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The Structures of (Dimethylaminopropyl)phenothiazine Drugs and Their Metabolites. III. Monode-*N*-methylchlorpromazine Sulphoxide, $C_{16}H_{17}ClN_2OS$, at 120 K

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Abstract. $M_r = 320{\cdot}7$, orthorhombic, *Pbca*, $a = 8{\cdot}088\ (2)$, $b = 19{\cdot}051\ (5)$, $c = 19{\cdot}604\ (5)$ Å, $V = 3021\ (1)$ Å^3, $Z = 8$, $D_m = 1{\cdot}35$, $D_x = 1{\cdot}410\ (1)$ g cm^{-3}, λ(Mo $K\alpha$) $= 0{\cdot}71069$ Å, $\mu = 3{\cdot}77$ cm^{-1}, $F(000) = 1408$, $R = 0{\cdot}039$ for 2140 contributing reflections. The central thiazine ring has a boat conformation with the sulphoxide O atom in an axial position. The 3-methylaminopropyl side chain has a conformation more similar to that of chlorpromazine sulphoxide than to that of chlorpromazine.

Introduction. The molecular and crystal structure of chlorpromazine sulphoxide (CPZSO), which is a metabolite of chlorpromazine (CPZ), has been reported from our laboratories (Hough, Hjorth & Dahl, 1985). CPZSO is less folded along the central S–N axis, and has a different conformation for the N(10)-substituted 3-dimethylaminopropyl side chain than CPZ (McDowell, 1969). (The structure of CPZSO was examined both at room temperature and at 120 K. Standard deviations in bond lengths and angles obtained from the low-temperature data were about half those obtained from the room-temperature data.)

CPZ is metabolized in man and other species by both sulphoxidation and oxidative *N*-demethylation, and a metabolite formed by a combination of these two pathways, 2-chloro-10-(3-methylaminopropyl)phenothiazine 5-oxide (monode-*N*-methylchlorpromazine sulphoxide, DCPZSO), has also been identified in man (Fishman & Goldenberg, 1960). This paper reports the molecular and crystal structure of DCPZSO at 120 K.

Experimental. DCPZSO kindly supplied by Rhône–Poulenc Industries, Paris, France. Single crystals by slow cooling of *m*-xylene solution in sealed glass ampoule, flat orthogonal prisms, with longest edge parallel to *a* axis. D_m by flotation in aqueous KI solution, single crystal $0{\cdot}1 \times 0{\cdot}2 \times 0{\cdot}4$ mm. Cell parameters from setting angles of 25 reflections ($\theta < 20°$). Data collection on Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Mo $K\alpha$ radiation, *hkl* ranges 0–10, 0–25, 0–25 respectively, 2θ range 4–56°. No decline in intensity of standards 173, 406 and 048 during data collection. 3727 unique reflections measured, 1587 unobserved [$I < 3\sigma(I)$]. Lp correction,

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no correction for absorption. Structure solved by direct methods (*MULTAN*; Germain, Main & Woolfson, 1971) and refined on $|F|$ with *XRAY*76 (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976), using 2140 reflections. Scattering factors from Cromer & Mann (1968) for C,O,N,S,Cl and Stewart, Davidson & Simpson (1965) for H. All H atoms located in ΔF map. Final refinement: non-hydrogen atoms anisotropic, H atoms isotropic, $R = 0.039$ and $wR = 0.049$ with $w = 1/\sigma^2(F)$, $(\Delta/\sigma)_{av} = 0.13$, $(\Delta/\sigma)_{max} = 0.57$, residual electron density in final ΔF map ± 0.4 e Å^{-3}. Calculations on a Cyber 171MP computer.*

Discussion. The positional parameters of DCPZSO are given in Table 1, and the molecular structure is shown in Fig. 1. Comparison of the bond lengths and angles (Table 2) in DCPZSO with those in CPZSO (Hough, Hjorth & Dahl, 1985) shows that with the exception of the C(6)–C(13) and C(8)–C(9) bonds, the phenothiazine systems in the two molecules are closely similar. It is interesting to note that, as in CPZSO, the C(6)–C(13) bond in CPZ (McDowell, 1969) is unusually long [1·422 (4) Å in CPZSO, 1·43 (7) Å in CPZ], but in DCPZSO it is normal [1·393 (6) Å].

