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Structure and Absolute Configuration of 3-(2-Methoxy-10-phenothiazinyl)-*N*,*N*,2-trimethylpropanamine

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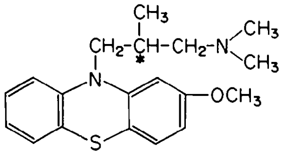
Abstract. $C_{19}H_{24}N_2OS$, $M_r = 328{\cdot}5$, orthorhombic, $P2_12_12_1$, $a = 12{\cdot}766$ (1), $b = 18{\cdot}807$ (2), $c = 7{\cdot}535$ (1) Å, $U = 1809{\cdot}2$ (3) Å^3, $Z = 4$, $D_x = 1{\cdot}21$ Mg m^{-3}, $R = 0{\cdot}036$ for 1975 non-zero reflexions. The absolute configuration around the C(15) atom was determined as *R* by the anomalous-dispersion method.

Introduction. *N*-substituted phenothiazines are familiar as the major tranquillizers. In relation to their asymmetric synthesis, the molecular structure of the title compound has been determined in order to establish the absolute configuration of the medically active L-(−) isomer.



$[\alpha]_D^{20\,^\circ\mathrm{C}} = -15{\cdot}3^\circ$

A colourless prismatic crystal with approximate dimensions 0·28 × 0·13 × 0·13 mm was used. Preliminary Weissenberg photographs showed $P2_12_12_1$ symmetry. Unit-cell parameters and integrated intensities were measured on a Rigaku automated four-circle diffractometer with Ni-filtered Cu $K\alpha$ ($\lambda = 1{\cdot}5418$ Å) radiation. The θ–2θ scan technique was employed. The scan width and scan rate were $\Delta 2\theta = (2{\cdot}0 + 0{\cdot}28 \tan\theta)^\circ$ and 4° min^{-1}, respectively. Two sets of $|F(hkl)|$ and $|F(hk\bar{l})|$ ($h,k,l \geq 0$) reflexions (a total of 2073 reflexions) were collected up to $2\theta = 110^\circ$, and 98 reflexions [$|F| < 3\sigma(F)$] were considered as unobserved. Four standard reflexions measured after every 60 reflexions showed no intensity decrease during the data collection. Corrections were made for the usual Lp effect but not for absorption or extinction [μ(Cu $K\alpha$) = 1·58 mm^{-1}]. The structure was solved by the *MULTAN* 74 program (Main, Woolfson, Lessinger, Germain & Declercq, 1974), and refined anisotropically by the block-diagonal least-squares procedure (*HBLS* V, Ashida, 1973). The function minimized was $\sum w(|F_o| - |F_c|)^2$. All the H atoms were located by the difference Fourier synthesis. They were included in the subsequent refinement with isotropic temperature factors. Atomic scattering factors for S, N, O and C were taken from *International Tables for X-ray Crystallography* (1974), and for H from Stewart, Davidson & Simpson (1965). Corrections for the anomalous-dispersion effect for S, N, O and C atoms (*International Tables for X-ray Crystallography*, 1974) were applied at the final stage of the refinement. The absolute configuration was determined by using 25 strong reflexions which gave significant Bijvoet differences in the calculated structure factors. At the final stage of the refinement, the *hkl* and $hk\bar{l}$ reflexions were treated as independent, taking care of the absolute configuration. The final *R* value was 0·036 for non-zero (0·042 for all) reflexions ($R_w = 0{\cdot}057$). The weighting scheme used was $w = (\sigma_{\rm cs}^2 + a|F_o| + b|F_o|^2)^{-1}$ for $|F_o| > 0$ and $w = c$ for $|F_o| = 0$, where $\sigma_{\rm cs}$ is the standard deviation obtained from the counting statistics. The values of *a*, *b* and *c* used in the final refinement were 0·0173, 0·0006 and 0·3604. The final atomic parameters are listed in Table 1.†

