The Crystal and Molecular Structure of Phenothiazine-10-propionic Acid

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The crystal structure of phenothiazine-10-propionic acid, $C_{12}H_8SNC_2H_4COOH$, was determined from three-dimensional X-ray diffraction data collected with a manual diffractomer using MoKα (λ 0.71069 Å) radiation. The space group is $P2_1/c$ with a = 7.888(2)Å, b = 8.703(2)Å, c = 19.700(8)Å, β = 101.42(1)°, Z = 4, D_{meas} = 1.35(2) g. cm^{-3} and D_{calc} = 1.36 g. cm^{-3} at 23°. The structure was determined by the direct method and refined with 500 observed reflections by full-matrix least squares to an R of 0.072. The molecule is folded along the S-N axis and the dihedral angle is 136.5°. The C-S-C angle is 98.5(7)° and the average C-S bond is 1.77(2)Å. The shortening of the C-S bond, the small value of the C-S-C angle and the folding of the molecule are typical of the phenothiazine class of compounds and are assumed to be due to sulfur d orbital participation in ring bonding.

Introduction.

The derivatives of phenothiazine continually receive considerable attention from workers in pharmacology (1). Phenothiazine (Figure I) is easily acylated and *N*-alkylated.

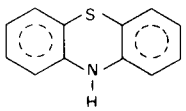


Figure 1. Phenothiazine.

Many *N*-substituted phenothiazines are utilized in chemotherapy; typical *N*-alkylated phenothiazine drugs are the tranquilizer chlorpromazine (3-chloro-10-(3-dimethylamino-*n*-propyl)phenothiazine), the antihistamine promethazine or Phenergen (10-(2-dimethylamino-*n*-propyl)-phenothiazine) and the anti-cholinergic, diethazine or Diparcol (10-(2-diethylaminoethyl)phenothiazine) which is used in the treatment of Parkinson's disease. Dahlbom and Willman (2) investigated the dialkylaminoalkyl ester, thioester, and amide derivatives of phenothiazine-10-propionic acid and found them to possess both weak cholinergic and antihistaminic activity. The present number of phenothiazine derivative structures which have been determined by X-ray diffraction is limited (3-9). Since an exact knowledge of the phenothiazine molecular structure and its variations with different derivative groups is of use in understanding its pharmacological action, the determination of phenothiazine-10-propionic acid (Figure II) was undertaken.

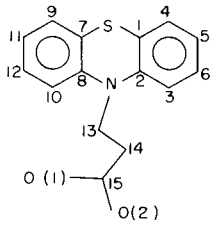


Figure 2. Phenothiazine-10-propionic acid showing numbering scheme used.

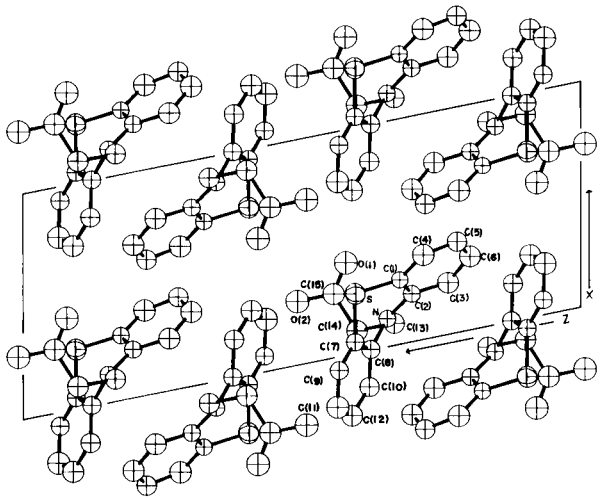


Figure 3. Projection of the unit cell on the xz plane.

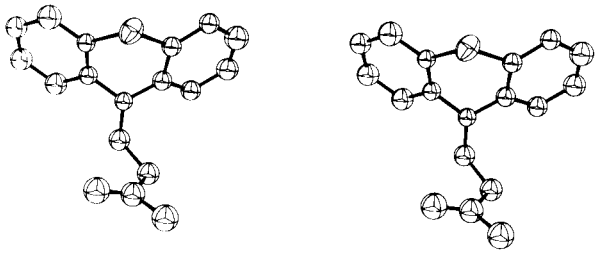


Figure 4. Ortep Stereoscopic view of $C_{12}H_8SNC_2H_4$-COOH, showing the anisotropic thermal ellipsoid of the sulfur atom.

Data Collection and Reduction.

