

axes parallel to **b**. The arrangement is essentially the same as that found in crystals of cytosine, but more complicated due to the existence of two types of molecules *A* and *B*. The hierarchy of structure in crystals of thiocytosine is interesting: molecules–dimers–ribbons–bundles or ribbons, each step being associated with progressively weaker bonds.

The hydrogen bonds conform to the general stereochemistry of the molecule, being nearly linear, lying approximately in molecular planes, and forming angles of about 120° with adjacent C–N bonds. For example the angle between the two N–H...S bonds of the amino group is 123·5° in molecule *A* and 124·3° in *B*. In general, the shortest hydrogen bonds are associated with the longest N–H distances, as is to be expected. The shortest intermolecular distance between hydrogen atoms is 2·46 Å (amino hydrogen atoms) and between nitrogen and sulfur atoms, 3·28 Å. The latter contact is, however, not a hydrogen bond, but rather a van der Waals contact, since there is no hydrogen atom between these two atoms.

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Calculating System which was used for most of the computational work in this study and to Dr C. K. Johnson for the *ORTEP* program.

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The Crystal Structure of 2'-Hydroxymethanesulfonanilide

BY HAROLD P. KLUG

Mellon Institute, Carnegie-Mellon University, Pittsburgh, Pa. 15213, U.S.A.

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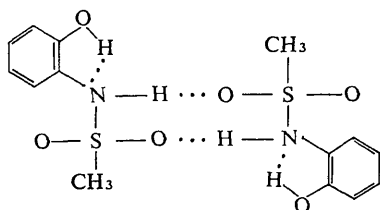
The simple compound, 2'-hydroxymethanesulfonanilide (HMSA), HO–C₆H₄–NH–SO₂CH₃, is related to a series of new compounds possessing blood-pressure-control activity. This biological activity is possibly related to the hydrogen atom of the phenyl –N–H portion of these compounds. Furthermore, the infrared study of this compound had revealed an interesting hydrogen bonding pattern in the crystal. A detailed study of HMSA has been carried out to determine the stereochemistry around the nitrogen atom and to verify the hydrogen bonding. The crystals of HMSA are orthorhombic, space group *P*2₁2₁2₁, with *a* = 5·5913 ± 0·004, *b* = 10·8101 ± 0·0009, *c* = 13·6305 ± 0·0012 Å. The unit cell contains four molecules. The structure was solved using three-dimensional intensity data obtained with an automatic single-crystal diffractometer. Phasing was done by the Hall–Maslen method, and refinement was by least-squares methods with anisotropic temperature factors. The hydrogen atoms were revealed by a three-dimensional ΔF difference synthesis. HMSA molecules through hydrogen bonding form infinite chains parallel to the *a* axis. Each HMSA molecule also has an intramolecular hydrogen bond between the OH group and its nitrogen atom. The amine hydrogen atom sticks out alone on one side of the benzene ring while the whole methylsulfone group is on the opposite side. The thermal motions of the molecule have been analyzed.

Introduction

The incorporation of the alkylsulfonamido group into the benzene ring of phenethanolamines unexpectedly leads to a series of compounds with interesting biological activity (Larsen & Lish, 1964). Many of these new compounds are strikingly similar in action to cer-

tain well-known phenolic phenethanolamines, *e.g.* phenylephrine and epinephrine. As an approach to an understanding of their biological activity a study of the crystal structure and stereochemistry of methanesulfonanilide (MSA), C₆H₅–NH–SO₂CH₃, was made (Klug, 1968). The related compound, 2'-hydroxymethanesulfonanilide (HMSA), HO–C₆H₄–NH–SO₂CH₃, also had

been prepared and investigated by infrared techniques. These studies (Larsen, 1968) led to the intriguing interpretation that the crystal contained hydrogen-bonded dimeric molecules in which each monomer unit further possessed an internal hydrogen bond, $O-H \cdots N$, involving the hydroxyl group hydrogen atom and the amido nitrogen atom. The structure of the dimer was depicted as the following:



It thus seemed desirable to investigate HMSA by X-ray diffraction methods to verify these interesting bonding predictions and to study other aspects of the molecule's stereochemistry.

Crystal data

HMSA is a nicely crystalline, colorless solid, m.p. 112.5–115.0°C (corrected). The material as supplied* yielded suitable crystals for study. The cell constants and their estimated standard deviations were calculated

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from single-crystal diffractometric measurements of 18 moderately high-angle reflections ($2\theta = 50-118^\circ$) with $Cu K\alpha$ (1.54178 Å) radiation by a CDC 1604 program adapted from the University of Washington *Param* refinement program. Reflections of all types were observed except $h00$ with h odd, $0k0$ with k odd, and $00l$ with l odd. The crystal data on HMSA are: $a = 5.5913 \pm 0.0004$, $b = 10.8101 \pm 0.0009$, $c = 13.6305 \pm 0.0012$ Å. $Z = 4$, M.W. 187.22, $D_x = 1.509$ g.cm⁻³. Orthorhombic, space group $P2_12_12_1$; piezoelectric test positive. $F(000) = 392$. For $Cu K\alpha$ radiation $\mu R = 0.79$ for $R = 0.025$ cm.

