The Crystal and Molecular Structure of
Benzenesulphonamide-p-(tetrahydro-2H-1,2-thiazin-2-yl)-S,S-dioxide

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Crystals of benzenesulphonamide-p-(tetrahydro-2H-1,2-thiazin-2-yl)-S,S-dioxide, Sulthiame, are orthorhombic, space group $Pca2_1$, with $a = 8.250$ (3), $b = 17.713$ (7), $c = 8.638$ (3) Å. The structure has been refined to $R = 0.063$ for 710 independent reflexions measured on an automatic four-circle diffractometer. The heterocyclic ring adopts the chair conformation and the basal plane of the chair makes a dihedral angle of $121.0°$ with the plane of the aromatic ring. Hydrogen bonds between the sulphonamide groups connect the molecules in layers parallel to (010).

Introduction

Benzenesulphonamide-p-(tetrahydro-2H-1,2-thiazin-2-yl)-S,S-dioxide, referred to hereafter as Sulthiame, is an effective anti-convulsant drug. In addition it may compete with other anti-epileptic drugs for metabolic pathways in the human body and as a consequence may inhibit the inactivation of these drugs in the body. The structural analysis of this compound was undertaken as part of a programme of study on convulsant and anti-convulsant drugs being carried out in this department.

Experimental

The sample of Sulthiame used in this analysis was provided by Professor R. G. Spector of Guy's Hospital Medical School, London. The crystals are colourless thin plates perpendicular to [010]. A single crystal measuring $0.18 \times 0.06 \times 0.23$ mm parallel to **a**, **b** and **c** respectively and mounted about the c axis was used for the X-ray measurements. Preliminary X-ray diffraction data were obtained from Weissenberg and precession photographs taken with copper radiation. Accurate unit-cell parameters were determined by least-squares refinement of the θ values of 20 reflexions measured on a Hilger–Watts Y290 automatic four-circle diffractometer with Cu $K\alpha_1$ radiation ($\lambda = 1.5405$ Å). Intensity data were also collected on this instrument using Ni-filtered copper radiation. The diffractometer is equipped with a pulse-height analyser and a scintillation counter. The $\omega/2\theta$ scanning method was used with steps of $0.01°$ in ω and $0.02°$ in 2θ at 2 s per step. The width of scan for each reflexion as an integral number of steps was evaluated from the expression $(A + B . \tan \theta)°$ where A ($= 1.282°$) was the scan width at a θ value of zero deduced from a value of $1.300°$ for the 120 reflexion at a θ value of $7.340°$ and B is a dispersion constant ($= 0.142°$) for Cu $K\alpha$ radiation. Stationary background counts were measured before and after each scan for one tenth of the

time taken to scan each reflexion. Gradual variations in the experimental conditions during the data collection were monitored by measuring three reference reflexions after every 50 reflexions and the reflexion data were scaled to these reference reflexions.

Reflexions on the Weissenberg photographs were not observable above a 2θ value of $100°$ and data for the hkl reflexions were collected on the diffractometer over the range $\leq 12\theta \leq 100°$. A second set of data was collected for the $h\bar{k}l$ reflexions over the range $1 \leq 2\theta \leq 60°$. Averaging of these two sets of diffractometer data gave 710 independent reflexions of which 559 had an intensity greater than 2.5 standard deviations and were thereby classified as 'significant'. Lorentz and polarization corrections were applied to all reflexions but no corrections were made for absorption; the absorption coefficient for this compound is $\mu(\text{Cu } K\alpha) = 37.9$ cm^{-1}.

Crystal data

The crystals are orthorhombic with unit-cell dimensions, measured at room temperature ($20 \pm 1°$C): $a = 8.250$ (3), $b = 17.713$ (7), $c = 8.638$ (3) Å. There are four molecules of $C_{10}H_{14}S_2O_4N_2$, formula weight 290.4, in the cell. The calculated density is 1.528 g cm.$^{-3}$ The conditions limiting possible reflexions, $0kl$, $l = 2n$ and $h0l$, $h = 2n$, indicate space group $Pca2_1$ (No. 29, C_{2v}^5) or $Pcam$ (an alternative orientation of No. 57, D_{2h}^{11}).