The crystals of $C_{12}H_8SNC_2H_4COOH$ were prepared by Dr. O. Schales in a private clinical laboratory. A mass spectrum of the white crystals confirmed the molecular formula. The melting point was 163°. The measured density 1.35(2) g. cm^{-3} obtained by suspension in a mixture of *n*-butyl bromide and 1-iodopropane is in agreement with the calculated density of 1.36 for four molecules per unit cell.

The rectangular-shaped crystal used for the diffractometer data collection measured 0.26 x 0.04 x 0.11 mm (all ± 0.01 mm) in the [010], [001], and [$\bar{1}$01] directions. The crystal was mounted with b* approximately parallel to the ϕ axis. The unit cell parameters at 23° are a = 7.888(2), b = 8.703(2), c = 19.700(8)Å, and β = 101.42(1)°; these were obtained by the least squares refinement (10) of the setting angles of 21 carefully centered reflections. The systematic absences of (hO1) reflections for l odd and (OkO) for k odd uniquely indicate space group $P2_1/c$ (C_{2h}^5; no. 14). Four molecules per unit cell in space group $P2_1/c$ imposes no required crystallographic symmetry on the molecules.

Reflection data were obtained using both a G.E. quarter-circle manually operated XRD-5 diffractometer and Weissenberg film techniques. For the diffractometer data the MoKα (λ 0.71069Å) radiation was filtered with 1 mil zirconium foil. Each reflection was scanned 1.5° in 2θ at a scan rate of 2° per minute with a take off angle at 3°. Stationary crystal-stationary counter background readings were taken for 10 seconds at each end of the scans. All peaks $0 < 2\theta < 40°$ were scanned. Of the 1281 in the MoKα sphere bounded by $2\theta < 40°$, only 425 had intensities greater than two standard deviations and these were considered the "observed" data from the diffractometer. The standard deviations for the diffractometer data were calculated by $\sigma = (S + BT^2 + 0.0016I^2)^{1/2}$ (where S = total scan count, B = sum of the background counts, T = scan time/total background time, and I = S - BT), except for reflections for which the two background readings differed by more than twice the calculated sigma due to tailing of the reflection peak. In these cases the standard deviations were set equal to the deviation of the background readings from the mean background value. The four standard reflections measured at regularly spaced intervals remained essentially constant during the eight-day data collection.

TABLE I

Final Positional and Thermal Parameters (a) for $C_{12}H_8SNC_2H_4COOH$

	x	y	z	B(Å^2)
S	0.261(1)	0.386(1)	0.4049(2)	----
N	0.121(1)	0.683(1)	0.3468(5)	2.9(2)
O(1)	0.407(1)	0.938(1)	0.4216(4)	5.3(3)
O(2)	0.278(1)	0.999(1)	0.5084(4)	5.0(3)
C(1)	0.283(1)	0.460(2)	0.3246(6)	2.8(3)
C(2)	0.211(1)	0.599(2)	0.3025(6)	3.0(3)
C(3)	0.228(2)	0.663(2)	0.2374(7)	4.6(4)
C(4)	0.373(2)	0.380(2)	0.2823(7)	4.5(4)
C(5)	0.403(2)	0.440(2)	0.2215(6)	3.8(3)
C(6)	0.325(2)	0.577(2)	0.1978(7)	4.5(4)
C(7)	0.047(1)	0.451(2)	0.4047(6)	3.2(3)
C(8)	0.000(2)	0.597(2)	0.3766(6)	3.3(3)
C(9)	-0.065(2)	0.361(2)	0.4334(6)	3.5(3)
C(10)	-0.165(2)	0.651(2)	0.3787(6)	3.8(3)
C(11)	-0.227(2)	0.419(2)	0.4360(7)	5.0(4)
C(12)	-0.277(2)	0.558(2)	0.4102(7)	4.4(4)
C(13)	0.094(2)	0.848(2)	0.3344(7)	4.1(3)
C(14)	0.095(2)	0.940(2)	0.4015(6)	4.1(4)
C(15)	0.279(2)	0.959(2)	0.4334(7)	4.5(4)
H(1)	0.172 (b)	0.773	0.220	5.0
H(2)	0.432	0.269	0.301	5.0
H(3)	0.477	0.377	0.190	5.0
H(4)	0.344	0.625	0.146	5.0
H(5)	-0.026	0.246	0.454	5.0
H(6)	-0.204	0.763	0.358	5.0
H(7)	-0.317	0.349	0.459	5.0
H(8)	-0.404	0.600	0.412	5.0
H(9)	0.195	0.905	0.310	5.0
H(10)	-0.025	0.865	0.295	5.0
H(11)	0.030	1.062	0.390	5.0
H(12)	0.015	0.880	0.435	5.0

(a) In all tables the numbers in parentheses are the standard deviations for the last digit given. (b) The hydrogen atom positions were calculated from the carbon atom positions and were not refined.