Determination of the structure

The structure has been determined with $Cu K\alpha$ intensity data obtained on a General Electric-Datex automatic single-crystal diffractometer by the moving-crystal, moving-counter technique ($\theta - 2\theta$ scan). The crystal used for the final intensity data measured approximately $0.27 \times 0.035 \times 0.27$ mm. All reflections in the copper sphere out to $\sin \theta/\lambda = 0.6191$ were measured. No correction was made for absorption, but in the course of the structure refinement it was found desirable to make an empirical extinction correction to 9 reflections that persistently calculated larger than observed. The procedure of Pinnock, Taylor & Lipson (1956) was used, and the overall improvement was dramatic for 8 of the 9 reflections. Other details of the data gathering and processing to observed structure factors, F_o values, have been presented earlier (Klug, 1968). The total number of reflections measured (ex-

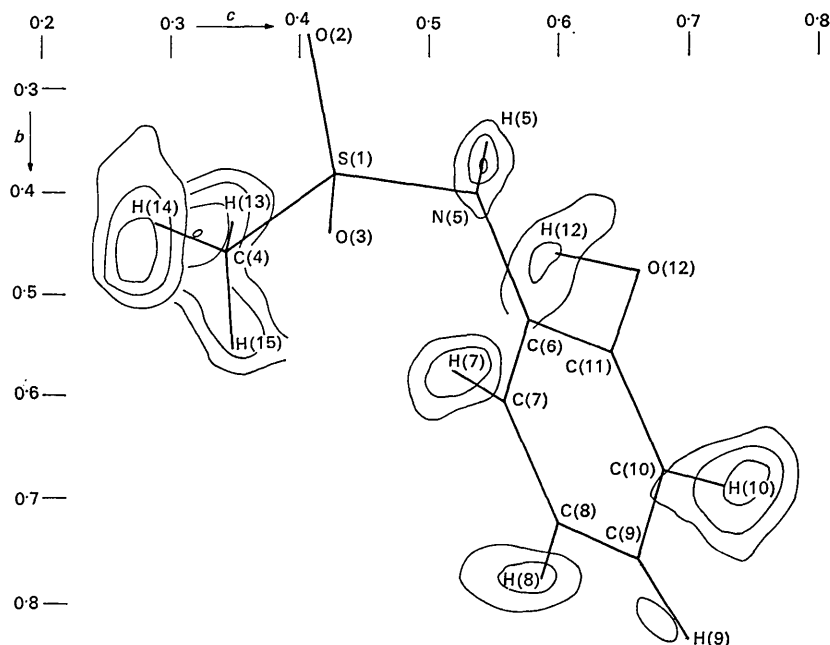


Fig. 1. Composite [100] projection of the hydrogen atoms of a molecule prepared from a three-dimensional $F_o - F_c$ synthesis. The contours are drawn at intervals of $0.1 \text{ e.}\text{\AA}^{-3}$ beginning with $0.2 \text{ e.}\text{\AA}^{-3}$. Values of F_c used had the contributions of the hydrogen atoms omitted. The final positions of the hydrogen atoms and of the rest of the molecule are superposed.

cluding space group absences) was 978 of which 940 were listed as observed.

The observed structure factors were treated by direct phasing programs for centrosymmetric space groups (Hall & Ahmed, 1968; Oh & Maslen, 1968). These programs determine preliminary scale and temperature factors and reduce the structure factors

to normalized structure factors, E values. Next, the programs use the \sum_2 relation and the tangent formula to calculate and refine a set of structure factor phases for all $|E|$ values above a specified minimum. This application provided 197 phases with $E \geq 1.29$. The three-dimensional E map from these phases should produce 12 major peaks in $\frac{1}{4}$ the cell volume. Actually, a series

Table 1. Observed and calculated structure factors

The data are separated into groups having common h and k values. The three columns of each group list values of l , $10F_o$ and $10F_c$ in that order. An asterisk indicates an unobserved reflection.

