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The Crystal Structure of *N*-Ethylphenothiazine

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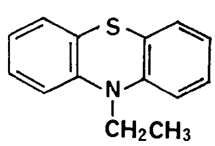
The crystal structure of *N*-ethylphenothiazine, $C_{14}H_{13}NS$, has been determined by the heavy-atom method. The refinement was carried out by the least-squares method with anisotropic temperature factors based on three-dimensional data to give a final R value of 0·033 for 1258 reflections. The space group is $Pna2_1$ with $Z=4$, and unit-cell parameters: $a=14·3136$ (8), $b=10·8141$ (8), and $c=7·6677$ (2) Å. All the hydrogen atoms were located on a difference Fourier synthesis. The best planes of the benzene rings make a dihedral angle of 135·0°. The average sulfur–carbon bond length is 1·766 (3) Å and the C–S–C bond angle is 97·4 (1)°. The packing of the molecules in the crystal is determined by the van der Waals interactions.

Introduction

The crystal structures of phenothiazine and a number of its derivatives have been determined by the X-ray diffraction method. These include phenothiazine (Bell, Blount, Briscoe & Freeman, 1968), *N*-methylphenothiazine (Chu & Van der Helm, 1974), phenothiazine-10-propionic acid (Malmstrom & Cordes, 1972), phenothiazine-10-propionitrile (Malmstrom & Cordes, 1973), chlorpromazine (McDowell, 1969), thiethylperazine (McDowell, 1970), thiazinamium (Marsau & Cam, 1973), promethazine (Marsau & Busetta, 1973), and methoxypromazine (Marsau & Gauthier, 1973). In this work, the crystal structure of *N*-ethylphenothiazine (I) has been determined with the objective of determining the effect of the *N*-substituent on the stereochemistry of phenothiazines in order to explain the difference in the chemical reactivity of the different *N*-substituted phenothiazines (Biehl, 1974). Since many phenothiazine derivatives are chemotherapeutic agents (Domino, 1967; Zirkle & Kaiser, 1970), this work will also contribute to the basic understanding of the correlation between the pharmacological activity and the molecular structure of the phenothiazine derivatives.



(I)

Experimental

Single crystals of *N*-ethylphenothiazine were obtained through the courtesy of Dr Edward R. Biehl of the Chemistry Department of Southern Methodist University. The crystals are clear needle prisms with the *a* axis parallel to the needle axis. The unit-cell parameters and the intensity data were measured on a Nonius-CAD 4 automatic diffractometer. The crystal data are summarized in Table 1. A $\theta/2\theta$ scanning mode with Ni-filtered Cu $K\alpha$ radiation was used to measure 1318 independent reflections with 2θ values below 150°, of which 1262 reflections were considered as observed. A reflection was considered as observed if its intensity was greater than $1·4\sigma(I)$, where $\sigma(I)$ was determined from counting statistics. The intensity data were reduced to structure factors by the application of Lorentz and polarization factors, and no absorption corrections were applied.

Table 1. *Crystal data of N-ethylphenothiazine*

Chemical formula: $C_{14}H_{13}NS$ M.W. 227·33
Crystal system: orthorhombic
Space group: $Pna2_1$ or $Pnam$ from the systematic extinctions: $0kl$ absent with $k+l$ odd and $h0l$ absent with h odd. $Pna2_1$ is the correct space group because of the short length of c.

$a=14·3136$ (8) Å	(obtained from + and	$V=1186·87$ Å^3
$b=10·8141$ (8)	− 2θ values of 40	$Z=4$
$c=7·6677$ (2)	reflections)	$F(000)=480$

$D_x=1·27$ g cm^{-3}
$D_m=1·28$ g cm^{-3} (by flotation in a mixture of ethyl alcohol and chloroform)
λ(Cu $K\alpha$) = 1·5418 Å
μ(Cu $K\alpha$) = 20·90 cm^{-1}
Crystal dimensions: 0·40 × 0·13 × 0·10 mm

Structure determination and refinement

The structure was determined by the heavy-atom method. The position of the sulfur atom was obtained from the Harker peaks of the E^2-1 Patterson synthesis. All carbon and nitrogen atoms were located in a Fourier synthesis. The refinement was carried out by the full-matrix least-squares method with anisotropic

Table 2. *Fractional atomic coordinates and thermal parameters* (*all* × 10⁴)

