

## The Crystal and Molecular Structure of 2-(2-Pyridylmethylthio)benzoic Acid

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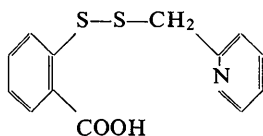
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2-(2-Pyridylmethylthio)benzoic acid, an active antiradiation drug, crystallizes in space group  $P2_12_12_1$  with  $a = 15.090$ ,  $b = 11.359$  and  $c = 7.371$  Å (all  $\pm 0.003$  Å) and  $Z = 4$ . The structure was readily solved by use of a known partial structure (the two S atoms were located in a Patterson map) in conjunction with the tangent formula. The molecular geometry can be compared to a clamp with the two rings nearly parallel to each other and the  $-\text{CH}_2\text{SS}-$  linkage acting as a hinge. The  $-\text{CSSC}-$  group is in the peroxide configuration. The molecule is not in a zwitterion form in the crystal. Diffractometer data were refined to an  $R$  index of 0.044.

### Introduction

2-(2-Pyridylmethylthio)benzoic acid,



is an active antiradiation drug. It gives good protection against the lethal effects of ionizing radiation (Field & Kim, 1966). This investigation was undertaken in order to determine whether the structure of the molecule could be correlated with its antiradiation activity. Of particular interest was the possibility of the existence of a zwitterion. In addition, the configuration about the  $-\text{S}-\text{S}-$  group has been of continuing interest in this laboratory.

### Experimental

Crystals suitable for X-ray study were kindly provided by Dr L. Field of Vanderbilt University. A crystal mounted parallel to the  $c$  axis was examined on the Picker automatic diffractometer. The space group and physical constants for this material are listed in Table 1. Intensities were measured by the  $\theta-2\theta$  technique with a  $1^\circ$  scan over  $\theta$ . The background was recorded on each side of each reflection and a reflection was considered to be unobserved if the total count was less than 1.2 times the background count. Reflections were measured to  $2\theta \sim 133^\circ$  ( $\sin \theta/\lambda = 0.595$ ). Both  $hkl$  and  $\bar{h}k\bar{l}$  were recorded and their intensities averaged. A total of 1286 independent reflections were collected, of which 1236 had intensities assigned greater than zero. The readings were corrected for Lorentz and polarization factors and structure factor magnitudes  $|F|$  as well as normalized structure factor magnitudes  $|E|$  were derived.

Table 1. Physical constants for 2-(2-pyridylmethylthio)benzoic acid

Mol. formula	$\text{C}_{13}\text{H}_{11}\text{NO}_2\text{S}_2$
Mol. weight	277.37
M.p.	176–178° dec.
Habit	Slender prisms
Crystal size	$\sim 0.1 \times 0.1 \times 0.5$ mm
Space group	$P2_12_12_1$
$a$	$15.090 \pm 0.003$
$b$	$11.359 \pm 0.003$
$c$	$7.371 \pm 0.003$
$Z$	4
Vol.	$1263.5 \text{ \AA}^3$
$\rho$ calc.	$1.458 \text{ g.cm}^{-3}$
$\lambda$ (Cu radiation with Ni filter)	$1.5418 \text{ \AA}$
No. independent reflections	1286

The positions of the two S atoms were readily located from an  $|E|^2 - 1$  Patterson function. They were used as a known partial structure for the application of the tangent formula (Karle & Hauptman, 1956),

$$\tan \varphi_h = \frac{\sum_k (E_k E_{h-k}) \sin (\varphi_k + \varphi_{h-k})}{\sum_k (E_k E_{h-k}) \cos (\varphi_k + \varphi_{h-k})}, \quad (1)$$

in a recycling procedure (Karle, 1968). Structure factors based on the two S atoms were computed and phases were accepted for input into equation (1) if both  $|E|_{\text{obs}} > 1.5$  and  $|F|_{\text{calc}} > 0.25|F|_{\text{obs}}$  for a particular reflection. From these initial phases, additional phases for reflections with  $|E| > 1.1$  were determined with the use of equation (1) and used in computing an  $E$  map. In this  $E$  map, all the remaining atoms in the molecule (except hydrogen atoms) were clearly resolved.