h = 0, k = 0	15 56 66	5 146 260	8 175 195	14 58 52	7 91 53	7 197 204	2 67 68	9 78 88	h = 5, k = 5
2 597 755	15 22 22	5 223 236	9 64 86	16 20 16	8 141 151	8 159 171	5 55 57	10 86 81	0 56 55
4 880 977	2 14*	7 208 208	11 65 71	10 35 35	9 164 160	4 100 104	11 150 153	0 56 55	2 70 70
7 158 264	h = 0, k = 7	8 6 6	8 150 147	13 77 86	10 25 25	11 17 42	6 49 53	2 70 70	4 75 81
10 189 170	1 112 286	9 160 152	14 68 57	0 264 455	12 124 125	12 189 142	h = 4, k = 7	0 31 34	5 91 96
12 177 166	2 14*	10 275 73	1 2 294 269	h = 2, k = 9	0 125 127	11 105 91	0 64 72	1 15 15	5 91 96
16 37 35	5 164 167	11 42 45	3 129 130	h = 3, k = 9	1 118 116	14 54 37	1 36 36	4 61 55	5 91 96
h = 0, k = 1	6 26 26	12 106 102	0 256 252	5 15* 25	4 195 192	h = 3, k = 12	h = 3, k = 12	4 61 55	5 91 96
1 301 289	7 283 295	13 79 78	5 205 202	8 131 123	5 172 170	0 64 72	0 64 72	4 61 55	5 91 96
2 116 114	8 43 44	14 81 73	6 85 84	9 143 142	6 34 34	1 154 152	2 196 228	9 15 12	0 72 76
3 391 465	9 15 15	15 89 89	7 47 48	10 62 59	7 113 127	3 91 84	0 376 369	7 64 90	0 41 30
4 212 215	10 39 39	16 74 68	8 82 87	11 148 145	8 85 98	4 174 170	5 174 170	8 64 90	2 3 110
5 307 341	11 45 45	17 59 59	9 89 89	12 101 89	9 37 43	5 154 152	3 148 150	10 50 44	0 41 30
6 29 26	12 14 31	18 30 30	10 82 82	13 101 89	10 153 164	6 70 73	4 137 138	h = 4, k = 0	2 3 110
7 159 162	h = 0, k = 2	0 332 336	11 82 87	14 26 26	11 148 145	7 73 75	5 137 138	h = 4, k = 0	4 36 30
8 351 316	1 288 218	1 228 218	12 37 40	15 40 40	12 101 89	8 90 97	6 351 349	h = 4, k = 0	4 36 30
9 14 11	2 290 296	2 290 296	13 27 27	16 40 40	13 101 89	9 96 115	7 84 79	0 227 227	4 36 30
10 213 206	3 307 297	3 339 327	14 27 27	17 40 40	14 100 100	10 97 115	8 193 191	1 113 115	4 36 30
11 56 53	4 410 410	4 418 427	15 27 27	18 40 40	15 81 78	11 170 177	9 54 54	2 85 80	4 36 30
12 12 12	5 507 515	5 539 547	16 27 27	19 40 40	16 81 78	12 147 147	10 54 54	3 85 80	4 36 30
13 103 97	6 216 209	7 295 319	17 27 27	20 40 40	17 81 78	13 147 147	11 54 54	4 85 80	4 36 30
14 66 55	7 57 54	8 292 309	18 27 27	21 40 40	18 81 78	14 147 147	12 54 54	5 85 80	4 36 30
15 92 82	8 82 82	9 298 315	19 27 27	22 40 40	19 81 78	15 147 147	13 54 54	6 85 80	4 36 30
16 84 78	9 19 11	10 56 47	20 27 27	23 40 40	20 81 78	16 147 147	14 54 54	7 85 80	4 36 30
h = 0, k = 2	10 234 248	11 10 56	0 113 119	21 40 40	21 81 78	17 147 147	15 54 54	8 85 80	4 36 30
1 304 397	2 74 76	1 200 202	1 200 202	22 40 40	22 81 78	18 147 147	16 54 54	9 85 80	4 36 30
2 768 684	3 16* 16*	2 268 240	2 268 240	23 40 40	23 81 78	19 147 147	17 54 54	10 85 80	4 36 30
3 787 787	4 82 82	3 480 440	3 480 440	24 40 40	24 81 78	20 147 147	18 54 54	11 85 80	4 36 30
4 112 111	5 19 11	4 840 800	4 840 800	25 40 40	25 81 78	21 147 147	19 54 54	12 85 80	4 36 30
5 237 241	6 85 85	5 1260 1260	5 1260 1260	26 40 40	26 81 78	22 147 147	20 54 54	13 85 80	4 36 30
6 152 157	7 16* 16*	6 1680 1680	6 1680 1680	27 40 40	27 81 78	23 147 147	21 54 54	14 85 80	4 36 30
7 407 399	8 74 76	7 2520 2520	7 2520 2520	28 40 40	28 81 78	24 147 147	22 54 54	15 85 80	4 36 30
8 74 96	9 15 15	8 3360 3360	8 3360 3360	29 40 40	29 81 78	25 147 147	23 54 54	16 85 80	4 36 30
9 254 254	10 77 78	9 4200 4200	9 4200 4200	30 40 40	30 81 78	26 147 147	24 54 54	17 85 80	4 36 30
10 316 308	11 25 25	10 5040 5040	10 5040 5040	31 40 40	31 81 78	27 147 147	25 54 54	18 85 80	4 36 30
11 316 308	12 25 25	11 6720 6720	11 6720 6720	32 40 40	32 81 78	28 147 147	26 54 54	19 85 80	4 36 30
12 316 308	13 25 25	12 8400 8400	12 8400 8400	33 40 40	33 81 78	29 147 147	27 54 54	20 85 80	4 36 30
13 316 308	14 25 25	13 10080 10080	13 10080 10080	34 40 40	34 81 78	30 147 147	28 54 54	21 85 80	4 36 30
14 316 308	15 25 25	14 11760 11760	14 11760 11760	35 40 40	35 81 78	31 147 147	29 54 54	22 85 80	4 36 30
15 316 308	16 25 25	15 13440 13440	15 13440 13440	36 40 40	36 81 78	32 147 147	30 54 54	23 85 80	4 36 30
16 316 308	17 25 25	16 15120 15120	16 15120 15120	37 40 40	37 81 78	33 147 147	31 54 54	24 85 80	4 36 30
17 316 308	18 25 25	17 16800 16800	17 16800 16800	38 40 40	38 81 78	34 147 147	32 54 54	25 85 80	4 36 30
18 316 308	19 25 25	18 18480 18480	18 18480 18480	39 40 40	39 81 78	35 147 147	33 54 54	26 85 80	4 36 30
19 316 308	20 25 25	19 20160 20160	19 20160 20160	40 40 40	40 81 78	36 147 147	34 54 54	27 85 80	4 36 30
20 316 308	21 25 25	20 21840 21840	20 21840 21840	41 40 40	41 81 78	37 147 147	35 54 54	28 85 80	4 36 30
21 316 308	22 25 25	21 23520 23520	21 23520 23520	42 40 40	42 81 78	38 147 147	36 54 54	29 85 80	4 36 30
22 316 308	23 25 25	22 25200 25200	22 25200 25200	43 40 40	43 81 78	39 147 147	37 54 54	30 85 80	4 36 30
23 316 308	24 25 25	23 26880 26880	23 26880 26880	44 40 40	44 81 78	40 147 147	38 54 54	31 85 80	4 36 30
24 316 308	25 25 25	24 28560 28560	24 28560 28560	45 40 40	45 81 78	41 147 147	39 54 54	32 85 80	4 36 30
25 316 308	26 25 25	25 30240 30240	25 30240 30240	46 40 40	46 81 78	42 147 147	40 54 54	33 85 80	4 36 30
26 316 308	27 25 25	26 31920 31920	26 31920 31920	47 40 40	47 81 78	43 147 147	41 54 54	34 85 80	4 36 30
27 316 308	28 25 25	27 33600 33600	27 33600 33600	48 40 40	48 81 78	44 147 147	42 54 54	35 85 80	4 36 30
28 316 308	29 25 25	28 35280 35280	28 35280 35280	49 40 40	49 81 78	45 147 147	43 54 54	36 85 80	4 36 30
29 316 308	30 25 25	29 36960 36960	29 36960 36960	50 40 40	50 81 78	46 147 147	44 54 54	37 85 80	4 36 30
30 316 308	31 25 25	30 38640 38640	30 38640 38640	51 40 40	51 81 78	47 147 147	45 54 54	38 85 80	4 36 30
31 316 308	32 25 25	31 40320 40320	31 40320 40320	52 40 40	52 81 78	48 147 147	46 54 54	39 85 80	4 36 30
32 316 308	33 25 25	32 42000 42000	32 42000 42000	53 40 40	53 81 78	49 147 147	47 54 54	40 85 80	4 36 30
33 316 308	34 25 25	33 43680 43680	33 43680 43680	54 40 40	54 81 78	50 147 147	48 54 54	41 85 80	4 36 30
34 316 308	35 25 25	34 45360 45360	34 45360 45360	55 40 40	55 81 78	51 147 147	49 54 54	42 85 80	4 36 30
35 316 308	36 25 25	35 47040 47040	35 47040 47040	56 40 40	56 81 78	52 147 147	50 54 54	43 85 80	4 36 30
36 316 308	37 25 25	36 48720 48720	36 48720 48720	57 40 40	57 81 78	53 147 147	51 54 54	44 85 80	4 36 30
37 316 308	38 25 25	37 50400 50400	37 50400 50400	58 40 40	58 81 78	54 147 147	52 54 54	45 85 80	4 36 30
38 316 308	39 25 25	38 52080 52080	38 52080 52080	59 40 40	59 81 78	55 147 147	53 54 54	46 85 80	4 36 30
39 316 308	40 25 25	39 53760 53760	39 53760 53760	60 40 40	60 81 78	56 147 147	54 54 54	47 85 80	4 36 30
40 316 308	41 25 25	40 55440 55440	40 55440 55440	61 40 40	61 81 78	57 147 147	55 54 54	48 85 80	4 36 30
41 316 308	42 25 25	41 57120 57120	41 57120 57120	62 40 40	62 81 78	58 147 147	56 54 54	49 85 80	4 36 30
42 316 308	43 25 25	42 58800 58800	42 58800 58800	63 40 40	63 81 78	59 147 147	57 54 54	50 85 80	4 36 30
43 316 308	44 25 25	43 60480 60480	43 60480 60480	64 40 40	64 81 78	60 147 147	58 54 54	51 85 80	4 36 30
44 316 308	45 25 25	44 62160 62160	44 62160 62160	65 40 40	65 81 78	61 147 147	59 54 54	52 85 80	4 36 30
45 316 308	46 25 25	45 63840 63840	45 63840 63840	66 40 40	66 81 78	62 147 147	60 54 54	53 85 80	4 36 30
46 316 308	47 25 25	46 65520 65520	46 65520 65520	67 40 40	67 81 78	63 147 147	61 54 54	54 85 80	4 36 30
47 316 308	48 25 25	47 67200 67200	47 67200 67200	68 40 40	68 81 78	64 147 147	62 54 54	55 85 80	4 36 30
48 316 308	49 25 25	48 68880 68880	48 68880 68880	69 40 40	69 81 78	65 147 147	63 54 54	56 85 80	4 36 30
49 316 308	50 25 25	49 70560 70560	49 70560 70560	70 40 40	70 81 78	66 147 147	64 54 54	57 85 80	4 36 30
50 316 308	51 25 25	50 72240 72240	50 72240 72240	71 40 40	71 81 78	67 147 147	65 54 54	58 85 80	4 36 30
51 316 308	52 25 25	51 73920 73920	51 73920 73920	72 40 40	72 81 78				