Solution and refinement of structure

The conditions limiting possible reflexion do not determine the space group unambiguously. With $Z = 4$ the holosymmetric spacegroup, $Pcam$, requires the molecule to exhibit a mirror plane, a twofold axis or a centre of symmetry. Since none of these geometries are possible the spacegroup is $Pca2_1$ with all atoms lying in general positions.

The sulphur atoms were located from a three-di-

mensional Patterson synthesis computed with sharpened coefficients. The z coordinate of one of the sulphur atoms was fixed at zero and the remaining non-

Table 1. *Analysis of weighting scheme*

sin θ/λ	Number of planes, n	$\sum w\Delta^2/n$
0·0–0·2	52	0·092
0·2–0·3	112	0·048
0·3–0·4	217	0·051
0·4–0·5	329	0·083

$|F_o|$	Number of planes, n	$\sum w\Delta^2/n$
0–11	84	0·085
11–22	125	0·097
22–44	245	0·064
44–88	190	0·045
88–176	56	0·073
>176	10	0·099

Table 2. *Positional and thermal parameters*

(a) Positional atomic parameters for the non-hydrogen atoms
Estimated standard deviations are given in parentheses.

	x/a	y/b	z/c
S(1)	0·1103 (3)	0·1063 (1)	0·0000
S(2)	0·6064 (4)	0·4141 (2)	0·1027 (5)
O(1)	0·0131 (9)	0·1077 (4)	0·1393 (10)
O(2)	0·2758 (9)	0·0839 (3)	0·0194 (11)
O(3)	0·5433 (13)	0·4621 (6)	0·2194 (13)
O(4)	0·7458 (15)	0·3719 (5)	0·1429 (17)
N(1)	0·1070 (9)	0·1887 (5)	−0·0844 (11)
N(2)	0·6506 (13)	0·4659 (6)	−0·0380 (13)
C(1)	0·4541 (13)	0·3487 (6)	0·0532 (15)
C(2)	0·2940 (14)	0·3591 (6)	0·0963 (15)
C(3)	0·1792 (13)	0·3061 (6)	0·0512 (14)
C(4)	0·2238 (12)	0·2441 (5)	−0·0336 (14)
C(5)	0·3853 (12)	0·2345 (6)	−0·0815 (14)
C(6)	0·4989 (13)	0·2876 (6)	−0·0368 (13)
C(7)	−0·0601 (11)	0·2164 (7)	−0·1177 (16)
C(8)	−0·1393 (14)	0·1644 (7)	−0·2324 (16)
C(9)	−0·1547 (13)	0·0849 (6)	−0·1742 (16)
C(10)	0·0113 (13)	0·0510 (6)	−0·1360 (15)

Table 2 (*cont.*)

(c) Calculated hydrogen atom positions. All hydrogen atoms were assigned an isotropic thermal parameter, $U = 0.06$ Å^2. The expression used is exp $(-8\pi^2 U . \sin \theta^2/\lambda^2)$

	x/a	y/b	z/c
H(2)	0·2614	0·4041	0·1589
H(3)	0·0631	0·3132	0·0809
H(5)	0·4173	0·1902	−0·1465
H(6)	0·6144	0·2817	−0·0697
H(71)	−0·0545	0·2685	−0·1618
H(72)	−0·1247	0·2171	−0·0198
H(81)	−0·0728	0·1639	−0·3292
H(82)	−0·2501	0·1841	−0·2561
H(91)	−0·2080	0·0534	−0·2557
H(92)	−0·2230	0·0849	−0·0786
H(101)	0·0781	0·0485	−0·2325
H(102)	−0·0038	−0·0011	−0·0935
H(21)	0·5629	0·4914	−0·0714
H(22)	0·6722	0·4407	−0·1261

hydrogen atomic positions were obtained by the iterative Fourier synthesis technique with the initial set of phases based on the sulphur-atom positions. The value of R_1 ($= \sum||F_o| - |F_c||/\sum|F_o|$) was 0·368.

