 1962), H (from ΔF synthesis) isotropic, $R = 0{\cdot}045$, $Rw = 0{\cdot}056$, $S = 1{\cdot}926$, $w = 1/\sigma(|F_o|)^2$, maximum shift/error < 0·01, peak heights from −0·21 to 0·27 e Å^{-3} in final ΔF synthesis, scattering factors for non-H from Cromer & Waber (1965), for H from Stewart, Davidson & Simpson (1965), anomalous-dispersion corrections from *International Tables for X-ray Crystallography* (1974).

Discussion. The title compound is shown in Fig. 1 and the final atomic coordinates for the atoms together with their isotropic temperature factors are listed in Table 1.* The intramolecular bond distances and angles of sulphamethazine are listed in Table 2. The weighted mean C—H and N—H distances are 0·92 (1) and 0·81 (2) Å respectively.

The slight distortion in the *para*-substituted phenyl ring may be attributed to the perturbation in the π-electron system by substituents (Domenicano, Vaciago & Coulson, 1975) and has been observed in a number of similar compounds (O'Connell & Maslen, 1967; Kruger & Gafner, 1971; Kálmán, Czugler & Argay, 1981; Donaldson, Leary, Ross, Thomas & Smith, 1981).

The arylamino nitrogen, N(2), and the sulphur, S, are, respectively, 0·001 (3) and 0·068 (1) Å away from

* Lists of structure factors, anisotropic thermal parameters and least-squares-planes' data have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38237 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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the plane of the phenyl ring. The atoms around the sulphur are arranged in a distorted tetrahedral configuration (Table 2) similar to those observed in sulphaguanidine monohydrate (Alléaume, Gulko, Herbstein, Kapon & Marsh, 1976), tolbutamide {*N*-[butylamino)carbonyl]-4-methylbenzenesulphonamide} (Donaldson *et al.*, 1981) and sulphacetamide {*N*-[(4-aminophenyl)sulphonyl]acetamide} (Basak, Mazumdar & Chaudhuri, 1982). Such distortions from the ideal configuration have been attributed to non-bonded interactions involving the two short S–O bonds, resulting in structures with minimum steric interference (Cotton & Stokley, 1970). The intramolecular contacts O(1)–O(2) [2·470 (2) Å], O(1)–N(1) [2·500 (2) Å] and O(2)–N(1) [2·402 (2) Å] observed in the present structure are comparable with those found in the crystal structures of dibenzenesulphonamide and its sodium salt (Cotton & Stokley, 1970) and sulphacetamide (Basak *et al.*, 1982).

The shortening of the S–N(1) and S–C(1) bond lengths from the expected single-bond distances have been attributed to $d\pi$–$p\pi$ interaction (Cotton & Stokley, 1970). The C(7)–N(1) distance is, however, shorter than the C(sp^2)–N(sp^2) single-bond distance of 1·470 (5) Å (Camerman, 1970). Although the dihedral angle between the plane defined by S–N(1)–C(7) and the plane of the pyrimidine ring is 34·0 (2)°, the effect of partial delocalization cannot be ruled out as a cause of this bond shortening, in addition to Coulomb interaction between N(1) and C(7) (Christoph & Fleischer, 1973). Such shortening has also been observed in two (forms I and III) of the three polymorphic forms of 2-sulphanilamido-5-methoxypyrimidine [4-amino-*N*-(5-methoxy-2-pyrimidinyl)benzenesulphonamide] (Giuseppetti, Tadini, Bettinetti & Giordano, 1977) and in tolbutamide (Donaldson *et al.*, 1981).

The four endocyclic C–N bond distances in the pyrimidine ring are in agreement with those reported in the literature (Voet & Rich, 1970). This ring is planar, with the two methyl carbons, C(11) and C(12), in plane and the amide nitrogen, N(1), slightly out of plane. The

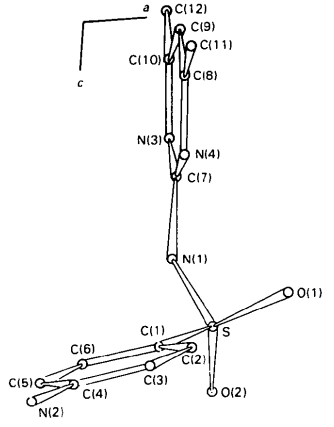

Fig. 1. Perspective view of the molecule down the *b* axis.