of peaks was generated with a not too distinct break in the heights after the 13th highest. In a plot of these 13 peaks on a [100] projection the molecule was not immediately recognizable. By comparison with a three-dimensional Patterson synthesis it was verified that the strongest E map peak was undoubtedly that due to the sulfur atom. At this point Karle's (1968) procedure was applied for phase determination when a portion of the structure is considered to be known. This application led to a set of phases identical to the original set. It was then concluded that the 12 strongest peaks of the E -map must be essentially correct and that, if so, they should refine to a recognizable and correct structure.

Table 2. Fractional atomic coordinates ($\times 10^4$) and their estimated standard deviations, σ

	x	y	z
S(1)	0140 (3)	3821 (2)	4259 (1)
O(2)	-0080 (11)	2509 (4)	4070 (4)
O(3)	2464 (9)	4384 (4)	4231 (4)
O(12)	2758 (10)	4806 (5)	6610 (4)
N(5)	-0884 (11)	4033 (5)	5356 (4)
C(4)	-1675 (15)	4574 (6)	3416 (5)
C(6)	-0902 (12)	5272 (6)	5766 (5)
C(7)	-2790 (13)	6087 (7)	5565 (5)
C(8)	-2722 (17)	7272 (7)	5969 (6)
C(9)	-0826 (16)	7597 (7)	6584 (6)
C(10)	0978 (15)	6786 (7)	6783 (6)
C(11)	0915 (14)	5611 (6)	6378 (5)
H(5)	-2036	3548	5421
H(7)	-3649	5792	5146
H(8)	-3979	7793	5855
H(9)	-0684	8386	6974
H(10)	2134	6935	7247
H(12)	2526	4608	5978
H(13)	-2977	4277	3469
H(14)	-1266	4303	2866
H(15)	-1828	5510	3457