The structure was refined by the method of full-matrix least-squares. Initially all atoms were treated isotropically but in subsequent cycles of refinement the two sulphur atoms and then, in addition, the four oxygen atoms and the sulphamide nitrogen atom were refined anisotropically; R_1 was reduced to 0·074. A difference Fourier synthesis showed electron-density maxima (0·2–0·5 e Å^{-3}) which could clearly be assigned to all the hydrogen atoms attached to the aromatic and thiazine rings. Because of the difficulty in determining the precise centres of gravity of the maxima these hydrogen atoms were placed in calculated positions assuming a carbon–hydrogen bond distance of 1·0 Å. Several maxima occurred in the region of the sulphamide nitrogen atom but it was not possible to chose unequivocal positions for the hydrogen

Table 2 (*cont.*)

(b) Anisotropic thermal parameters for the non-hydrogen atoms. The expression used is

$$\exp\,[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{23}klb^*c^* + 2U_{31}lhc^*a^* + 2U_{12}hka^*b^*)].$$

	U_{11}	U_{22}	U_{33}	$2U_{23}$	$2U_{31}$	$2U_{12}$
S(1)	0·040 (1)	0·038 (1)	0·046 (2)	0·009 (3)	−0·010 (3)	0·003 (2)
S(2)	0·059 (2)	0·055 (2)	0·051 (2)	−0·004 (4)	−0·024 (4)	−0·022 (3)
O(1)	0·062 (5)	0·073 (5)	0·040 (4)	0·013 (8)	0·024 (8)	−0·025 (9)
O(2)	0·047 (5)	0·051 (4)	0·083 (6)	−0·003 (9)	−0·021 (9)	0·001 (7)
O(3)	0·104 (8)	0·117 (8)	0·096 (8)	−0·11 (1)	0·05 (1)	−0·10 (1)
O(4)	0·075 (5)	0·090 (5)	0·14 (1)	−0·01 (1)	−0·10 (1)	−0·03 (1)
N(1)	0·031 (4)	0·048 (6)	0·064 (6)	−0·013 (9)	−0·01 (1)	−0·008 (8)
N(2)	0·093 (8)	0·073 (6)	0·070 (7)	0·01 (1)	−0·04 (1)	−0·06 (1)
C(1)	0·054 (7)	0·041 (6)	0·050 (6)	0·00 (1)	−0·01 (1)	−0·03 (1)
C(2)	0·055 (9)	0·059 (7)	0·060 (8)	−0·01 (1)	0·03 (1)	−0·01 (1)
C(3)	0·043 (6)	0·056 (7)	0·065 (8)	0·00 (1)	0·01 (1)	0·00 (1)
C(4)	0·040 (6)	0·043 (6)	0·055 (7)	0·01 (1)	0·01 (1)	0·01 (1)
C(5)	0·047 (6)	0·042 (6)	0·057 (7)	0·00 (1)	−0·02 (1)	0·00 (1)
C(6)	0·050 (6)	0·051 (6)	0·046 (7)	0·01 (1)	0·00 (1)	−0·01 (1)
C(7)	0·035 (6)	0·061 (7)	0·075 (8)	0·05 (1)	−0·01 (1)	0·01 (1)
C(8)	0·048 (7)	0·070 (8)	0·079 (9)	0·03 (2)	−0·02 (1)	−0·01 (1)
C(9)	0·048 (6)	0·067 (7)	0·073 (8)	0·02 (2)	0·00 (1)	0·00 (1)
C(10)	0·051 (6)	0·056 (7)	0·058 (8)	0·00 (1)	0·00 (1)	0·00 (1)

atoms attached to it. These hydrogen atoms were also placed in calculated positions assuming a nitrogen–hydrogen bond distance of 0·9 Å and a geometrical arrangement similar to that found in β-sulphanilamide (O'Connell & Maslen, 1967). No attempt was made to refine the positional or thermal parameters of the hydrogen atoms.