The estimated standard deviations are given in parentheses and refer to the last positions of respective values. The expression for the temperature factor exponent consistent with β values is $[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
S	2322 (0)	662 (1)	0 (0)	42 (0)	149 (1)	181 (1)	3 (0)	−19 (1)	8 (1)
N	3761 (2)	518 (2)	2742 (3)	48 (1)	104 (2)	126 (4)	−2 (1)	−13 (2)	−3 (2)
C(1)	3312 (3)	2741 (3)	−839 (6)	69 (2)	115 (3)	233 (6)	30 (2)	8 (3)	29 (4)
C(2)	4001 (3)	3644 (3)	−538 (6)	84 (2)	91 (3)	340 (10)	17 (2)	27 (4)	30 (4)
C(3)	4599 (3)	3488 (3)	832 (7)	74 (2)	81 (3)	373 (10)	−6 (2)	29 (4)	−26 (4)
C(4)	4549 (2)	2461 (3)	1904 (5)	53 (1)	103 (2)	235 (7)	2 (2)	−2 (3)	−40 (4)
C(5)	4104 (2)	−1694 (3)	2257 (5)	53 (1)	111 (3)	191 (6)	2 (2)	19 (2)	30 (3)
C(6)	3944 (3)	−2783 (3)	1362 (5)	84 (2)	92 (3)	264 (8)	−5 (2)	57 (4)	22 (4)
C(7)	3309 (3)	−2818 (3)	4 (7)	94 (2)	104 (3)	256 (7)	−32 (2)	53 (5)	−23 (5)
C(8)	2835 (2)	−1764 (3)	−441 (4)	68 (2)	133 (3)	170 (6)	−36 (2)	13 (2)	−21 (3)
C(11)	3238 (2)	1739 (2)	272 (4)	45 (1)	91 (3)	171 (7)	14 (2)	4 (3)	−2 (4)
C(12)	3858 (2)	1570 (2)	1663 (4)	44 (1)	84 (3)	153 (5)	10 (2)	3 (3)	−16 (3)
C(13)	3622 (2)	−634 (2)	1853 (4)	42 (1)	97 (2)	126 (4)	−5 (1)	10 (2)	9 (3)
C(14)	2969 (2)	−684 (3)	489 (4)	44 (1)	114 (3)	139 (5)	−16 (1)	6 (2)	1 (3)
C(15)	4212 (2)	509 (3)	4431 (4)	61 (2)	140 (3)	145 (5)	−4 (2)	−26 (2)	−8 (3)
C(16)	3661 (3)	−184 (4)	5784 (5)	67 (2)	188 (5)	139 (5)	26 (3)	1 (3)	17 (4)

Table 2 (*cont.*)

Hydrogen atom coordinates (× 10³)

	x	y	z
H(1)	286 (3)	279 (3)	−183 (5)
H(2)	403 (3)	450 (3)	−143 (7)
H(3)	503 (3)	391 (3)	112 (6)
H(4)	495 (3)	251 (3)	277 (5)
H(5)	452 (2)	−173 (3)	313 (5)
H(6)	438 (2)	−354 (3)	171 (5)
H(7)	325 (3)	−368 (3)	−62 (5)
H(8)	249 (3)	−172 (3)	−130 (5)
H(15)1	493 (3)	16 (4)	437 (4)
H(15)2	417 (2)	141 (3)	477 (4)
H(16)1	404 (3)	−19 (4)	697 (5)
H(16)2	310 (3)	25 (4)	586 (5)
H(16)3	353 (3)	−128 (4)	551 (5)

temperature factors. All the hydrogen atoms were located on a difference Fourier synthesis. Their positional parameters were refined; their thermal parameters were assigned the same values as those of the atoms to which they are bonded. Cruickshank's (1965) weighting scheme was used, and the weight of each reflection was calculated according to the formula $1/w=(0{\cdot}15-0{\cdot}02|F_o|+0{\cdot}002|F_o|^2)$. The quantity $\sum w\{||F_o|-|F_c||\}^2$ was minimized. The final R index $(\sum||F_o|-|F_c||/\sum|F_o|)$ was 0·033. The magnitude of $[\sum(F_o-F_c)^2/(m-n)]^{1/2}$, where m is the number of reflections and n is the number of parameters refined, was 0·91. There are four low-order reflections (201, 311, 002, 202) with calculated structure amplitudes much higher than the observed values due to extinction. These were given zero weight in the least-squares refinement and were excluded in the calculation of the final disagreement index. An anomalous dispersion correction (Cromer & Liberman, 1970) for S was added in the least-squares refinement. The atomic scattering factors used for sulfur, nitrogen, and carbon atoms were those from *International Tables for X-ray Crystallography* (1962). For hydrogen, the values given by Stewart, Davidson & Simpson (1965) were used. The final positional and thermal parameters are given in Table 2.*

The crystal of *N*-ethylphenothiazine belongs to a polar space group and the polarity of the crystal was determined by the refinement of atomic parameters with positive and negative z values for $+h+k+l$ data (Ibers & Hamilton, 1964). Refinement for the atomic parameters of the molecule reported in Table 2 gave an R value of 0·033 and the refinement for the atomic parameters with opposite z values gave an R value of 0·039. Therefore, the crystal with the reported atomic parameters (Table 2) has the correct polarity at greater than 99·5% confidence level using Hamilton's (1965) R-value significance test.