Structure factors calculated with isotropic B values, the original atomic coordinates and phases yielded an R index of 0.414. After two cycles of least-squares refinement R dropped to 0.305. At this point a [100] projection of the peaks of a three-dimensional Fourier synthesis disclosed all of the nonhydrogen atoms of the molecule except one carbon atom C(9) of the benzene ring. With the position of C(9) estimated, two more isotropic cycles of least-squares refinement reduced R to 0.101. With the introduction of anisotropic B_{ij} 's, two additional cycles of least-squares refinement reduced R to 0.088, a reduction rather less than expected. Examination of the F_o and F_c values revealed a serious discrepancy for reflection 521 whose F_o proved to be in error. The need for an extinction correction was also revealed at the same time, and 9 reflections, 002, 004, 014, 021, 023, 103, 104, 111 and 112, were corrected as previously mentioned. The heavy atoms (nonhydrogen atoms) then refined in two further least-squares cycles to an R of 0.071, with a final average shift/error for the 109 parameters refined of 0.099. In the last cycle the maximum change in any x, y , or z was 0.0017, and the maximum change in a B_{ij} was -0.22.

A three-dimensional difference Fourier synthesis with F_c values calculated from the refined heavy-atom positions clearly indicated (Fig. 1) the 9 hydrogen atoms in their expected positions. The H(9) position comes out poorest and that of H(15) is not too well defined. The ΔF synthesis gives evidence of strong anisotropic motion of the hydrogen atoms, particularly of the methyl hydrogen atoms, in the x direction. A few spurious peaks of equivalent height are observed, but in positions not chemically probable for hydrogen peaks. Attempts to refine the hydrogen positions by

Table 3. Thermal parameters* of the atoms and their estimated standard deviations, σ

B_{ij} values are in \AA^2 . Hydrogen atoms were treated as isotropic.

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
S(1)	2.08 (6)	1.81 (6)	2.43 (6)	0.01 (7)	-0.08 (8)	-0.20 (6)
O(2)	4.86 (28)	1.18 (17)	4.71 (26)	0.10 (25)	-0.07 (32)	-0.80 (18)
O(3)	1.83 (20)	3.45 (24)	4.06 (25)	-0.60 (20)	0.40 (25)	-0.44 (24)
O(12)	2.80 (24)	2.86 (24)	3.53 (25)	0.03 (22)	-1.21 (22)	-0.12 (21)
N(5)	3.66 (33)	1.73 (25)	2.78 (24)	-0.62 (23)	-0.25 (23)	0.13 (21)
C(4)	4.22 (42)	2.75 (32)	2.42 (31)	0.22 (31)	-0.97 (31)	0.04 (28)
C(6)	3.14 (31)	1.75 (25)	2.31 (26)	-0.21 (25)	0.45 (30)	0.08 (27)
C(7)	2.67 (31)	2.99 (32)	3.26 (34)	0.28 (32)	0.20 (27)	-0.33 (30)
C(8)	4.46 (47)	2.93 (35)	3.80 (41)	0.89 (35)	0.95 (37)	-0.08 (31)
C(9)	4.76 (48)	2.06 (29)	3.55 (36)	-0.23 (33)	1.08 (34)	-0.38 (30)
C(10)	3.35 (40)	2.48 (31)	3.36 (36)	-0.45 (32)	-0.19 (32)	-0.41 (31)
C(11)	3.01 (36)	2.02 (29)	2.52 (30)	-0.25 (29)	0.12 (27)	-0.15 (26)
H(5)	8.00					
H(7)	7.00					
H(8)	7.00					
H(9)	7.00					
H(10)	7.00					
H(12)	8.00					
H(13)	8.00					
H(14)	8.00					
H(15)	8.00					

* For the heavy atoms the expression is: $\exp[-\frac{1}{4}(h^2a^*B_{11} + \dots + 2klb^*c^*B_{23})]$.

least-squares techniques were disappointing. Some of the hydrogen atoms invariably moved from what had been chemically acceptable positions to positions with too short or too long bond distances. Accordingly, the hydrogen positions have been manually adjusted by reference to the peaks of the difference synthesis, the accepted stereochemical concepts, and the observed change in the final R value. The reported hydrogen atom positions are chemically reasonable and lead to a final R of 0.062 for the structure. This procedure unfortunately does not provide a standard deviation for the hydrogen parameters and bond lengths. There can be little doubt, however, but that the hydrogen atoms are close to the reported positions. This type of hydrogen refinement problem may arise when the temperature motions are moderately strong or stronger. A solution would be to collect the intensity data with Mo $K\alpha$ radiation (to reduce absorption effects due to sulfur) and at low temperature (to reduce the thermal motion). The interest in this structure did not warrant the remeasurement of the data at low temperature.

In the refinement above the residual minimized was $\sum w(|F_o| - k|F_c|)^2$. The overall scale factor k was refined

at each cycle. The weight w of each observation F_o was taken as $w = 1/\sigma^2(F_o)$ where σ is the standard deviation σ_F previously described (Klug, 1968). The calculations in this study were made on the IBM 7090 and CDC 1604 computers with the integrated systems of programs known as *X-ray 63* and *X-ray 67*. All least-squares refinements were done with the full-matrix program. The scattering factors used were those applied in the study of MSA (Klug, 1968). The observed and calculated structure factors are listed in Table 1. The fractional atomic coordinates, the atomic thermal parameters, and the estimated standard deviations of each (for the non-hydrogen atoms only) are presented in Tables 2 and 3.