Coordinates of the atoms as obtained from the  $E$  map were refined in a full-matrix least-squares procedure, first with isotropic thermal parameters to  $R = 13.2\%$  and then with anisotropic thermal parameters to  $R = 6.7\%$ . A difference map computed at this point revealed the approximate positions of the eleven H atoms, Fig. 1. Additional least-squares refinement in

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Table 2. *Observed and calculated structure factors*  
The column headers are the index *h*,  $|F_o|$ ,  $|F_c|$  and  $\phi$  (radians).

A large table with 22 columns representing different reflections. Each column contains numerical data for observed structure factors ( $|F_o|$ ), calculated structure factors ( $|F_c|$ ), and phases ( $\phi$  in radians). The columns are labeled with their respective indices (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22).



which the coordinates of the hydrogen atoms were varied as well as the coordinates and thermal parameters of the heavier atoms reduced the  $R$  index to 4.9% for a weighting of unity and 4.4% for a weighting function based on counting statistics. The function minimized was  $\sum w(|F_o| - |F_c|)^2$ . The weighting function  $w=0$  for  $F_o=0$ ,  $w=0.9$  for  $0 < |F_o| \leq 15.0$ , and  $w=14.0/|F_o|$  for  $|F_o| > 15.0$  approximates quite well to the weighting curve obtained from combining counting statistics and an assumed 1% random error in each measurement. The bond distances differed by an average of 0.004 Å and the bond angles by an average of 0.3° for the two weighting schemes. The differences are well within the quoted standard deviations. The values for the atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1962).

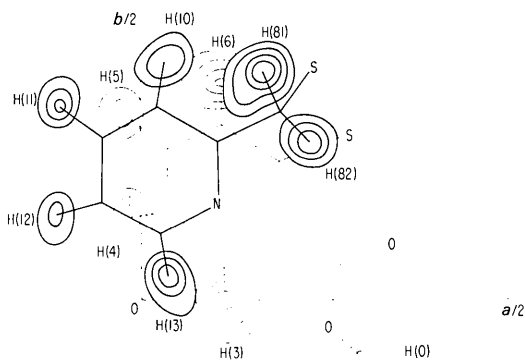


Fig. 1. Sections from a difference map used to locate H atoms. The contours are spaced at  $0.2 \text{ e.}\text{\AA}^{-3}$  and start with the  $0.2 \text{ e.}\text{\AA}^{-3}$  contour.

Observed and calculated structure factors are listed in Table 2. An electron density map based on the least-squares results is shown in Fig. 2 and the final coordinates and thermal parameters are listed in Tables 3 and 4.

Table 4. *Coordinates of hydrogen atoms*

	$x$	$y$	$z$
H(0)	0.3097	-0.0969	0.4066
H(3)	0.1086	0.0055	0.2659
H(4)	-0.0226	0.1151	0.2565
H(5)	-0.0284	0.3323	0.3611
H(6)	0.1104	0.4074	0.5777
H(81)	0.1704	0.4095	1.1117
H(82)	0.2411	0.2946	1.0494
H(10)	0.0353	0.4490	1.0170
H(11)	-0.1187	0.3495	0.8898
H(12)	-0.1109	0.1298	0.7984
H(13)	0.0378	0.0279	0.7747

Standard deviation			
	0.0042	0.0056	0.0095

### Discussion

The geometry of the molecule can be best described by analogy to a clamp. The molecule is folded in two, with the  $-\text{CH}_2\text{SS}-$  group acting as a hinge, and the two rings are nearly parallel to each other. The dihedral angle between the planes of the two rings is  $12.6^\circ$ . The stereodiagram in Fig. 3 shows the configuration. It also shows the thermal ellipsoids. The two rings have very slightly elongated ellipsoids (along the  $c$  axis) perpendicular to their planes. The anisotropy in the  $c$  direction for the two S atoms and the two O atoms is much more pronounced.