Table 3. *Tensor analysis of the anisotropic thermal vibration ellipsoids for the non-hydrogen atoms*

	Direction cosines, D_j, of ellipsoids w.r.t. unit orthogonal axes			R.m.s. amplitude (Å)
	D_1	D_2	D_3	
S(1)	0·5534	−0·6905	0·4659	0·1848
	0·7310	0·6704	0·1271	0·2026
	0·3997	−0·2704	−0·8758	0·2227
S(2)	0·6132	0·4702	0·6347	0·1944
	0·1122	0·7451	−0·6574	0·2353
	0·7820	−0·4747	−0·4040	0·2671
O(1)	0·4489	0·2676	−0·8525	0·1764
	0·7052	0·4797	0·5220	0·2488
	0·5486	−0·8357	0·0265	0·2850
O(2)	0·9656	0·0028	0·2600	0·2099
	0·0232	−0·9992	−0·0327	0·2257
	0·2597	0·0411	−0·9648	0·2933
O(3)	0·3691	0·7126	0·5967	0·2164
	0·7718	0·1227	−0·6239	0·2767
	0·5718	−0·6909	0·5046	0·4397
O(4)	0·8525	0·2911	0·4342	0·2151
	0·2340	−0·9552	0·1812	0·3067
	0·4675	−0·0526	−0·8824	0·4087
N(1)	0·9373	0·2626	0·2291	0·1674
	0·3137	−0·9216	−0·2273	0·2174
	0·1510	0·2851	−0·9465	0·2587

	D_1	D_2	D_3	R.m.s. amplitude (Å)
N(2)	0·6095	0·6169	0·4980	0·2208
	0·0005	−0·5734	0·8193	0·2610
	0·7921	−0·4976	−0·3535	0·3449
C(1)	0·5807	0·8125	0·0502	0·1698
	0·1231	−0·1500	0·9810	0·2217
	0·8045	−0·5632	−0·1887	0·2579
C(2)	0·7655	0·0044	−0·6434	0·2045
	0·2716	0·9040	0·3302	0·2339
	0·5831	−0·4272	0·6910	0·2767
C(3)	0·9614	0·1355	−0·2393	0·2024
	0·1259	−0·9895	−0·0706	0·2368
	0·2456	−0·0367	0·9687	0·2573
C(4)	0·8998	−0·3702	−0·2310	0·1907
	0·2397	0·8638	−0·4432	0·2042
	0·3637	0·3434	0·8659	0·2433
C(5)	0·8286	−0·2623	0·4945	0·2007
	0·1741	0·9616	0·2120	0·2042
	0·5312	0·0923	−0·8422	0·2532
C(6)	0·0457	−0·4018	0·9416	0·2107
	0·8087	0·5529	0·2010	0·2189
	0·5862	−0·7324	−0·3464	0·2343
C(7)	0·8495	−0·3925	0·3524	0·1724
	0·5249	0·6986	−0·4863	0·2186
	0·0551	−0·5982	−0·7994	0·3055
C(8)	0·9599	0·0859	0·2670	0·2115
	0·0789	0·8242	−0·5608	0·2431
	0·2683	−0·5590	−0·7846	0·3059
C(9)	0·9915	−0·0507	0·1195	0·2184
	0·1144	0·7887	−0·6041	0·2410
	0·0635	−0·6125	−0·7879	0·2866
C(10)	0·9602	0·2384	−0·1457	0·2235
	0·2419	−0·9676	0·0723	0·2378
	0·1337	0·1046	0·9855	0·2417

Further cycles of full-matrix least-squares refinement were computed with all the non-hydrogen atoms treated anisotropically until all the parameter shifts were less than 0·2 of the corresponding estimated standard deviations. Relative weights were assigned to the unscaled observed structure factors during the refinement according to a function of the type

$$w = a \text{ for } |F_o| \leq |F_o|_{min} ,$$

otherwise

$$w = 1/(b + |F_o| + c \cdot |F_o|^2 + d \cdot |F_o|^3) ,$$

where $|F_o|_{min}$ is a threshold value for the significant reflexions. Values of $a = 0·002$, $b = 40·0$, $c = 0·06$ and $d = 0·001$ were chosen for the final least-squares cycle. An analysis of the weighting scheme is shown in Table 1. The final value of R_1 for all reflexions was 0·063 and that of $R_2 = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2}$ was 0·068.*

Throughout the structure-factor calculations the atomic scattering factors listed by Hanson, Herman, Lea & Skillman (1964) were used. All computations were performed on the CDC 6400 and 6600 computers at the University of London Computer Centre.