TABLE II

Final Anisotropic Thermal Parameters for $C_{12}H_8SNC_2H_4COOH$

The thermal correction was of the form
$\exp-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)$.

A. Beta Values	$\beta_{11}\times10^4$	$\beta_{22}\times10^4$	$\beta_{33}\times10^4$	$\beta_{12}\times10^4$	$\beta_{13}\times10^4$	$\beta_{23}\times10^4$
S	198(9)	173(9)	26(1)	50(8)	15(3)	1(4)

B. Root-mean-square amplitudes of vibration (Å) along the principal axes of the ellipsoids

	Major	Intermediate	Minor
S	0.28	0.22	0.21

TABLE III

Distances from the Least Squares Planes in $C_{12}H_8SNC_2H_4COOH$

S,N,C(1)-C(6) Plane		S,N,C(7)-C(12) Plane	
S	-0.01	S	-0.03
N	-0.03	N	0.01
C(1)	0.01	C(7)	0.02
C(2)	0.02	C(8)	0.00
C(3)	0.02	C(9)	0.04
C(4)	0.03	C(10)	0.00
C(5)	-0.05	C(11)	-0.01
C(6)	0.00	C(12)	-0.02

TABLE IV

Bond Distances and Bond Angles for $C_{12}H_8SNC_2H_4COOH$

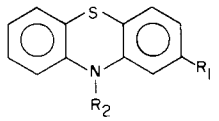
Bond Distances, Å		Bond Angles, deg.	
S-C(1)	1.75(1)	C(1) - S - C(7)	98.5(7)
S-C(7)	1.79(1)	C(2) - N - C(8)	115.4(11)
N-C(2)	1.43(2)	C(2) - N - C(13)	118.5(9)
N-C(8)	1.43(2)	C(8) - N - C(13)	119.6(8)
N-C(13)	1.47(2)	S - C(1) - C(2)	119.7(6)
O(1) - C(15)	1.19(2)	S - C(7) - C(8)	117.5(10)
O(2) - C(15)	1.33(2)	N - C(2) - C(1)	119.6(7)
C(1) - C(2)	1.37(2)	N - C(8) - C(7)	119.3(7)
C(2) - C(3)	1.43(2)	N - C(13) - C(14)	112.4(8)
C(3) - C(6)	1.42(2)	O(2) - C(15) - O(1)	123.9(13)
C(5) - C(6)	1.38(2)	O(1) - C(15) - C(14)	124.9(9)
C(4) - C(5)	1.36(2)	O(2) - C(15) - C(14)	111.2(13)
C(1) - C(4)	1.38(2)	C(2) - C(1) - C(4)	119.1(7)
C(7) - C(8)	1.41(2)	C(1) - C(2) - C(3)	121.5(13)
C(8) - C(10)	1.39(2)	C(2) - C(3) - C(6)	116.2(15)
C(10) - C(12)	1.42(2)	C(1) - C(4) - C(5)	122.3(15)
C(11) - C(12)	1.33(2)	C(4) - C(5) - C(6)	119.0(9)
C(9) - C(11)	1.39(2)	C(3) - C(6) - C(5)	121.8(14)
C(7) - C(19)	1.38(2)	C(8) - C(7) - C(9)	123.0(13)
Wtd. ave. of 12 ring		C(7) - C(8) - C(10)	117.0(13)
C-C, with RMS dev	1.39(3)	C(7) - C(9) - C(11)	117.3(13)
C(13) - C(14)	1.55(2)	C(8) - C(10) - C(12)	119.8(7)
C(14) - C(15)	1.53(2)	C(9) - C(11) - C(12)	122.2(16)
		C(10) - C(12) - C(11)	120.6(12)
		C(13) - C(14) - C(15)	111.2(12)

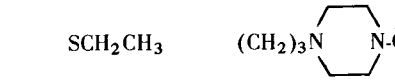
The film data were collected using multiple film, equi-inclination Weissenberg techniques with Ni filtered CuKα (λ 1.5418) radiation. Layers 0-7 were recorded on the *b* axis and were merged using the diffractometer data. These data were assigned individual sigma values proportioned to the estimated uncertainty of the visual intensity estimation (11). No extinction corrections were made for either data set. The linear absorption coefficient for MoKα is 2.4 cm^{-1} with the maximum range of transmission factors from 0.988 to 0.995, and for CuKα the linear absorption coefficient is 21.3 cm^{-1} with the maximum range of transmission factors from 0.880 to 0.939 for the data used. An absorption correction was made for the Cu data, but not for the Mo data. The scattering factors used were those of Cromer and Waber (12). The sulfur scattering factor was corrected for real and imaginary anomalous dispersion using Cromer's (13) values. In view of the fact that 85% of the data used in the final refinement was from the MoKα radiation data set, the correction relative to this radiation was used.