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† Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35284 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Fractional atomic coordinates* ($\times 10^4$, *for* H $\times$ 10^3) *and isotropic thermal parameters with e.s.d.'s in parentheses*

	x	*y*	*z*	B_{eq}/B (Å^2)
S	5106·8 (7)	4693·8 (4)	4384 (2)	4·7
O	8688 (2)	6647 (2)	4836 (4)	5·7
N(*A*)	5094 (2)	6130 (2)	5966 (3)	3·6
N(*B*)	6644 (3)	7426 (2)	9762 (4)	5·0
C(1)	6073 (2)	5944 (2)	5208 (4)	3·1
C(2)	6937 (2)	6383 (2)	5351 (5)	3·5
C(3)	7885 (3)	6175 (2)	4574 (5)	4·1
C(4)	9720 (3)	6429 (3)	4413 (8)	7·5
C(5)	7979 (3)	5551 (2)	3649 (5)	4·4
C(6)	7099 (3)	5117 (2)	3525 (5)	4·3
C(7)	6163 (3)	5296 (2)	4328 (4)	3·5
C(8)	4079 (3)	5312 (2)	4170 (4)	3·9
C(9)	3175 (3)	5143 (2)	3215 (5)	4·7
C(10)	2382 (3)	5628 (3)	3076 (6)	5·6
C(11)	2487 (3)	6298 (2)	3829 (5)	5·3
C(12)	3385 (3)	6471 (2)	4759 (5)	4·3
C(13)	4182 (2)	5975 (2)	4977 (4)	3·5
C(14)	5087 (3)	6651 (2)	7391 (4)	3·6
C(15)	5571 (3)	6345 (2)	9063 (4)	3·7
C(16)	4866 (3)	5794 (2)	9894 (5)	5·9
C(17)	5834 (3)	6937 (2)	10399 (5)	4·9
C(18)	7678 (3)	7118 (3)	9872 (6)	6·5
C(19)	6625 (4)	8076 (3)	10810 (8)	8·8
H(1)	691 (3)	688 (2)	609 (4)	5·3 (8)
H(2)	1018 (3)	686 (3)	467 (6)	10 (2)
H(3)	985 (3)	607 (2)	507 (5)	7·0 (9)
H(4)	973 (4)	593 (3)	341 (7)	12 (2)
H(5)	866 (3)	540 (2)	307 (5)	4·7 (7)
H(6)	718 (2)	471 (2)	287 (4)	3·9 (6)
H(7)	314 (3)	463 (2)	272 (5)	5·8 (8)
H(8)	177 (3)	550 (2)	239 (5)	7·0 (9)
H(9)	189 (3)	670 (2)	359 (4)	4·4 (7)
H(10)	348 (2)	697 (2)	527 (4)	4·5 (7)
H(11)	438 (3)	680 (2)	759 (4)	5·5 (8)
H(12)	544 (3)	712 (2)	703 (4)	3·9 (6)
H(13)	628 (3)	611 (2)	875 (4)	4·7 (7)
H(14)	519 (3)	549 (2)	1091 (6)	9 (1)
H(15)	434 (3)	562 (2)	920 (6)	9 (2)
H(16)	424 (4)	607 (3)	1068 (6)	9 (2)
H(17)	602 (3)	670 (2)	1168 (4)	5·1 (7)
H(18)	527 (3)	721 (2)	1076 (5)	7·2 (9)
H(19)	775 (4)	661 (3)	914 (6)	9 (2)
H(20)	822 (3)	746 (2)	925 (6)	8 (1)
H(21)	783 (4)	706 (3)	1126 (6)	10 (2)
H(22)	715 (4)	840 (3)	1041 (6)	10 (2)
H(23)	596 (4)	844 (3)	1020 (6)	11 (2)
H(24)	630 (4)	807 (3)	1214 (6)	10 (2)

Discussion. Fig. 1 is an *ORTEP* (Johnson, 1976) drawing of the molecular structure together with the atom-numbering scheme. Interatomic distances and bond angles are given in Tables 2 and 3, respectively.