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30337 (8pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 4. *Molecular geometry*

(a) Least-squares planes defined by atomic positions and, in brackets, distances of atoms (Å) from these planes. X, Y and Z refer to orthogonal coordinates (Å).

Plane (1): C(1), C(2), C(3), C(4), C(5) and C(6)
0·1768X − 0·5201Y + 0·8356Z = −2·1795
[C(1) 0·013, C(2) −0·005, C(3) −0·009, C(4) 0·015, C(5) −0·007, C(6) −0·007, S(2) −0·009, N(1) −0·013]

Plane (2): S(1), C(7), C(8) and C(10)
0·7316X + 0·1824Y − 0·6569Z = 1·0068
[S(1) 0·002, C(7) −0·003, C(8) 0·003, C(10) −0·002, N(1) 0·728, C(9) −0·678]

(b) Torsion angles (°)

S(1)—N(1)—C(7)—C(8)	−64·3
N(1)—C(7)—C(8)—C(9)	60·9
C(7)—C(8)—C(9)—C(10)	−59·7
C(8)—C(9)—C(10)–S(1)	57·5
C(9)—C(10)–S(1)—N(1)	−54·9
C(10)–S(1)—N(1)–C(7)	59·5

(c) Inter-molecular hydrogen bond distances (Å)

O(3)$^{i}\cdots$N(2)^{ii}	2·93
O(3)$^{i}\cdots$N(2)^{iii}	3·28
O(4)$^{i}\cdots$N(2)^{iii}	3·33

i, ii and iii refer to the equivalent positions

i	x,	y,	z
ii	$1-x$,	$1-y$,	$\frac{1}{2}+z$
iii	$1\frac{1}{2}-x$,	y,	$\frac{1}{2}+z$, respectively.

The final atomic coordinates and thermal parameters are given in Table 2. Table 3 contains a tensor analysis of the anisotropic thermal vibrations for the non-hydrogen atoms.

Discussion

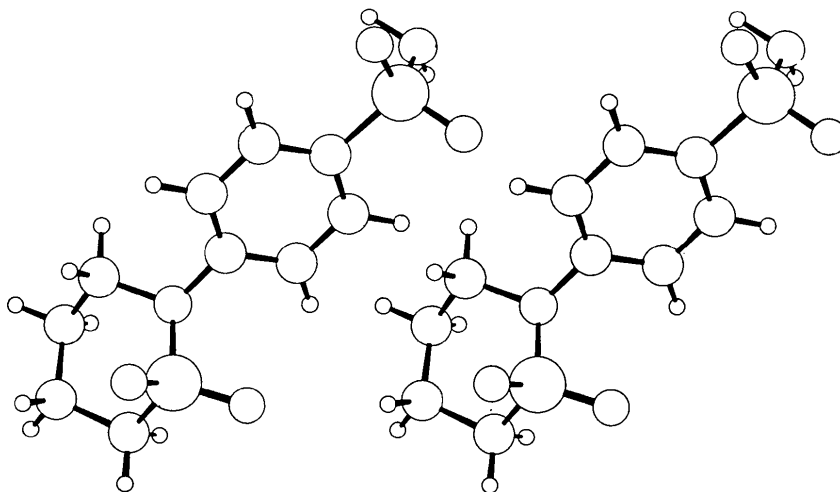Fig. 1 is a stereo drawing of the molecule looking down the unit-cell c-axis. Fig. 2 is a schematic drawing

Fig. 1. A stereo drawing of the molecule of Sulthiame viewed along the unit-cell c axis.