The structure was solved by the direct method using the diffractometer data. E values were calculated with the program FAME (14). The phase determination was carried out using the reiterative Sayre's method of Long (15); it was applied to the 112 non-zero-index reflections with $E \geqslant 1.5$. Of the 16 possible permutations generated by assigning arbitrary signs to 4 reflections in the starting set, the solution with the highest consistency index (0.79) and the least number of cycles (three) revealed the structure; 111 of the 112 signs predicted were later shown to

TABLE V

Comparison of Central Ring Bond Distances and Angles and Dihedral Angles from X-ray Diffraction Data of Phenothiazine and Its Derivatives (a)



R_1	R_2	C-S-C Angle	C-N-C Angle	Average CS Bond	Average CN Bond	Dihedral Angle	S Dis to planes	N Dis to planes	Ref.
H	H	99.6°	121.5°	1.770(3)Å	1.406(2)Å	153.3°	0.18 0.17	0.03 -0.01	(22)
H	$CH_2CH(CH_3)N(CH_3)_2HCl$	97.5°	116.5°	1.77Å	1.42Å	141.8° (c)	-1.59 -0.13	0.11 0.03	(6)(b)
H	$CH_2CH(CH_3)N(CH_3)_2HBr$	99.1°	119.5°	1.75Å	1.44Å	140.7°	-0.04 0.05	0.06 0.00	(7)(b)
Cl	$(CH_2)_3N(CH_3)_2$	97.3(3)°	118.4(5)°	1.75(1)Å	1.41(1)Å	139.4°	-0.14 -0.02	0.01 -0.06	(3)
SCH_2CH_3		99.0(7)°	118.1(10)°	1.78(2)Å	1.425(2)Å	139.0°	-0.14 0.00	-0.05 0.01	(25)
H	$(CH_2)_2N(C_2H_5)_2HCl$	97.5°	116.4°	1.76Å	1.42Å	138.0°	0.06 0.03	-0.02 -0.02	(4)
H	$CH_2CH(CH_3)N(C_2H_5)_2HCl$	97.6°	118.1°	1.76Å	1.43Å	137.4°	0.04 0.01	-0.01 0.01	(8)(b)
H	C_2H_4COOH	98.5(7)°	115.4(11)°	1.77(2)Å	1.43(2)Å	136.5°	-0.03 -0.01	0.01 -0.03	(this work)

(a) The "thiazinamium" derivative reported by Cam & Marsau, *C. R. Acad. Sci., Paris,* Ser. C, **270**, 309 (1970) could not be used in this comparison as the positional parameters listed gave impossible distances and angles for the molecule. (b) Information was calculated from positional parameters given in paper. (c) This dihedral angle is the angle between the two phenyl ring planes; the S was not included in the calculation of these planes because of its deviations from the planes.

be correct. The E map based on these 112 signs clearly showed the ring portions of the molecule, excluding hydrogens. A three dimensional difference Fourier synthesis phased by these 14 atoms using the 425 diffractometer reflections yielded the positions of all nonhydrogen atoms in the alkyl chain.

Since refinement of all non-hydrogen atoms with isotropic thermal factors involves 77 parameters, and refinement with anisotropic thermal corrections for the sulfur atom would require 82 parameters, the 425 observed reflections from the diffractometer data set are only marginally adequate for these refinements. The Weissenberg film data set, which used CuKα radiation and long exposure multiple-film techniques, provided 75 additional reflections that had been too weak to determine with the diffractometer. The combined data sets were used for the final refinement.

Fourier and full matrix least squares refinement with all of the temperature factors isotropic led to an unweighted R_1 ($\Sigma||Fo|-|Fc||/\Sigma|Fo|$) of 0.076 and a weighted residual R_2 ($[\Sigma w(|Fo|-|Fc|)^2/\Sigma w|Fo|^2]^{1/2}$, where $w = 1/\sigma$) of 0.066. The function minimized in the least squares was $\Sigma w(|Fo|-|Fc|)^2$. The sulfur atom was then refined anisotropically and R_1 reduced to 0.072 and R_2 to 0.065, which is a significant drop according to Hamilton's R-factor ratio test (16).