The average C–S and C–N(*A*) bond distances within the central ring of the phenothiazine moiety are 1·761 (3) and 1·415 (3) Å, and the C–S–C and C–N(*A*)–C bond angles are 98·2 (2) and 117·6 (3)°, respectively. All are in good agreement with those of *N*-substituted phenothiazine derivatives (Marsau & Cam, 1973; Marsau & Busetta, 1973; Chu & van der

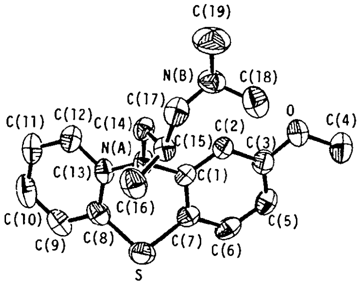

Fig. 1. Molecular structure with the atom-numbering scheme. All the non-hydrogen atoms are drawn as thermal ellipsoids at the 50% probability level. H atoms are omitted for clarity.

Table 2. *Interatomic bond distances* (Å) *with e.s.d.'s in parentheses*

S–C(7)	1·762 (3)	S–C(8)	1·760 (3)
O–C(3)	1·370 (4)	O–C(4)	1·416 (6)
N(*A*)–C(1)	1·418 (3)	N(*B*)–C(17)	1·464 (5)
N(*A*)–C(13)	1·412 (4)	N(*B*)–C(18)	1·444 (5)
N(*A*)–C(14)	1·454 (4)	N(*B*)–C(19)	1·455 (6)
C(1)–C(2)	1·382 (4)	C(1)–C(7)	1·392 (4)
C(2)–C(3)	1·401 (4)	C(3)–C(5)	1·371 (5)
C(5)–C(6)	1·391 (4)	C(6)–C(7)	1·381 (4)
C(8)–C(9)	1·397 (4)	C(8)–C(13)	1·394 (4)
C(9)–C(10)	1·367 (5)	C(10)–C(11)	1·390 (5)
C(11)–C(12)	1·382 (5)	C(12)–C(13)	1·390 (4)
C(14)–C(15)	1·517 (4)	C(15)–C(16)	1·509 (5)
C(15)–C(17)	1·539 (5)		

C–H = 0·86 (4) ~ 1·21 (6); av. 1·03

Table 3. *Bond angles* (°) *with e.s.d.'s in parentheses*

C(7)–S–C(8)	98·3 (2)	S–C(7)–C(1)	119·2 (3)
S–C(7)–C(6)	121·1 (3)	S–C(8)–C(9)	120·8 (3)
S–C(8)–C(13)	118·7 (3)		
C(3)–O–C(4)	118·4 (4)	O–C(3)–C(2)	113·9 (3)
O–C(3)–C(5)	124·3 (3)		
C(1)–N(*A*)–C(13)	117·6 (3)	C(1)–N(*A*)–C(14)	118·0 (3)
C(13)–N(*A*)–C(14)	121·6 (3)	N(*A*)–C(1)–C(2)	121·6 (3)
N(*A*)–C(1)–C(7)	118·7 (3)	N(*A*)–C(13)–C(8)	119·5 (3)
N(*A*)–C(13)–C(12)	121·8 (3)	N(*A*)–C(14)–C(15)	110·8 (3)
C(17)–N(*B*)–C(18)	112·0 (3)	C(17)–N(*B*)–C(19)	109·7 (4)
C(18)–N(*B*)–C(19)	108·8 (4)	N(*B*)–C(17)–C(15)	113·2 (3)
C(2)–C(1)–C(7)	119·7 (3)	C(1)–C(2)–C(3)	119·3 (3)
C(2)–C(3)–C(5)	121·8 (3)	C(3)–C(5)–C(6)	117·8 (3)
C(5)–C(6)–C(7)	121·7 (3)	C(6)–C(7)–C(1)	119·6 (3)
C(9)–C(8)–C(13)	120·4 (3)	C(8)–C(9)–C(10)	120·0 (4)
C(9)–C(10)–C(11)	120·3 (4)	C(10)–C(11)–C(12)	119·9 (4)
C(11)–C(12)–C(13)	120·7 (3)	C(12)–C(13)–C(8)	118·6 (3)
C(14)–C(15)–C(16)	111·3 (3)	C(14)–C(15)–C(17)	110·9 (3)
C(16)–C(15)–C(17)	110·8 (3)		