Table 1. *Fractional atomic coordinates and thermal parameters with e.s.d.'s in parentheses [the equivalent isotropic temperature factors* B_{eq}(Å^2) *(Hamilton, 1959) for non-hydrogen atoms and isotropic temperature factors* B(Å^2) *for hydrogen atoms]*

	x	*y*	*z*	B_{eq}/B
S	0·9450 (1)	0·3186 (1)	0·5917 (1)	2·55
O(1)	1·1133 (3)	0·3425 (1)	0·5512 (2)	3·31
O(2)	0·9509 (3)	0·2721 (1)	0·7132 (2)	3·42
N(1)	0·8332 (3)	0·2731 (1)	0·4580 (2)	2·92
N(2)	0·5194 (4)	0·5689 (1)	0·7061 (3)	3·97
N(3)	0·8131 (3)	0·2243 (1)	0·2309 (2)	2·78
N(4)	0·8327 (3)	0·3496 (1)	0·2626 (2)	2·89
C(1)	0·8150 (4)	0·3925 (1)	0·6196 (3)	2·42
C(2)	0·8942 (4)	0·4586 (1)	0·6265 (3)	2·99
C(3)	0·7967 (4)	0·5169 (1)	0·6548 (3)	3·15
C(4)	0·6157 (4)	0·5106 (1)	0·6773 (3)	2·83
C(5)	0·5379 (4)	0·4433 (2)	0·6723 (3)	3·10
C(6)	0·6363 (4)	0·3849 (1)	0·6447 (3)	3·02
C(7)	0·8271 (4)	0·2837 (1)	0·3081 (3)	2·47
C(8)	0·8197 (4)	0·3571 (2)	0·1170 (3)	3·17
C(9)	0·8017 (4)	0·2998 (2)	0·0271 (3)	3·66
C(10)	0·7999 (4)	0·2329 (2)	0·0862 (3)	3·08
C(11)	0·8231 (5)	0·4307 (2)	0·0600 (4)	4·96
C(12)	0·7862 (5)	0·1679 (2)	−0·0061 (3)	4·46
H(N1)	0·800 (4)	0·236 (1)	0·485 (3)	3·2 (6)
H(C2)	1·015 (4)	0·463 (2)	0·607 (3)	3·9 (7)
H(C3)	0·849 (4)	0·560 (1)	0·659 (3)	3·1 (6)
H(C5)	0·418 (4)	0·441 (2)	0·685 (3)	4·0 (7)
H(C6)	0·584 (4)	0·339 (1)	0·645 (3)	3·6 (6)
H(N2)1	0·413 (3)	0·563 (1)	0·699 (3)	2·8 (6)
H(N2)2	0·576 (4)	0·610 (2)	0·701 (3)	4·3 (7)
H(C9)	0·790 (5)	0·303 (2)	−0·072 (3)	4·9 (8)
H(C11)1	0·909 (7)	0·459 (3)	0·113 (5)	12·1 (15)
H(C11)2	0·732 (9)	0·451 (3)	0·065 (6)	14·8 (19)
H(C11)3	0·830 (6)	0·434 (2)	−0·033 (4)	8·1 (11)
H(C12)1	0·675 (7)	0·139 (3)	0·003 (5)	11·6 (15)
H(C12)2	0·875 (7)	0·142 (3)	0·025 (6)	12·5 (16)
H(C12)3	0·780 (7)	0·182 (2)	−0·098 (5)	9·7 (13)

Table 2. *Bond lengths* (Å) *and angles* (°)