The computer programs used in this analysis were

* A table of calculated and observed structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30822 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

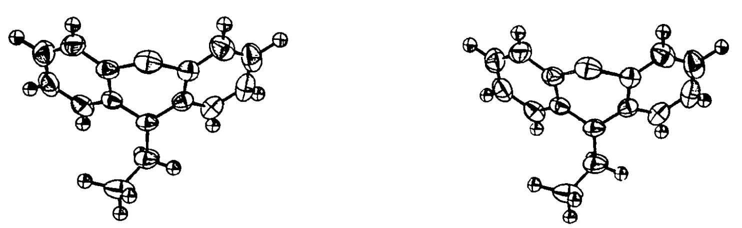


Fig. 1. The stereoscopic drawing of one molecule of *N*-ethylphenothiazine.

ORFLS (Busing, Martin & Levy, 1962), the Zalkin Fourier synthesis program modified by Dr R. Shiono of the University of Pittsburgh, and a number of structure interpretation programs (Shiono, 1971; Chu, 1973) All calculations were carried out on a CDC CYBER 72 computer in the Computing Laboratory at Southern Methodist University.

Description of the structure

A stereoscopic view of the configuration of an *N*-ethylphenothiazine molecule is shown in Fig. 1 (Johnson, 1965). The identification of the atoms and the bond lengths and bond angles with their standard deviations are shown in Fig. 2.

Table 3. *Comparison of* C–S *and* C–N *bond lengths,* C–S–C *and* C–N–C *bond angles and dihedral angles in phenothiazine derivatives*

	Within the central ring				Outside ring		Dihedral	
Compounds	C–S (Å)	C–N (Å)	C–S–C(°)	C–N–C(°)	C–N (Å)	C–N–C(°)	angle(°)	References
1. Phenothiazine	1·770 (3)	1·406 (2)	99·6 (2)	121·5 (2)			153·3	Bell, Blount, Briscoe & Freeman (1968)
2. *N*-Methylphenothiazine	1·764 (2)	1·402 (2)	97·4 (1)	118·0 (2)	1·455 (5)	118·1 (3)	143·7	Chu & Van der Helm (1974)
3. *N*-Ethylphenothiazine	1·766 (3)	1·412 (4)	97·4 (1)	116·7 (2)	1·460 (4)	118·6 (2)	135·0	This work
4. Phenothiazine-10-propionitrile	1·76 (1)	1·42 (1)	98·7 (7)	117·6 (9)	1·48 (2)	118·1 (9)	135·4	Malmstrom & Cordes (1973)
5. Phenothiazine-10-propionic acid	1·77 (1)	1·43 (2)	98·5 (7)	115·4 (11)	1·47 (2)	119·1 (8)	136·5	Malmstrom & Cordes (1972)
6. Chlorpromazine	1·75 (1)	1·41 (1)	97·3 (3)	118·4 (5)	1·51 (1)	117·8 (5)	139·4	McDowell (1969)
7. Thiethylperazine	1·78 (2)	1·43 (2)	99·0 (7)	118·1 (10)	1·48 (2)	117·9 (11)	139·0	McDowell (1970)
8. Thiazinamium	1·772 (6)	1·411 (7)	98·0 (3)	117·2 (5)	1·478 (8)	119·5 (5)	135·6	Marsau & Cam (1973)
9. Promethazine	1·766 (5)	1·414 (6)	98·8 (2)	118·5 (4)	1·453 (7)	119·1 (4)	140·6	Marsau & Busetta (1973)
10. Methoxypromazine	1·758 (7)	1·413 (7)	99·8 (3)	122·3 (5)	1·476 (8)	117·5 (5)	157·7	Marsau & Gauthier (1973)