The bond angles in the N(10)-substituted side chain and in the ring system are very similar for DCPZSO (Table 2) and CPZSO (Hough, Hjorth & Dahl, 1985). The largest differences in bond angles between the two structures are seen in the endocyclic S–C–C angles of the thiazine ring, which are 2·0–2·2 (4)° smaller in DCPZSO than in CPZSO. All the other angles differ by 1·3 (4)° or less (average differences 0·5°) between DCPZSO and CPZSO. In the structure of the parent compound CPZ (McDowell, 1969), the S–C–C angles are smaller than in the structures of its two metabolites CPZSO and DCPZSO, the difference being 1·5–2·3 (6)° between CPZ and DCPZSO.

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39817 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

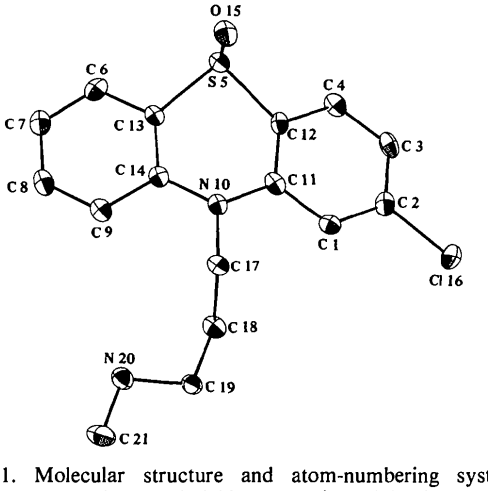

Fig. 1. Molecular structure and atom-numbering system of monode-*N*-methylchlorpromazine sulphoxide.

Table 1. *Positional parameters and equivalent isotropic thermal parameters* (Å$^2 \times 10^3$)

$U_{eq} = (U_1U_2U_3)^{1/3}$.

	x	y	z	U_{eq}
C(1)	0·6383 (4)	0·3334 (2)	0·1557 (2)	17 (2)
C(2)	0·7133 (5)	0·3318 (2)	0·2194 (2)	19 (2)
C(3)	0·7514 (5)	0·2707 (2)	0·2538 (2)	19 (2)
C(4)	0·7087 (5)	0·2083 (2)	0·2228 (2)	19 (2)
S(5)	0·5548 (1)	0·12602 (5)	0·13217 (5)	16·3 (5)
C(6)	0·5877 (4)	0·0846 (2)	0·0024 (2)	17 (2)
C(7)	0·5753 (5)	0·0905 (2)	−0·0680 (2)	21 (2)
C(8)	0·5426 (5)	0·1560 (2)	−0·0954 (2)	19 (2)
C(9)	0·5269 (5)	0·2150 (2)	−0·0550 (2)	17 (2)
N(10)	0·5329 (4)	0·2693 (2)	0·0579 (1)	15 (1)
C(11)	0·5988 (4)	0·2698 (2)	0·1238 (2)	14 (2)
C(12)	0·6326 (4)	0·2076 (2)	0·1591 (2)	16 (2)
C(13)	0·5691 (4)	0·1433 (2)	0·0439 (2)	13 (2)
C(14)	0·5422 (4)	0·2098 (2)	0·0167 (2)	13 (2)
O(15)	0·3744 (3)	0·1251 (2)	0·1496 (1)	23 (1)
Cl(16)	0·7669 (1)	0·41193 (5)	0·25588 (5)	26·3 (5)
C(17)	0·4838 (4)	0·3365 (2)	0·0266 (2)	15 (2)
C(18)	0·6260 (5)	0·3772 (2)	−0·0063 (2)	19(2)
C(19)	0·5628 (5)	0·4305 (2)	−0·0576 (2)	18 (2)
N(20)	0·5110 (4)	0·3958 (2)	−0·1208 (2)	21 (2)
C(21)	0·4579 (6)	0·4478 (3)	−0·1706 (2)	30 (2)

Table 2. *Bond lengths* (Å), *bond angles* (°) *and some relevant torsion angles* (°)