S–O(1)	1·435 (2)	C(6)–C(1)	1·391 (4)
S–O(2)	1·431 (2)	C(4)–N(2)	1·367 (3)
S–N(1)	1·632 (2)	C(7)–N(3)	1·333 (3)
S–C(1)	1·746 (3)	C(7)–N(4)	1·324 (3)
N(1)–C(7)	1·406 (3)	N(4)–C(8)	1·353 (3)
C(1)–C(2)	1·383 (3)	C(8)–C(9)	1·367 (5)
C(2)–C(3)	1·371 (3)	C(8)–C(11)	1·497 (5)
C(3)–C(4)	1·398 (4)	C(9)–C(10)	1·385 (5)
C(4)–C(5)	1·400 (4)	C(10)–N(3)	1·347 (3)
C(5)–C(6)	1·374 (4)	C(10)–C(12)	1·499 (5)

O(1)–S–O(2)	118·9 (1)	O(1)–S–N(1)	109·0 (1)
O(1)–S–C(1)	108·1 (1)	S–N(1)–C(7)	128·0 (2)
N(1)–S–C(1)	108·2 (1)	O(2)–S–N(1)	103·1 (1)
O(2)–S–C(1)	109·0 (1)	S–C(1)–C(6)	120·4 (2)
S–C(1)–C(2)	119·7 (2)	C(2)–C(1)–C(6)	119·7 (2)
C(1)–C(2)–C(3)	120·5 (2)	C(2)–C(3)–C(4)	120·6 (2)
C(3)–C(4)–C(5)	118·3 (2)	C(3)–C(4)–N(2)	120·4 (2)
C(5)–C(4)–N(2)	121·3 (2)	C(4)–C(5)–C(6)	120·9 (3)
C(1)–C(6)–C(5)	119·8 (2)	N(1)–C(7)–N(3)	113·8 (2)
N(1)–C(7)–N(4)	117·1 (2)	N(4)–C(7)–N(3)	129·1 (2)
C(7)–N(4)–C(8)	114·8 (2)	N(4)–C(8)–C(9)	121·1 (3)
N(4)–C(8)–C(11)	116·9 (3)	C(9)–C(8)–C(11)	122·1 (3)
C(8)–C(9)–C(10)	119·5 (3)	N(3)–C(10)–C(12)	117·6 (3)
C(9)–C(10)–N(3)	120·4 (3)	C(9)–C(10)–C(12)	122·0 (3)
C(7)–N(3)–C(10)	115·2 (2)		

dihedral angle between the pyrimidine and phenyl rings is 75·5 (1)° and is comparable to the values 80·7 and 86·7° in form (I) and 87·7° in form (III) of 2-sulphanilamido-5-methoxypyrimidine (Giuseppetti *et al.*, 1977). The C(8)–C(11) and C(10)–C(12) distances are close to the expected $C(sp^2)$–$C(sp^3)$ distance. The endocyclic angles of the pyrimidine ring are in agreement with those observed in substituted pyrimidines (Voet & Rich, 1970).

The C(2)–C(1)–S–N(1) and C(6)–C(1)–S–N(1) torsion angles of −129·3 (2) and 55·1 (3)° lie outside the clustering range of $|\varepsilon_1| = 70$–120°, but the C(1)–S–N(1)–C(7) torsion angle of 83·0 (3)° lies within the range $|\varepsilon_2| = 60$–90° (Kálmán *et al.*, 1981). The dispositions of the two sulphonyl oxygens, O(1) and O(2), with respect to the phenyl ring are found to be somewhat asymmetrical as indicated by the torsion angles O(1)–S–C(1)–C(2) = −11·4 (3), O(1)–S–C(1)–C(6) = 173·0 (2), O(2)–S–C(1)–C(2) = 119·3 (3) and O(2)–S–C(1)–C(6) = −56·3 (3)°. The angle between the S–N(1)–C(7) plane and the phenyl ring is 102·4 (1)° and compares well with 102·86° in the 1:1 complex of sulphacetamide with caffeine (Leger, Alberola & Carpy, 1977).

The molecular packing viewed down the *a* axis is illustrated in Fig. 2. Two distinct types of ring stacking are observed; the pyrimidine rings stack with the pyrimidine rings while the phenyl rings stack with the phenyl rings.