Discussion of the molecular structure

Bond distances and angles in the HMSA molecule are presented in Fig. 2. The average standard deviation for bonds to the sulfur atom is ± 0.006 Å, and for C-C, N-C, and C-O bonds it is ± 0.010 Å. The angles at the sulfur atom have $\sigma = \pm 0.3^\circ$; the inner angles of the benzene ring have an average $\sigma = \pm 0.7^\circ$. No standard

Table 4. Comparison of bonds to the tetrahedral sulfur atom

Bond	HMSA (This work)	MSA (Klug, 1968)	β -Sulfanilamide (O'Connell & Maslen, 1967)	γ -Sulfanilamide (Alléaume & Decap, 1965a,b)
S-O(2)	1.447	1.443	1.454 \pm 0.002 Å	1.452 \pm 0.014 Å
S-O(3)	1.435	1.425	1.448 \pm 0.001	1.438 \pm 0.019
S-N	1.617	1.633	1.620 \pm 0.002	1.666 \pm 0.015
S-C	1.736	1.746	1.750 \pm 0.002	1.739 \pm 0.014

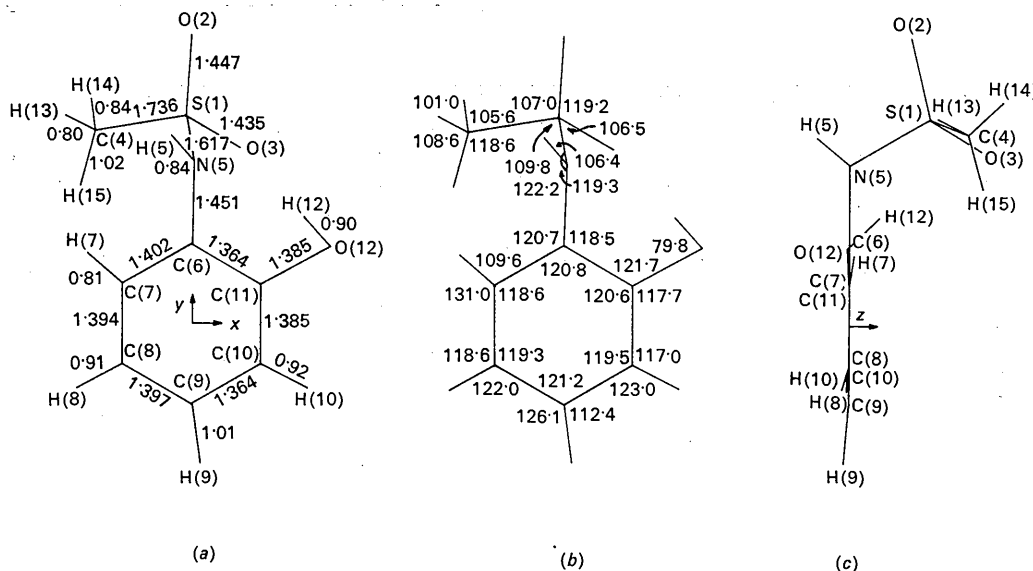


Fig. 2. Orthographic projection of the HMSA molecule onto the plane of the benzene ring. (a) Observed bond distances (Å), and molecular axial system chosen. Positive Z is perpendicular to the plane of the ring and directed upward. (b) Observed bond angles ($^\circ$). (c) Orthographic projection of the molecule edge-on to the plane of the benzene ring in the direction of positive X .

deviations can be given for bond distances and angles involving hydrogen atoms.

The HMSA molecule is presented in Fig. 2(a) and (b) as the orthographic projection on the least-squares plane of its benzene ring. The hexagonal benzene ring is only very slightly distorted. Ring C–C distances vary from 1.364 to 1.402 Å with the average 1.388 Å. Some of these differences in C–C distances could be significant. Recent studies of molecules containing a benzene ring with two or more different substituent groups reveal that such a spread is probably to be expected. The substituent groups apparently stabilize slightly different C–C distances around the ring. See, for instance, potassium *p*-nitrophenyldicyanomethide (Sass & Bugg, 1967), bis(*N*-isopropyl-3-methylsalicylaldimino)palladium (Jain & Lingafelter, 1967), and tetryl, *N*-methyl-*N*,2,4,6-tetranitroaniline (Cady, 1967). With such deviations of the C–C bonds some deviations of the inner angles of the benzene ring from 120° are to be expected. Such deviations are evidently small, and the total spread in these angles is 2.58°, only slightly greater than $3\sigma = 2.1^\circ$.

The seven C–H distances in the molecule vary from 0.80 to 1.02 Å with the average 0.90 Å, a value a bit on the short side (see Klug, 1968; Reeke & Marsh, 1966; and High & Kraut, 1966). The single N–H distance is 0.84 Å, again a little shorter than the average value 0.895 Å found in 5-ethyl-6-methyluracil (Reeke & Marsh, 1966). The O–H distance is 0.90 Å, the same as the average O–H distance observed in tetrahydroxy-*p*-benzoquinone (Klug, 1965). The C–N distance in the anilide group is 1.451 ± 0.010 Å, to be compared with 1.438 ± 0.003 Å found in MSA (Klug, 1968) and $1.43 \pm$

0.01 Å reported for acetanilide (Sutton, 1965). This C–N bond is essentially a pure single bond. Its LCAO–MO double bond order p is only 0.08 as calculated by the method of Coulson (1939) as modified by Liquori & Vacicago (1956). Bonding around the sulfur atom is distorted somewhat from regular tetrahedral [Fig. 2(b)]. The various observed bond distances are compared with those reported in MSA and β - and γ -sulfanilamide (Table 4).