C(1)–C(2)	1·389 (5)	C(8)–C(9)	1·380 (6)
C(1)–C(11)	1·402 (6)	C(9)–C(14)	1·416 (5)
C(2)–C(3)	1·380 (6)	N(10)–C(11)	1·397 (5)
C(2)–Cl(16)	1·740 (4)	N(10)–C(14)	1·393 (5)
C(3)–C(4)	1·379 (6)	N(10)–C(17)	1·475 (5)
C(4)–C(12)	1·391 (5)	C(11)–C(12)	1·400 (6)
S(5)–C(12)	1·758 (4)	C(13)–C(14)	1·391 (5)
S(5)–C(13)	1·765 (4)	C(17)–C(18)	1·530 (6)
S(5)–O(15)	1·498 (3)	C(18)–C(19)	1·516 (6)
C(6)–C(7)	1·388 (6)	C(19)–N(20)	1·465 (5)
C(6)–C(13)	1·393 (6)	N(20)–C(21)	1·456 (6)
C(7)–C(8)	1·383 (6)		

C(2)–C(1)–C(11)	118·8 (4)	C(7)–C(6)–C(13)	120·5 (4)
C(1)–C(2)–C(3)	123·7 (4)	C(6)–C(7)–C(8)	118·2 (4)
C(1)–C(2)–Cl(16)	117·3 (3)	C(6)–C(13)–C(14)	121·7 (3)
C(1)–C(11)–N(10)	120·4 (3)	C(7)–C(8)–C(9)	122·0 (4)
C(1)–C(11)–C(12)	117·9 (3)	C(8)–C(9)–C(14)	120·3 (4)
C(3)–C(2)–Cl(16)	118·9 (3)	C(9)–C(14)–N(10)	120·9 (3)
C(2)–C(3)–C(4)	117·1 (4)	C(9)–C(14)–C(13)	117·3 (3)
C(3)–C(4)–C(12)	121·0 (4)	C(11)–N(10)–C(14)	121·4 (3)
C(4)–C(12)–S(5)	115·9 (3)	C(11)–N(10)–C(17)	118·8 (3)
C(4)–C(12)–C(11)	121·5 (4)	N(10)–C(11)–C(12)	121·8 (3)
C(12)–S(5)–C(13)	96·1 (2)	C(14)–N(10)–C(17)	118·6 (3)
C(12)–S(5)–O(15)	106·9 (2)	N(10)–C(14)–C(13)	121·8 (3)
S(5)–C(12)–C(11)	122·0 (3)	N(10)–C(17)–C(18)	114·5 (3)
C(13)–S(5)–O(15)	106·8 (2)	C(17)–C(18)–C(19)	111·4 (3)
S(5)–C(13)–C(6)	115·5 (3)	C(18)–C(19)–N(20)	110·8 (3)
S(5)–C(13)–C(14)	122·4 (3)	C(19)–N(20)–C(21)	110·1 (3)

C(11)–N(10)–C(17)–C(18)	−82·8 (3)
C(14)–N(10)–C(17)–C(18)	84·9 (3)
N(10)–C(17)–C(18)–C(19)	160·0 (3)
C(17)–C(18)–C(19)–N(20)	75·5 (4)
C(18)–C(19)–N(20)–C(21)	177·4 (4)

The deviations of the atoms of the rings from least-squares planes, calculated by equal weighting, range from 0·002 (4) to 0·014 (4) Å in both the aromatic rings.

As in the structures of its congeners CPZSO and levomepromazine sulphoxide (Hough, Hjorth & Dahl, 1982), the smallest deviations of individual atoms in DCPZSO from the least-squares plane were found for the C atoms of the central thiazine ring, and were 0·005 (4) for all four atoms. N(10) and S(5) lie on the same side of this plane, and the thiazine ring has a 'boat' conformation in DCPZSO as in CPZ and CPZSO, with the sulphoxide oxygen atom O(15) in an axial position. In both DCPZSO and CPZSO the thiazine ring is flatter than in CPZ, and the distance of N(10) from the plane of the four C atoms is 0·19 (4) and 0·18 (4) Å in DCPZSO and CPZSO respectively, and 0·40 (7) Å in CPZ.