All the available hydrogen atoms take part in hydrogen bonding. The molecules form dimers through centrosymmetric pairs of N(2)–H···N(4) hydrogen bonds. These dimers are linked together into infinite chains along the *y* direction by N(2)–H···N(3) hydrogen bonds between screw-related molecules, and along the *x* direction by N(1)–H···O(1) hydrogen bonds between glide-related molecules. The geometrical details of the hydrogen bondings are as follows [symmetry code: (i) $-\frac{1}{2}+x, \frac{1}{2}-y, z$; (ii) $\frac{3}{2}-x, \frac{1}{2}+y, 1-z$; (iii) $1-x, 1-y, 1-z$]:

A–H···*B*	*A*–H (Å)	*A*···*B* (Å)	H···*B* (Å)	*A* H···*B* (°)
N(1) H(N1)···O(1^{i})	0·80 (2)	2·947 (2)	2·20 (2)	158 (2)
N(2) H(N2)2···N(3^{ii})	0·89 (3)	3·219 (3)	2·37 (3)	159 (2)
N(2) H(N2)1···N(4^{iii})	0·79 (2)	3·092 (3)	2·53 (2)	129 (2)

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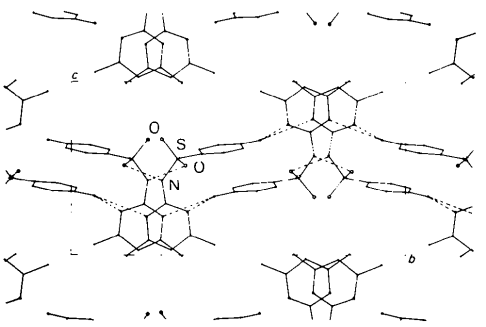

Fig. 2. Projection of the crystal structure of sulphamethazine on the *bc* plane.

References

ALLÉAUME, M., GULKO, A., HERBSTEIN, F. H., KAPON, M. & MARSH, R. E. (1976). *Acta Cryst.* B**32**, 669–682.

BASAK, A. K., MAZUMDAR, S. K. & CHAUDHURI, S. (1982). *Cryst. Struct. Commun.* Accepted for publication.

BUSING, W. R., MARTIN, K. O. & LEVY, H. A. (1962). *ORFLS.* Report ORNL-TM-306. Oak Ridge National Laboratory, Tennessee.

CAMERMAN, A. (1970). *Can. J. Chem.* **48**, 179–181.

CHRISTOPH, G. G. & FLEISCHER, E. B. (1973). *Acta Cryst.* B**29**, 121–130.

COTTON, F. A. & STOKLEY, P. F. (1970). *J. Am. Chem. Soc.* **92**, 294–302.

CROMER, D. T. & WABER, J. T. (1965). *Acta Cryst.* **18**, 104–109.

DOMENICANO, A., VACIAGO, A. & COULSON, C. A. (1975). *Acta Cryst.* B**31**, 221–234.

DONALDSON, J. D., LEARY, J. R., ROSS, S. D., THOMAS, J. K. & SMITH, C. H. (1981). *Acta Cryst.* B**37**, 2245–2248.

GIUSEPPETTI, G., TADINI, C., BETTINETTI, G. P. & GIORDANO, F. (1977). *Cryst. Struct. Commun.* **6**, 263–274.

HAMILTON, W. C. (1959). *Acta Cryst.* **12**, 609–610.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press.

KÁLMÁN, A., CZUGLER, M. & ARGAY, GY. (1981). *Acta Cryst.* B**37**, 868–877.

KRUGER, G. J. & GAFNER, G. (1971). *Acta Cryst.* B **27**, 326–333.

LEGER, J. M., ALBEROLA, S. & CARPY, A. (1977). *Acta Cryst.* B**33**, 1455–1459.

MAIN, P., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J. P. & WOOLFSON, M. M. (1978). *MULTAN* 78. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffration Data.* Univs. of York, England, and Louvain, Belgium.

NITYA ANAND (1979). *Burger's Medicinal Chemistry*, Part II, edited by M. E. WOLFF, pp. 1–40. New York: John Wiley.

O'CONNELL, A. M. & MASLEN, E. N. (1967). *Acta Cryst.* **22**, 134–145.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

VOET, D. & RICH, A. (1970). *Prog. Nucleic Acid Res. Mol. Biol.* **10**, 183–265.