C–C–H (aromatic)	116 (2) ~ 124 (2); av. 120
C–C–H (aliphatic)	105 (2) ~ 117 (3); av. 111
O–C–H (aliphatic)	105 (3) ~ 112 (3); av. 108
N(*A*)–C–H (aliphatic)	109 (2) ~ 112 (2); av. 110
N(*B*)–C–H (aliphatic)	105 (3) ~ 120 (3); av. 111

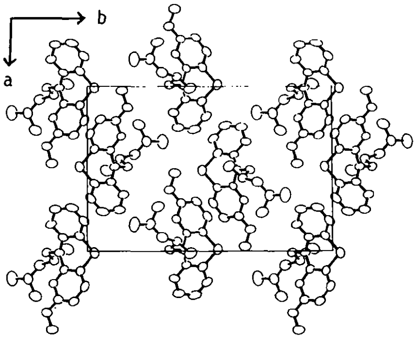

Fig. 2. Crystal structure projected down the c axis.

Helm, 1976). The other interatomic distances and bond angles in the phenothiazine ring are also normal (McDowell, 1976). The phenothiazine ring is folded about the axis passing through the S and N(*A*) atoms with a dihedral angle of 135·4°, which agrees well with that of the thiazinamium ion (135·6°) (Marsau & Cam, 1973). However, the geometry around the N(*A*) atom is approximately planar. N(*A*) deviates from the plane defined by C(1), C(13) and C(14) by 0·140 (2) Å.

The crystal structure viewed along the *c* axis is given in Fig. 2. All the intermolecular atomic contacts are usual van der Waals distances.

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Trifluoperazine Hydrochloride, a Phenothiazine Derivative

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Abstract. $C_{21}H_{26}F_3N_3S^{2+}.2Cl^-$, 10-[3-(4-methyl-1-piperazinyl)propyl]-2-trifluoromethylphenothiazine dihydrochloride (trade name Stelazine), monoclinic, $C2/c$, $a = 35{\cdot}290$ (2), $b = 5{\cdot}665$ (2), $c = 23{\cdot}595$ (2) Å, $\beta = 101{\cdot}24$ (8)°, $D_m = 1{\cdot}36$, $D_c = 1{\cdot}38$ Mg m^{-3}, $Z = 8$, final $R_w = 0{\cdot}097$. In the tricyclic group, C—S—C is 97·7 (7)°, C—S (mean) = 1·758 (15), C—N (mean) = 1·415 (16), C—F (mean) = 1·285 (16) Å. The angle between the planes of the benzene rings is 141·1°.

Introduction. A sample of trifluoperazine, kindly supplied by Smith, Kline & French Laboratories, was recrystallized from 333–353 K petroleum spirit with a small volume of ethyl alcohol to give colourless transparent needles. The systematic absences were *hkl*, $h + k \neq 2n$ and $h0l$, $l \neq 2n$, indicating space groups *Cc* or $C2/c$. Faint layer lines between the normal lines were observed in all oscillation films taken about **b**, but the corresponding Weissenberg photographs did not exhibit discrete reflexions. A Philips PW 1100 four-circle diffractometer with graphite-monochromated Mo $K\alpha$ ($\lambda = 0{\cdot}7107$ Å) radiation at 293 K was used to collect 2446 intensities, including 286 systematically extinct and 1112 unobserved [$I < 2\sigma(I)$], within a sphere $\theta_{\max} = 20°$. The ω-scan mode was used with a scan rate of 0·03° s^{-1} and a scan width of 0·9° in θ. Background counts of 15 s on each side of the reflexion were taken. The cell parameters were obtained by least squares from 25 reflexions. No absorption corrections were applied as μr for the crystal (0·4 × 0·3 × 0·05 mm) was <0·1.

The space group $C2/c$ was indicated by the analysis of the $|E|$ statistics and distribution. With *SHELX* 76 (Sheldrick, 1976), the correct phasing of eight reflexions, which were hand-selected out of 388 with $E_{\min} \geq 1{\cdot}2$, produced an E map which located all 28 non-H atoms of the main molecule. In addition, the two Cl atoms were represented by the three strongest peaks, and it was found that the subsequent refinement of the structure could not be continued without the inclusion of all three. Full-matrix least-squares refinement of coordinates and individual isotropic B's of non-H

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