The values of the two endocyclic S—C—C angles in DCPZSO lie between the corresponding values in CPZSO and CPZ, while the C—S—C angle in DCPZSO [96·1 (2)°] is slightly smaller than in CPZSO [96·8 (2)°] and in CPZ [97·3 (3)°]. This places the S atom in DCPZSO 0·57 (4) Å from the plane of the C atoms of the thiazine ring, a value that lies between that in CPZSO [0·44 (4) Å] and in CPZ [0·63 (7) Å].

The angle between the planes of the two phenyl rings is 155·3 (3)°, which is smaller than in CPZSO [159·5 (3)°] but outside the usual range of 134–146° which has been found for most psychoactive phenothiazine derivatives (Tollenaere, Moereels & Koch, 1977).

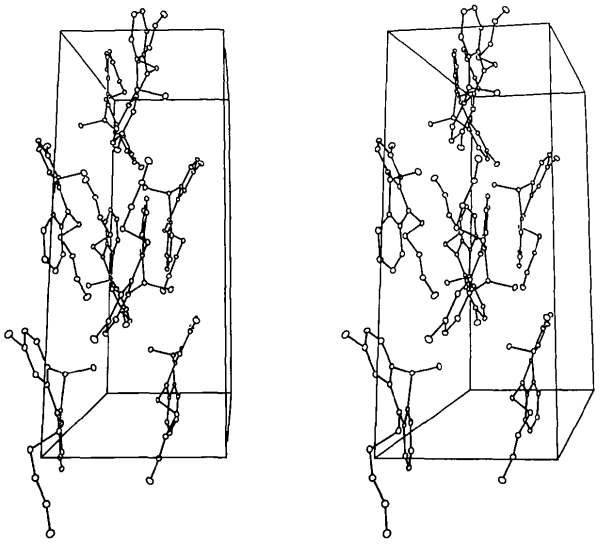

Fig. 2. Stereoscopic illustration of the molecular packing, viewed approximately down the *b* axis.

The N(10)—C(17) bond lies equatorial to the central thiazine ring, and the C(11)—N(10)—C(17)—C(18) torsion angle is −82·8 (3)° (Table 2), which places C(19) and the N(20) methylamino group on the opposite side of the plane of the thiazine ring, compared with the sulphoxide oxygen O(15). The same conformation was found in CPZSO, where the C(11)—N(10)—C(17)—C(18) torsion angle was −83·9 (3)°. As may be seen from Fig. 1, the terminal part of the side chain in DCPZSO is, however, tilted away from the C(2)-substituted Cl atom, which distinguishes the DCPZSO structure from the structures of CPZ and CPZSO.

Fig. 2 shows the crystal packing of DCPZSO. The molecules are packed in layers approximately perpendicular to the *a* axis. One of the intermolecular contact distances, between the terminal nitrogen atom N(20) of the side chain and O(15) of the neighbouring molecule, is 3·02 (4) Å, which is slightly smaller than the sum of the corresponding van der Waals radii (3·07 Å) (Bondi, 1964). This might indicate that a hydrogen bond is formed between the secondary amino group on the side chain and the O atom of the nearest sulphoxy group.

As discussed by Tollenaere, Moereels & Koch (1977), the terminal part of the side chain has relatively low rotational-energy barriers. It seems likely, therefore, that formation of hydrogen bonds between the methylamino group of the side chain and a sulphoxy group of another molecule may have forced the methylamino group away from the substituted phenyl ring. Both levomepromazine (Sato, Miki, Tanaka, Kasai, Ishimaru & Munakata, 1980), levomepromazine sulphoxide (Hough, Hjorth & Dahl, 1982), CPZ and CPZSO have torsion angles around the C—C bond in the side chain corresponding to the C(18)—C(19) bond in DCPZSO, which place the terminal amino group nearer to the substituted than to the unsubstituted phenyl ring.

The donation of monode-*N*-methylchlorpromazine sulphoxide by Rhône–Poulenc Industries, Paris, France, is gratefully acknowledged.