In the last refinement cycle no positional or thermal parameter was shifted more than 0.02 times its estimated standard deviation. The standard deviation of an observation of unit weight for the combined data is 0.97. A final difference Fourier over the asymmetric unit showed no peak height greater than .75 $e^-/Å^3$; this is approximately 12% of the height of an average carbon atom peak in the final Fourier map. This map failed to reveal any of the hydrogen atoms (possibly due to the paucity of data); in the last cycles of least squares the calculated positions of the H's were included but were not refined in the least squares treatment. The final $\Delta F/\sigma$ value revealed no apparent dependence on θ of F values for either data set, therefore, the weighting schemes appeared reasonable. The data merge did not appear to bias the refinement: the weighted and unweighted R values and the standard deviations of an observation of unit weight were 0.060, 0.056 and 0.96 for the 425 diffractometer reflections, and were 0.112, 0.137 and 0.99 for the 75 weak reflections obtained by film measurement. There were no positional differences of over 1 σ in comparing the least squares refinement of the diffractometer-only data to that of the combined data set.

Results and Discussion.

Table I contains the final positional and isotropic thermal parameters and Table II contains the anisotropic parameters for the sulfur atom. In Figure III the crystal packing is shown in a projection of the unit cell on the xz plane. The most noticeable feature is the folding of the molecule on the S-N axis forming a dihedral angle of 136.5° between the two planes. The displacements of the atoms from the planes of the two benzene rings are given in Table III.

Table IV gives the intratomic distances and angles for $C_{12}H_8SNC_2H_4COOH$. The C-S-C bond angle of 98.5° is very close to that found previously for phenothiazine and its derivatives. In Table V a comparison of pertinent distances and angles of the phenothiazine structures which have been reported to data is tabulated. The average C-S bond distance of 1.77(2)Å found in this report is in agreement with previously reported structures and is shorter than the C-S single bond value of 1.81Å (17). This supports the general theory of Lucken (18) and the quantum mechanical treatment of Craig and Magnussen (19) in which dπ bonding is assumed to take place in the phenothiazine ring. This tendency has been found in other aromatic substances such as dibenzenesulphonyl sulfide (20). The C-N distance is 1.43(2)Å, which is equal to that given for aromatic C-N (17). The C-C average ring distance of 1.39(3)Å is in agreement with that found for benzene (17).

Malrieu and Pullman (21), in a theoretical study of phenothiazine, reported that because the molecule is folded and the nitrogen and sulfur are assumed to be in the sp^3 hybridization state, the hydrogen atom attached to nitrogen can either bend in or away from the dihedral angle, and these two forms are not electronically equivalent. When the N substituent is bent toward the dihedral angle the unshared pair of electrons on nitrogen can conjugate with the benzene π system; when the group bends away from the dihedral angle the lone pair is pushed into a position which decreases the participation of the nitrogen in the delocalized system. Bell and his co-workers (22) reported the location of hydrogen in phenothiazine to be in a quasi-equatorial position. In the present structure, as would be expected from steric considerations, the alkyl chain attached to the nitrogen bends away from the dihedral angle. As seen from Table V, the dihedral angle is considerably decreased in the derivatives with N-chains as compared to phenothiazine itself. On this basis the structure of phenothiazine-10-propionic acid suggests less participation of the nitrogen lone pair in the π system since there exists a greater deviation from planarity than in phenothiazine.

Table V also shows, for the phenothiazine structures reported thus far, the C-S and C-N bond lengths as well as the C-S-C bond angles are relatively constant, and the C-N-C bond angle is the central-ring parameter which varies the most with the dihedral angle. Although the

range of these parameters is not large among the phenothiazine derivatives, the structure of this report appears to possess both the smallest C-N-C bond angle and the smallest molecular dihedral angle.

There is strong evidence for hydrogen bonding between the 0(1) atom of one molecule and the 0(2) of a nearby molecule related by a crystallographic center of symmetry (see Figure III). This O- - -O intermolecular distance is 2.65 Å, which is within the accepted hydrogen bond range of O- -H· · ·O (23) and less than Van der Waal's distance of 2.8 Å (24). The intermolecular hydrogen bonding effectively "dimerizes" two phenothiazine molecules with two hydrogen bonds each, and the packing becomes a simple packing of these "dimer" units (Figure III). All other intermolecular distances are greater than Pauling's non-bonding radii values.

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