The equation for the least-squares best plane passing through the six carbon atoms of the benzene ring is:

$$-0.50895 X - 0.33775 Y + 0.79175 Z = 4.5661.$$

Here X , Y and Z are the atomic coordinates in Å units referred to the crystallographic axes, and 4.5661 is the distance from the plane to the origin in Å units. The standard deviation of the atoms defining the plane from the plane is $\sigma = 0.0084$ Å. The perpendicular distances of the various atoms from this plane are as follows:

C(6)	0.012 Å	H(5)	−0.568 Å
C(7)	−0.011	H(7)	0.089
C(8)	0.005	H(8)	−0.040
C(9)	−0.001	H(9)	−0.093
C(10)	0.002	H(10)	−0.116
C(11)	−0.008	H(12)	0.516
N(5)	0.007		
O(12)	−0.028		

The excellent planarity of the benzene ring is very evident. Also the N(5) and O(12) atoms are essentially in the plane of the ring. Since the hydrogen atom positions are not accurately determined, the deviations of the ring hydrogen atoms from the ring plane have very

Table 5. *Intermolecular distances in the structure*

Atoms defining distance	Observed distance	Type of contact	Expected value or limit
I O(2) ··· II N(5)	2.983 Å	Hydrogen bond	> ~ 3.00 Å
I O(2) ··· II O(12)	2.930	O ··· O	> ~ 2.8*
II O(12) ··· III C(9)	3.596	O ··· CH	> ~ 3.1*
I C(4) ··· III C(10)	4.154	CH ₃ ··· CH	> ~ 3.7*
I C(4) ··· III C(11)	4.258	CH ₃ ··· C	> ~ 3.7*
I C(4) ··· III O(12)	3.362	CH ₃ ··· O	> ~ 3.4*
I C(4) ··· II C(9)	3.839	CH ₃ ··· CH	> ~ 3.7*
I O(3) ··· II C(8)	3.627	O ··· CH	> ~ 3.1*
I C(7) ··· II C(8)	3.943	CH ··· CH	> ~ 3.4*
I C(7) ··· II C(7)	4.417	CH ··· CH	> ~ 3.4*
I C(8) ··· II C(8)	3.877	CH ··· CH	> ~ 3.4*
I C(8) ··· II C(7)	3.888	CH ··· CH	> ~ 3.4*

* Pauling (1960).

Table 6. *Principal values of the T and ω tensors for the HMSA molecule relative to the orthogonal molecular axes X, Y, Z*

R.m.s. amplitude of translation	Direction angles with respect to X, Y, Z			R.m.s. amplitude of oscillation	Direction angles with respect to X, Y, Z		
0.126 (10) Å	105.5°	47.5°	46.5°	2.74 (30)°	152.4°	95.2°	63.0°
0.171 (7)	68.8	126.3	43.9	5.38 (8)	106.8	29.1	113.0
0.143 (17)	153.3	116.2	85.0	3.06 (37)	68.8	61.4	36.9

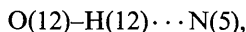
Error of fit is 1.85.

little significance. These features are depicted in an orthographic projection [Fig. 2(c)] of the HMSA molecule as viewed edge-on to the plane of the benzene ring. The distribution of all atoms of the molecule relative to the least-squares plane is strikingly shown, and is very similar to that found in MSA (Klug, 1968). In both HMSA and MSA the amine hydrogen atom H(5) in HMSA, clearly sticks out alone on the opposite side of the benzene plane from the methyl sulfone group.

Hydrogen bonding

Hydrogen bonding is very important in HMSA, as postulated from the infrared studies (Larsen, 1968). Instead of the suggested centrosymmetric dimers, hydrogen bonding between the N-H of one molecule and the O(2) of a neighboring molecule leads to infinite chains along the *a* axis. In Fig. 3 the distance, $\text{II N}(5) \cdots \text{I O}(2)$, in these N-H \cdots O bonds is 2.98 Å. It compares well with the corresponding hydrogen bond distance, 3.03 Å, in the centrosymmetric dimer of MSA (Klug, 1968) and with a similar bond, 3.02 Å, in sulfamide (Trueblood & Mayer, 1956).

The intramolecular hydrogen bond



also predicted from the infrared studies, is less

satisfactorily established (Fig. 1). The distance $\text{O}(12) \cdots \text{N}(5)$ is 2.79 Å, a typical O-H \cdots N hydrogen bond distance. For example, Fuller (1959) reports 2.81 Å for such bonds in both $\text{NaCN} \cdot 2\text{H}_2\text{O}$ and formamidoxime. This represents a rather strong intramolecular O-H \cdots N bond, and, the infrared investigator suggests, is favored by the increased electron density of the N(5) atom as a result of the formation of the N-H \cdots O bonds in the chain. Indeed, the O-H \cdots N and N-H \cdots O bonds mutually reinforce each other. This may account for the angle $\text{C}(11) - \text{O}(12) - \text{H}(12)$ being strongly distorted from an expected value of $\sim 105^\circ$ to only $\sim 80^\circ$.*

The environment of the amine hydrogen atom H(5), is believed to be of prime importance in the biological activity of the compound. According to the infrared results (Larsen, 1968), in a highly polar aqueous medium at physiological pH the HMSA would no longer be present as a chain, but as the monomer with a free NH group and with no intramolecular OH \cdots N bond.