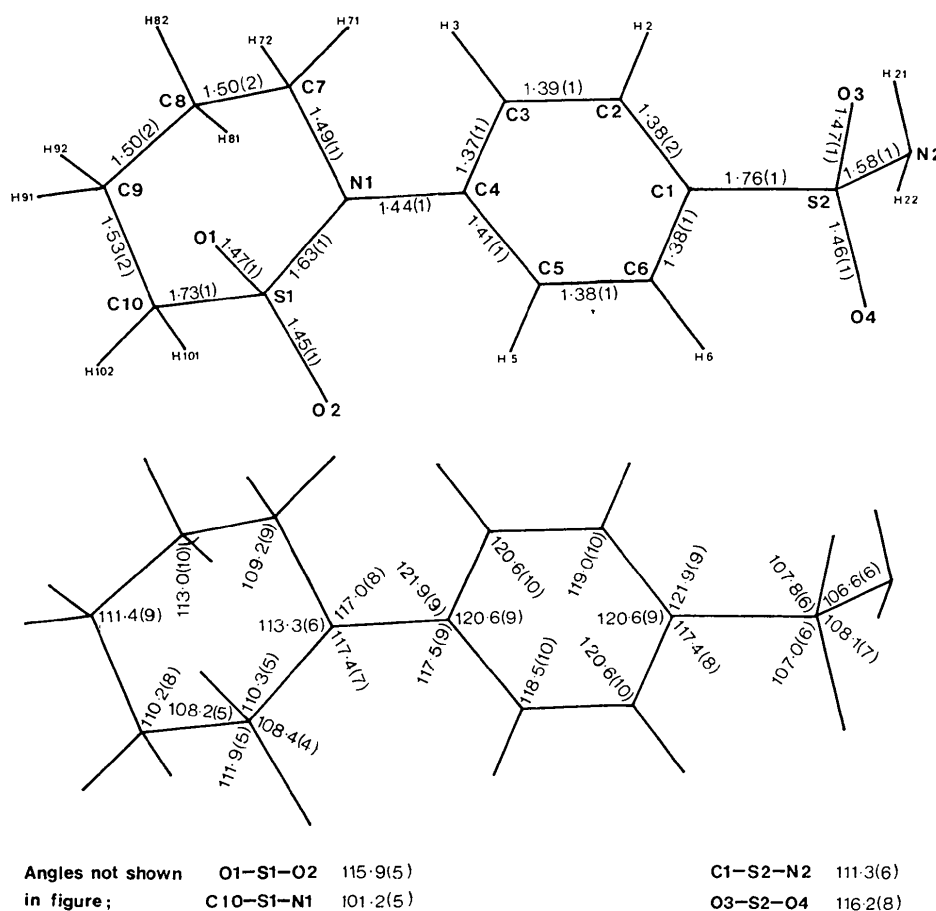| Angles not shown | O1—S1—O2 | 115·9(5) | | C1—S2—N2 | 111·3(6) |
| in figure; | C10—S1—N1 | 101·2(5) | | O3—S2—O4 | 116·2(8) |

Fig. 2. A schematic drawing of sulthiame showing the labelling of the atoms and the intramolecular bond lengths and angles.

of the molecule showing the labelling of the atoms and the intramolecular bond lengths and angles. Estimated standard deviations, given in parentheses, are those evaluated from the least-squares matrix and do not allow for additional errors due to inadequate corrections for anisotropic thermal vibration. Further details of the molecular geometry are given in Table 4.

The tetrahydrothiazine ring adopts the chair conformation and is attached to the aromatic ring through the nitrogen atom in the *para* position with respect to the sulphamide group. The C(4)–N(1) bond length, 1·44 (1) Å, is significantly closer to the value of 1·47 Å for a single carbon–nitrogen bond than to that of 1·29 Å for a double bond, and compares with the values of 1·385 (26) Å found in β-sulphanilamide (O'Connell & Maslen, 1967), 1·40 (2) Å in α-sulphanilamide (O'Connor & Maslen, 1965), 1·383 (25) Å in γ-sulphanilamide (Alléaume & Decap, 1965) and 1·377 (16) Å in sulphanilamide monohydrate (Alléaume & Decap, 1968). The increase in the single-bond character of the C(4)–N(1) interaction in Sulthiame compared with the sulphanilamides may be explained in terms of the restricted possibility of overlap between the lone pair of electrons on the nitrogen atom and the π orbitals on the aromatic ring. This restriction is caused by the rotation of the thiazine ring about the C(4)–N(1) bond. The dihedral angle between the least-squares plane through the atoms S(1), C(7), C(8) and C(10) defining the base of the thiazine chair and the least-squares plane through the carbon atoms of the aromatic ring is 121·0°. This rotation minimizes the non-bonded contacts between O(2) and H(5), 2·64(1) Å, and between H(3) and H(71) and H(72), 2·44 and 2·46 Å respectively. Any alteration in the value of the dihedral angle would cause one or more of these separations to decrease significantly below the van der Waals non-bonded contact distances, (2·60 Å for O–H and 2·40 Å for H–H).