Table 3. *Fractional coordinates and thermal parameters for 2-(2-pyridylmethylthio)benzoic acid*

The thermal parameters are of the form

$$T = \exp [ - (\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl) ], \times 10^4.$$

	$x$	$y$	$z$	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
S(1)	0.2808	0.3026	0.6366	30	53	249	-2	9	-12
S(2)	0.2339	0.4285	0.8102	45	39	257	-10	12	-11
O(1)	0.2521	-0.0475	0.4201	36	43	411	2	-20	-17
O(2)	0.3407	0.1064	0.4582	26	54	354	-1	12	-19
N	0.1019	0.1725	0.9055	34	46	168	4	5	4
C(1)	0.2671	0.0654	0.4431	34	53	202	5	16	2
C(2)	0.1850	0.1385	0.4375	31	49	164	3	12	7
C(3)	0.1094	0.0953	0.3539	34	79	178	3	5	15
C(4)	0.0330	0.1618	0.3454	37	102	166	9	0	10
C(5)	0.0332	0.2763	0.4174	41	104	169	21	1	22
C(6)	0.1088	0.3199	0.5028	40	69	202	13	18	18
C(7)	0.1851	0.2517	0.5138	33	58	173	3	10	18
C(8)	0.1885	0.3431	0.9998	43	69	205	-10	-7	6
C(9)	0.1011	0.2884	0.9523	37	46	157	2	5	9
C(10)	0.0226	0.3522	0.9517	48	60	216	12	13	11
C(11)	-0.0556	0.2987	0.9066	41	94	256	18	7	33
C(12)	-0.0550	0.1797	0.8577	38	101	250	-7	-6	4
C(13)	0.0252	0.1209	0.8613	44	65	227	-4	9	-13
Standard deviations									
S	0.0001	0.0001	0.0003	1	1	4	1	1	2
O	0.0003	0.0003	0.0008	2	3	15	2	5	6
N	0.0003	0.0004	0.0007	2	4	10	2	4	6
C	0.0004	0.0006	0.0010	3	5	15	3	6	8

Bond distances and angles are illustrated in Fig. 4. The standard deviations based on the least-squares fit range from 0.003 Å for the S-S bond to 0.010 Å for C-C bonds and  $\sim 0.6^\circ$  for CCC angles. Actual standard deviations are probably about twice as large. The bond lengths for the phenyl group and the pyridine ring have the values usually obtained for such rings. In the carboxyl group, the C=O and C-O distances have values consistent with a -COOH group rather than an ion; and, in fact, a hydrogen atom was found to be bonded to O(1), Fig. 1. The -SS- bridge assumes the peroxide configuration with a dihedral angle of  $99.1^\circ$ , similar to that found in other molecules containing this type of linkage. Table 5 compares the S-S and C-S distances, the C-S-S angles and the -CSSC- dihedral angles in molecules containing the -SS- bridge.

Least-squares planes for the phenyl and pyridyl rings are represented, respectively, by the equations (Schomaker, Waser, Marsh & Bergman, 1959)

$$-4.6554x - 4.2420y + 6.4275z = 1.3671 \quad (2)$$

$$\text{and} \quad -2.2501x - 2.8113y + 7.0336z = 5.6571, \quad (3)$$

where the value on the right-hand side is the origin-to-plane distance in Å units. The deviations of individual atoms in the rings from their least-squares planes