* One reviewer proposed a possible alternative hydrogen bond, $\text{IO}(12) - \text{H}(12) \cdots \text{IO}(2)$. The distance involved, 2.93 Å, is, however, a bit on the long side for an O-H \cdots O bond. There is also no evidence for such a bond in the difference Fourier synthesis. The somewhat inconclusive bond to the nitrogen atom is the only possible hydrogen bond involving the OH group for which the data provide any support.

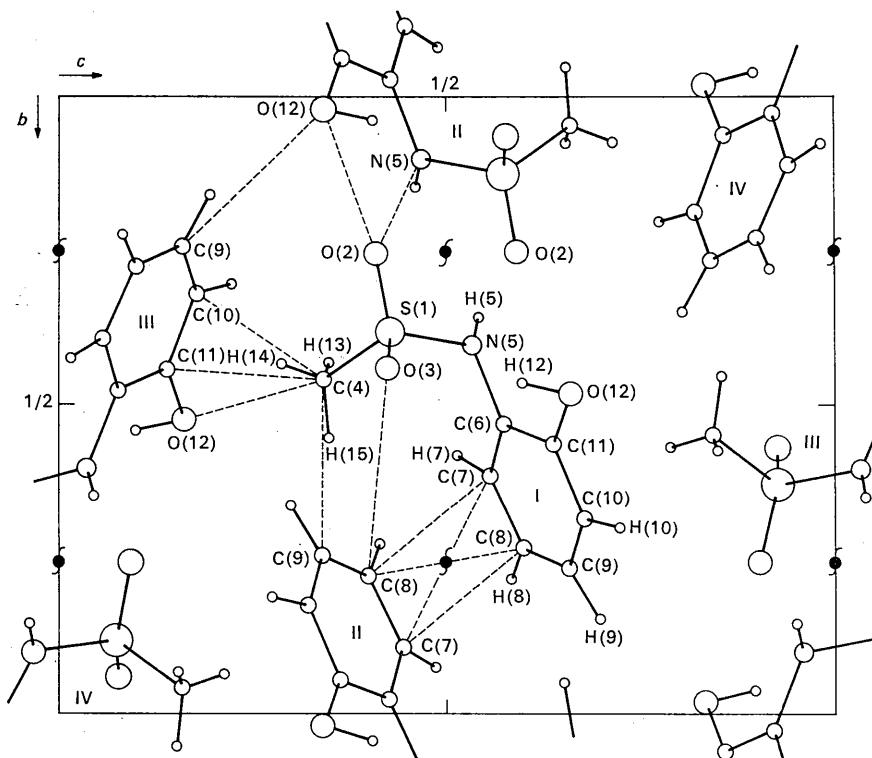
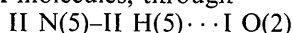


Fig. 3. Projection of the structure onto the (100) plane. Positive *a* is vertical and upward. The screw axes parallel to [100] have been indicated. Atoms of the asymmetric unit (molecule I) have been identified by chemical symbol and number. Selected atoms in other molecules are given their corresponding symbol and number as an aid in identifying the intermolecular distances (dashed lines in the Figure) listed in Table 5.

Thus, the exposed position of H(5), Fig. 2(c), on the opposite side of the benzene ring plane from the methyl sulfone group should make it readily available for reaction with a biological receptor molecule.

Molecular packing

The molecular packing in the crystal cell is depicted in Fig. 3. HMSA molecules, through



hydrogen bonds, form infinite chains along the screw axis at $y=0.25$, $z=0.50$ and the equivalent screw axis at $y=0.75$, $z=0$. All other contacts between molecules are of the van der Waals type, and are always in the expected range. Some of these contacts are marked on Fig. 3 and listed in Table 5.

Analyses of thermal motion

The thermal motions of the heavy atoms in the HMSA molecule have been analyzed in terms of possible rigid-body motions by the method of Cruickshank (1956a). The calculations were done with a program *DIAGUS* for the IBM 7090 computer written by Stewart (1966). The application of *DIAGUS* has been briefly described in connection with MSA (Klug, 1968).

Molecular axes of reference [Fig. 2(a) and (c)] for HMSA were defined in the following manner. Positive Z was taken as the direction of the unit normal to the least-squares plane of the benzene ring. The direction C(9) to C(6) was used to define a vector Y' . The description and definition of the axial system is then completed by the vector relations $X=Y' \times Z$ and $Y=Z \times X$. The HMSA molecule does indeed vibrate as a unit. Table 6 presents the root-mean-square amplitudes of the translational motion and angular libration corresponding to the three principal axes of the T and ω ellipsoids respectively, and the orientation of these axes relative to the molecular axes, X, Y, Z . The molecule's translational motions are only slightly anisotropic, and its librations are somewhat more anisotropic. The maximum librational motion of the molecule is approximately a 5° oscillation about the ω_2 axis of the ω tensor. This axis lies close to the YZ plane and makes an angle of $\sim 29^\circ$ with positive Y . This motion, essentially a torsional wobble of the molecule about a direction close to the Y axis, appears from Fig. 3 to be in complete harmony with the hydrogen bonding scheme.

The observed mean-square amplitudes of vibration, U_{ij} values, of the atoms when compared with the values

calculated from the rigid-body model showed completely satisfactory agreement. The r.m.s. $\Delta U=0.0061 \text{ \AA}^2$, and the corresponding $\sigma(U_{ij})=0.0067$. The Cruickshank (1956b) corrections to bond lengths due to rotational oscillations of the molecule were not calculated. These corrections in a molecule such as HMSA would be expected to increase the bond lengths of Fig. 2(a) by approximately $0.005\text{--}0.008 \text{ \AA}$.

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