The partial double-bond character of the N(1)–S(1) interaction, 1·63 (1) Å, can be explained in terms of π bonding between the sulphur $3d$ orbitals and the lone pair of electrons which are available on the nitrogen atom. The opening out of the S(1)–N(1)–C(4) and C(4)–N(1)–C(7) angles to 117·4 (7) and 117·0 (8)° respectively from the tetrahedral value is consistent with this view; the third angle, S(1)–N(1)–C(7), is held at 113·3 (6)° by the ring geometry. The geometry around S(1) is closely similar to that observed in 4-methylthiomorpholine-1,1-dioxide (Herdklotz & Sass, 1969).

The aromatic ring is planar within experimental error and both N(1) and S(2) lie in the plane. The average carbon–carbon separation is 1·385 Å and the internal ring angles are all within two estimated standard deviations of 120°.

The geometry of the sulphamide moiety is typical of that found in other sulphonyl amides (Karle, 1973 and references therein) although the magnitudes of the anisotropic thermal vibrations and the corres-

ponding unreliability of the estimated standard deviations do not permit precise comparisons to be made. The arrangement of the bonds around both sulphur atoms is distorted tetrahedral, with the O–S–O angles, average 116·0°, giving oxygen–oxygen separations of 2·44 Å for O(1)–O(2) and 2·40 Å for O(3)–O(4). The latter distance is comparable with the values of 2·39 and 2·41 Å for O(3)–N(2) and O(4)–N(2) respectively.

The magnitudes of the anisotropic vibrational parameters for the sulphamide group presumably explain why it was not possible to locate the two amino hydrogen atoms. The longest axes of the thermal vibration ellipsoids for all four sulphamide atoms are nearly perpendicular, within 7°, to the C(4)–C(1) direction. The longest ellipsoid axes for S(2) and N(2) are also nearly perpendicular, within 6°, to the normal to the least-squares plane through the aromatic ring whereas the corresponding axes for O(3) and O(4) make angles of 28 and 129° with this direction. In β-sulphanilamide the situation is similar, with the sulphamide group oscillating about the long axis of the molecule. All the sulphur–oxygen bond lengths, and the sulphamide S(2)–N(2) distance, were corrected for thermal motion effects (Busing & Levy, 1964) assuming that the oxygen and nitrogen atoms ride on the respective sulphur atoms. The corrections were 0·022, 0·017, 0·052, 0·045 and 0·019 Å for the S(1)–O(1), S(1)–O(2), S(2)–O(3), S(2)–O(4) and S(2)–N(2) distances respectively.

The molecular packing is shown in Fig. 3 in projection along the c axis. The molecules lie in layers parallel to (010). Each layer is comprised of two sub-layers of thickness $b/2$ which are linked together by hydrogen bonds across the plane at $y = \frac{1}{2}$. These hydrogen bonds, denoted by dashed lines in the figure, are of the N–H...O type and involve molecules related by the twofold screw axes; the N(2)...O(3) distance
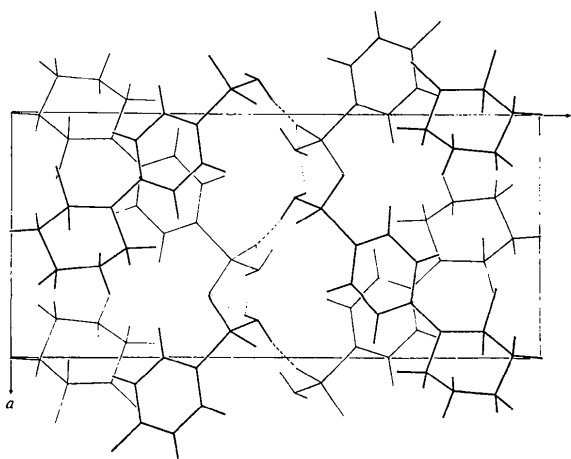