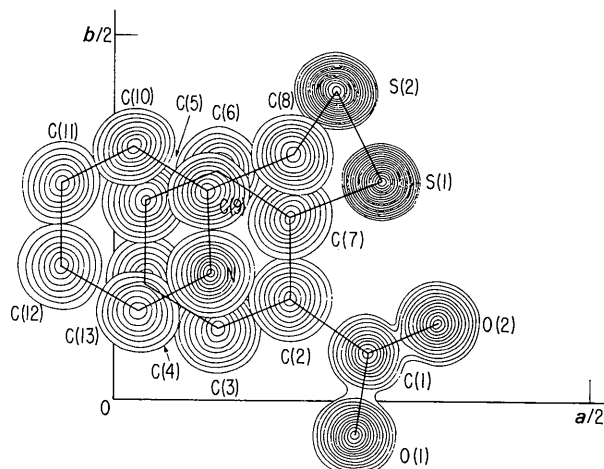


Fig. 2. The composite electron density map for 2-(2-pyridylmethylthio)benzoic acid. Contours are spaced by  $1 \text{ e.}\text{\AA}^{-3}$  except for the S atoms where they are spaced by  $2 \text{ e.}\text{\AA}^{-3}$ .

Table 5. Comparison of parameters in compounds containing a -CSSC- grouping

Structure	S-S	$\angle \text{CSS}$	Dihedral $\angle$ -CSSC-	C-S	Reference
	2.04 Å	103.6° 105.1	99.1°	1.83 Å 1.80	Present study
$[(\text{C}_2\text{H}_5)_2\text{NCS}]_2$	2.00	103.4 103.6	96.4	1.82 1.81	Karle, Estlin & Britts (1967a)
$(\text{CH}_3)_2\text{NCSSC}(\text{CH}_3)_3$	2.00	106.1 105.4	99.6	1.80 1.85	Mitchell (1968)
L-Cystine . HCl	2.04	103.0	101	1.87	Steinrauf, Peterson & Jensen (1958)
N,N'-Diglycyl-L-cystine . 2H <sub>2</sub> O	2.04	103.8	101	1.86	Yakel & Hughes (1954)
	2.01	92.7* 95.9	35*	1.81 1.85	Karle, Estlin & Britts (1967b)

\* Constrained by ring closure.

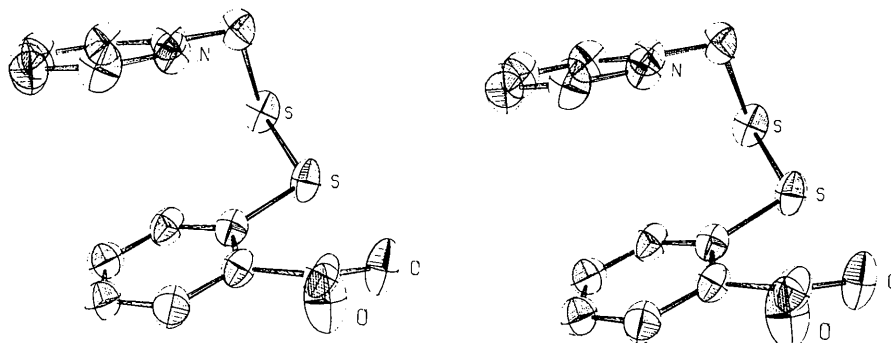


Fig. 3. Stereodiagram for 2-(2-pyridylmethylthio)benzoic acid (prepared from a computer program by Johnson, 1965).

are all within  $\pm 0.005$  Å, except for C(4) and C(5), where the deviations are  $\pm 0.013$  and  $-0.011$  Å respectively. The  $-\text{COOH}$  group is not coplanar with the adjacent phenyl group but is twisted by  $21.7^\circ$  about the C(1)–C(2) bond.

It had been thought that 2-(2-pyridylmethylthio)benzoic acid was in the form of a zwitterion and that the zwitterion formation was important in the antiradiation activity of this material (Field & Kim, 1966). In the crystalline state, the molecule is not in the zwitterion form. All the hydrogen atoms were located in a difference map (Fig. 1). Inclusion of the approximate coordinates of the hydrogen atoms in the least-squares refinement and the refinement of their positions not only improved the agreement between observed and calculated structure factors but also shifted the C–H bond lengths to more acceptable values (1.0–1.2 Å) in spite of the presence of the moderately heavy S atoms. A hydrogen atom is definitely present on the carboxyl group and no hydrogen atom was found near the N atom.