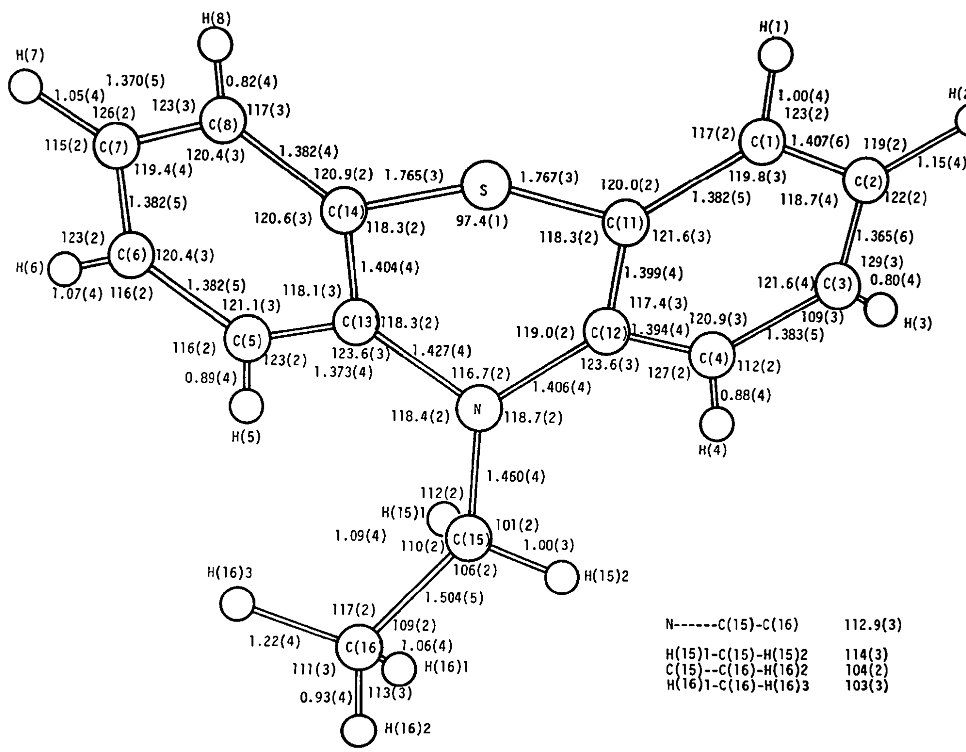


Fig. 2. Bond lengths (Å) and bond angles (°) of *N*-ethylphenothiazine with e.s.d.'s in parentheses.

Table 3 (*cont.*)

Compounds	R	R′
1	H	H
2	H	CH_3
3	H	CH_2CH_3
4	H	CH_2CH_2CN
5	H	CH_2CH_2COOH
6	Cl	$(CH_2)_3N(CH_3)_2$
7	SCH_2CH_3	$(CH_2)_3N\quad NCH_3$
8	H	$CH_2CHCH_3N(CH_3)_2.SO_4(CH_3)_2$
9	H	$CH_2CHCH_3N(CH_3)_2.HBr$
10	OCH_3	$(CH_2)_3N(CH_3)_2.C_4H_4O_4$

The mean value of the two carbon–sulfur bond lengths is 1·766 (3) Å, and the carbon–sulfur–carbon bond angle is 97·4°; both are in good agreement with those obtained in *N*-methylphenothiazine (Chu & Van der Helm, 1974). For comparison, the C–S and C–N bond lengths and the C–S–C and C–N–C bond angles in phenothiazine derivatives are summarized in Table 3. The C–S and C–N bond lengths of the central ring are not significantly different for the phenothiazine derivatives; however, the C–S–C and C–N–C bond angles are significantly different. All C–N–C angles are close to 120°, indicating that the three N–C bonds around the nitrogen atom are approximately planar in configuration.

The least-squares planes in *N*-ethylphenothiazine are shown in Table 4. The dihedral angle between the least-squares planes of the two benzene rings is 135·0°. A comparison of the dihedral angles in phenothiazine derivatives is also summarized in Table 3. Owing to the non-bonded interactions between the *N*-substituent and the benzene ring, the dihedral angle is smaller for substituted phenothiazines. The non-bonded hydrogen distances in *N*-ethylphenothiazine are 2·24, 2·33, and 2·37 Å between H(4)...H(15)2, H(5)···H(15)1, and H(5)···H(16)3, respectively. However, the dihedral angle of 157·7° in methoxypromazine (Marsau & Gauthier, 1973) is larger than the dihedral angle of 153·3° in phenothiazine (Bell, Blount, Briscoe & Freeman, 1968). The reason for the large dihedral angle in methoxypromazine is that the *N*-substituent extends to the concave side of the tricyclic ring instead of to the convex side as in all other phenothiazine derivatives. This is illustrated by the torsion angle about the N–C(15) bond in methoxypromazine as compared with that in ethylphenothiazine (Fig. 3).