Fig. 3. The molecular packing viewed in projection along the unit-cell c axis. The dashed lines denote hydrogen bonds of the type N–H···O between molecules related by the twofold screw axes and with a N(2)···O(3) distance of 2·93 Å. The dotted lines denote hydrogen bonds of the same type between molecules related by the c glide planes and with an average N···O distance of 3·30 Å.

is 2·93 Å. Within each sub-layer molecules related by the c-glide planes are held together by much weaker hydrogen bonds, denoted by dotted lines in the figure, and of average length 3·30 Å. The layers themselves are held together by van der Waals forces and this presumably accounts for the pronounced (010) cleavage plane in the crystal.

References

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The Crystal and Molecular Structure of Guanosine 3′, 5′-Cyclic Monophosphate (Cyclic GMP) Sodium Tetrahydrate

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The crystal structure and conformation of cyclic GMP (as sodium guanosine 3′,5′-cyclic monophosphate tetrahydrate) has been determined by the single-crystal X-ray diffraction technique. The crystals are orthorhombic, space group $P2_12_12_1$ with unit-cell constants $a = 18·664$ (3), $b = 7·384$ (2) and $c = 12·706$ (3) Å; $Z = 4$, $D_o = 1·66$, $D_c = 1·665$ g cm^{-3} assuming one sodium ion and four molecules of water per nucleotide. The structure was solved by direct methods using the program MULTAN and refined by least-squares methods to a final R value of 0·034 based on 1637 diffractometer intensities. The base displays the syn conformation with a glycosyl torsion angle $\chi[C(8)-N(9)-C(1')-O(1')]$ of 258°. The cyclization of the phosphate group forces the ribose to the $_4T^3$ [C(4')exo, C(3')endo] conformation which is characteristic of the cyclic nucleotides. The bond distances and angles in the ribose ring show significant differences from those of the common nucleotides. The phosphate ring is locked into a chair conformation, being puckered most about the C(3')–C(4') bond and flattened at the phosphate end. The sodium ion is not directly attached to the phosphate oxygen atoms but is coordinated to six water molecules at distances ranging from 2·32 to 2·68 Å. Adjacent sodium octahedra share edges to form an infinite column parallel to b. The crystal packing consists of alternating layers of stacked nucleotides with the interstitial holes filled by the sodium-water octahedra.

Introduction

Cyclic AMP has been known for some time to mediate a large number of hormonal and regulatory mechanisms (Sutherland & Rall, 1960), but only recently has it come to light that cyclic GMP is also involved in metabolic control and regulatory functions (Hardman, 1971). In continuation of the studies on the structure of cyclic nucleotides in this laboratory (Sundaralingam & Abola, 1972a,b), we have now carried out the structure determination of guanosine 3′,5′-cyclic monophosphate (cyclic GMP). Cyclic GMP has been found in a number of mammalian tissues and body fluids (Hardman, 1971). A number of studies have suggested separate roles for cyclic GMP and cyclic AMP in hormonal or metabolic control and regulatory functions (Hardman, 1971; Kuo, Lee, Reyes, Walton,

Donnelly & Greengard, 1972). The recognition of the biological importance of cyclic GMP made it highly desirable that a detailed crystal-structural study of its molecular conformation be undertaken. In addition to the present work on cyclic GMP (see also preliminary communication; Chwang & Sundaralingam, 1973), the crystal structures of cyclic C-AMP (5′-methylene adenosine 3′,5′-cyclic monophosphate) (Sundaralingam & Abola 1972a,b), cyclic UMP (Coulter, 1969) and cyclic AMP (Watenpaugh, Dow, Jensen & Furberg, 1968) have been reported.

Experimental

Single crystals of cyclic GMP suitable for the structure determination were found in a sample of 'salt-free' cyclic GMP purchased from Nutritional Biochemicals,