Hydrogen bonding between different molecules occurs between the  $-\text{COOH}$  and the N atom of the pyridyl group in such a way as to form a continuous spiral

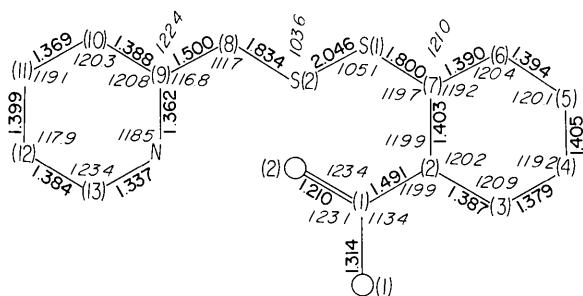


Fig. 4. Bond distances and angles.

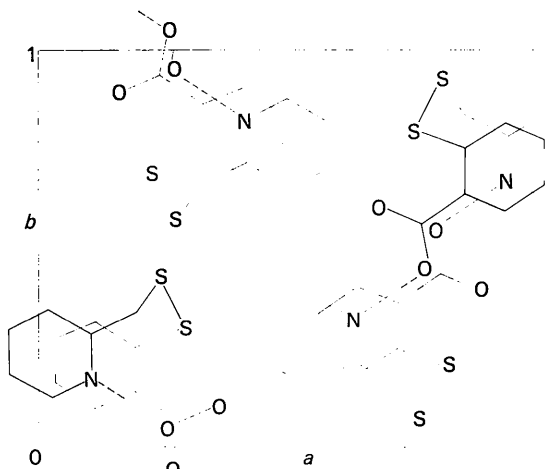


Fig. 5. Contents of a unit cell.

of molecules around the screw axes parallel to  $c$ . Projection of the spirals on the  $ab$  plane shows a herringbone pattern which can be seen in the packing diagram in Fig. 5.

The closest intermolecular distance is the  $\text{OH}\cdots\text{N}$  hydrogen bond at 2.62 Å. Other near approaches are  $\text{O}(2)\cdots\text{N}'$  at 3.31 Å and  $\text{O}(2)\cdots\text{C}'(13)$  at 3.36 Å in the vicinity of the hydrogen bond; and  $\text{O}(2)\cdots\text{C}'(5)$  and  $\text{O}(2)\cdots\text{C}'(11)$  at 3.33 and 3.28 Å, both in the  $a$  direction. The nearest intermolecular approach between carbon atoms is at 3.60 Å between C(13) and C'(4) along the  $c$  direction and between sulfur atoms it is at 3.90 Å between S(1) $\cdots$ S'(2) along the screw axis parallel to  $c$ .

There are several short intramolecular approaches. In the pyridyl ring which is approximately parallel to the phenyl ring, the N atom is only 3.40, 3.42, 3.40 and 3.27 Å from C(4), C(5), C(6) and C(7), respectively. These separations are near the sum of the van der Waals radii for C and N. In molecular complexes such as tetracyanoquinodimethan–tetramethyl- $p$ -phenylenediamine (Hanson, 1965), acepleiadylene- $s$ -trinitrobenzene (Hanson, 1966) and tetracyanoethylene–naphthalene (Williams & Wallwork, 1967), the planar unsaturated molecules arrange themselves in parallel layers with a spacing of 3.26–3.30 Å between the layers. There appears to be an attraction between unlike molecules which overlap each other and C $\cdots$ N distances between layers are of the order of 3.20–3.40 Å. The layered arrangement of the two unlike rings of the molecule in the present investigation (Fig. 2) and the magnitude of the C $\cdots$ N separations between the two rings suggests a similar attraction between two unlike parts of the same molecule in contrast to a charge-transfer between two different molecules in the molecular complexes.

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