The packing of the molecules in the crystal is shown in the stereoscopic drawing in Fig. 4. There are no intermolecular contacts less than van der Waals distances. The closest intermolecular distance is 3·485 Å between C(5) and C(15).

The rigid-body thermal analysis of the 16 non-hydrogen atoms was carried out by the method of Schomaker & Trueblood (1968). The r.m.s. value of ΔU_{ij}, the difference between observed U_{ij} and calculated U_{ij} based on the rigid-body model, is 0·0038 Å^2. A comparison of this value with the mean $\sigma(U_{ij})$ value of 0·0017 Å^2, calculated from the estimated standard deviation of the β_{ij} of the least-squares refinement, indicates that the rigid-body model is only moderately satisfactory.

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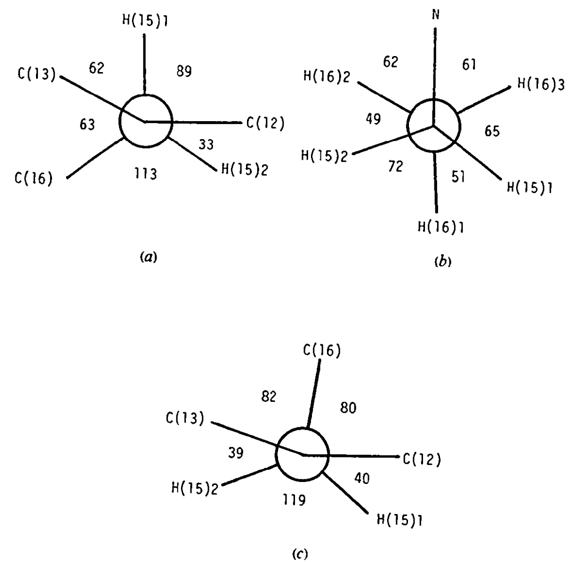

Fig. 3. The torsion angles (°) about the (*a*) N–C(15) and (*b*) C(15)–C(16) bonds in *N*-ethylphenothiazine and about the (*c*) N–C(15) bond in methoxypromazine.

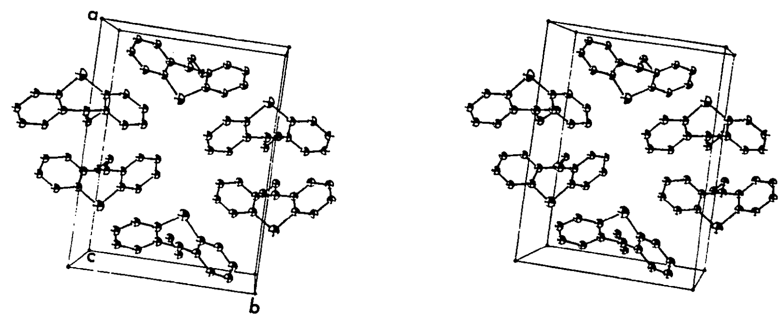

Fig. 4. The stereoscopic drawing of molecular packing of *N*-ethylphenothiazine, excluding hydrogen atoms, in the unit cell.

Table 4. *Least-squares planes and displacements* (Å) *of atoms from the planes*

Equation of planes: $Ax+By+Cz=D$, where x,y,z are in Å.

Plane	A	B	C	D
(a)	0·6226	−0·5061	−0·5968	1·8208
(b)	0·6055	−0·5162	−0·6057	1·6878
(c)	0·7218	0·2520	−0·6446	2·6522
(d)	0·7109	0·2572	−0·6546	2·5794
(e)	0·7444	−0·1484	−0·6511	3·0319

Benzene ring

	(a)	(b)		(c)	(d)
C(1)	0·015	−0·045	C(5)	0·010	−0·033
C(2)	−0·003	0·017	C(6)	−0·009	0·024
C(3)	−0·012	0·043	C(7)	−0·003	−0·008
C(4)	0·015	−0·004	C(8)	0·014	−0·025
C(11)	−0·012	−0·035	C(13)	0·010	0·002
C(12)	−0·003	−0·003	C(14)	−0·013	0·036
S	−0·114*	0·021	S	−0·073*	−0·001
N	0·000	0·007	N	0·028*	0·006

Central ring

	(e)
C(11)	0·004
C(12)	−0·003
C(13)	0·003
C(14)	−0·004
S	−0·664*
N	−0·468*

Dihedral angles between the least-squares planes

(a) and (c)	135·0°
(b) and (d)	134·0
(a) and (b)	1·2
(c) and (d)	0·9

* Indicates atoms excluded from the calculation of the least-squares planes.

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