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Structure of 4:1 Sulfuric Acid–*N,N'*-(*p*-Phenylene)dibenzamide Complex, $C_{20}H_{16}N_2O_2.4H_2SO_4$

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Abstract. $M_r = 708{\cdot}66$, triclinic, $P\bar{1}$, $a = 9{\cdot}747\ (1)$, $b = 10{\cdot}313\ (1)$, $c = 7{\cdot}879\ (1)$ Å, $\alpha = 108{\cdot}67\ (1)$, $\beta = 111{\cdot}41\ (1)$, $\gamma = 89{\cdot}20\ (1)°$, $V = 693{\cdot}8$ Å^3, $Z = 1$, $D_x = 1{\cdot}696$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 4{\cdot}128$ cm^{-1}, $F(000) = 366$, $T = 173$ K, $R = 0{\cdot}026$, 2877 reflections with $I \geq 2\sigma(I)$. The structure of the 4:1 sulfuric acid complex with PPDB shows a more planar conformation of the three rings than does the uncomplexed analogue. The carbonyl oxygens are protonated to give a sulfuric acid/bisulfate salt. The sulfuric acid and bisulfate groups form hydrogen-bonded layers, which alternate with sheets of PPDB molecules.

Introduction. Aromatic polyamides (aramids) form a class of polymers having exceptional thermal and mechanical properties. One member of the class, poly(*p*-phenyleneterephthalamide) (PPTA) has been commercialized by Du Pont as KEVLAR® aramid fibers. In order to gain insight into the structure of PPTA, the crystal structure of *N,N'*-(*p*-phenylene)-dibenzamide (PPDB) has been determined (Harkema & Gaymans, 1977; Adams, Fratini & Wiff, 1978). It has been reported recently that certain aramids co-crystallize with solvent to form regular crystal solvates (Iovleva & Papkov, 1982). PPTA has been found to form a crystal solvate with sulfuric acid (Iovleva, Banduryan, Ivanova, Platonov, Milkova, Khanin, Volokhina & Papkov, 1979). In this paper we report the crystal structure of a 4:1 complex between sulfuric acid and PPDB.

Experimental. Colorless pyramidal crystal, *ca* 0·25 × 0·25 × 0·40 mm, obtained from slow cooling of supersaturated H_2SO_4 solution, sealed in capillary under N_2 in dry box; Syntex $R3$ diffractometer at low temperature (173 K). Lattice parameters from 23 reflections with $20 < 2\theta < 27°$ averaged with Friedel pairs; azimuthal scans indicated only statistical variation of intensities; no correction applied. 3456 data measured, $4 < 2\theta < 55°$; ω scans; h,k,l ±13, ±12, 10. Twenty reflections that exceeded the counting capacity of the detector omitted; data normalized for 10% fluctuation of intensity during collection (200 reflections collected during 6% standard intensity fluctuation omitted), 2877 unique data with $I > 2\sigma(I)$ (115 unobserved). Structure solved with some difficulty using direct methods (*MULTAN*; Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) in space group $P\bar{1}$. However, an examination of the thermal ellipsoids of some of the sulfate oxygens prompted investigation of the acentric equivalent. The centric domination was broken by a series of Fourier refinements, and further full-matrix least-squares refinement then proceeded smoothly using space group $P1$. All hydrogen atoms obtained from difference electron density maps and refined isotropically with remaining anisotropic non-hydrogen atoms (refinement on F, 490 parameters) to give $R = 0{\cdot}026$, $R_w = 0{\cdot}032$ and $S = 1{\cdot}49$ with av. Δ/σ 0·1. Statistical weights employed, with $\sigma(F) \propto 1/[\sigma(I)^2 + (0{\cdot}03I)^2]$. Coordinates used correspond to enantiomorph with lowest R value. Largest residuals in final difference map (0·20–0·25 e Å^{-3}) correspond to density between carbon atoms in phenyl rings. Scattering factors from *International Tables for X-ray Crystallography* (1974) and included terms for anomolous scattering of sulfur (*International Tables for X-ray Crystallography*, 1972). All incidental programs (data reduction, Fourier, least squares) were written by one of us (JCC). Plots made with *ORTEP* (Johnson, 1976).*

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39712 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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