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The Structures of (Dimethylaminopropyl)phenothiazine Drugs and Their Metabolites. I. Levomepromazine Sulphoxide at 120 K

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(*Received* 19 *January* 1982; *accepted* 29 *March* 1982)

Abstract

Levomepromazine sulphoxide [10-(3-dimethylamino-2-methylpropyl)-2-methoxyphenothiazine 5-oxide], $C_{19}H_{24}N_2O_2S$, crystallizes in the orthorhombic space group $P2_12_12_1$, $Z = 4$, with unit-cell dimensions: $a = 7{\cdot}636$ (2), $b = 12{\cdot}783$ (7), $c = 18{\cdot}317$ (7) Å and $V = 1787{\cdot}94$ Å^3 at 120 K; $a = 7{\cdot}689$ (2), $b = 12{\cdot}908$ (4), $c = 18{\cdot}599$ (5) Å, $V = 1845{\cdot}94$ Å^3, $D_m = 1{\cdot}223$, $D_c = 1{\cdot}239$ g cm^{-3} at 293 K. The structure was determined by the multiple tangent-formula method, and refined by full-matrix least squares to a final R of 0·037, using 2529 reflections. The sulphoxide O atom lies in the boat-axial conformation, and the N(10) side chain has the same conformation as that in chlorpromazine and several other psychoactive phenothiazine derivatives.

Phenothiazine drugs and their metabolites

The phenothiazine derivatives form a class of drugs which are used as neuroleptics, sedatives, analgesics and anti-emetics. Receptor-binding studies have demonstrated that they show high binding affinity to dopaminergic, anticholinergic, anti-adrenergic and anti-histaminic neurotransmitter receptors (Peroutka & Snyder, 1980; Bylund, 1981). The crystal structures of several phenothiazines have been reported in the literature, as reviewed by Horn, Post & Kennard (1975) and Tollenaere, Moereels & Koch (1977). The present studies are being carried out in parallel with pharmacodynamic and pharmacokinetic investigations, and will include metabolites of chlorpromazine (CPZ) and levomepromazine (LM), the latter also known as methotrimeprazine in the United States.

The chemical structures of LM, CPZ and their major metabolites in man are shown in Fig. 1. In addition to the metabolic pathways indicated in Fig. 1, levomepromazine is metabolized in man by *O*-demethylation of the R^1 substituent (Johnsen & Dahl, 1982), and both LM and CPZ may undergo several steps of biotransformation, yielding a large number of different metabolites. As reviewed previously (Dahl, 1981), the

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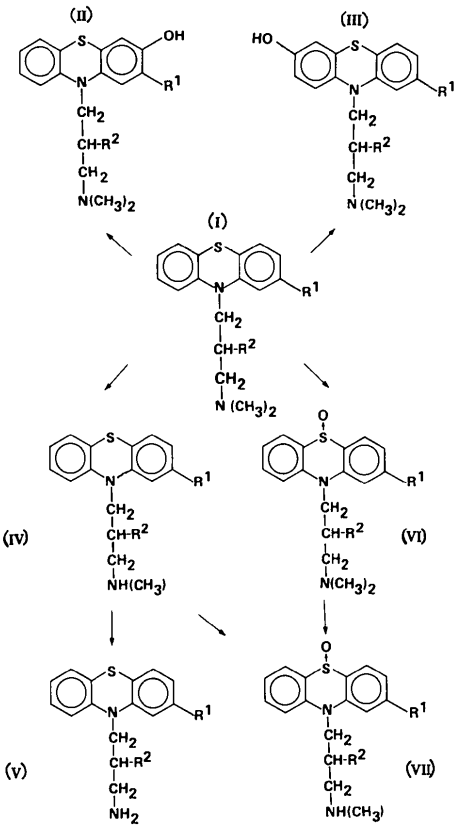


Fig. 1. Chemical structures of levomepromazine [(I) $R^1 = OCH_3$; $R^2 = CH_3$], chlorpromazine [(I) $R^1 = Cl$; $R^2 = H$], and their major metabolites in man.

pharmacological activity of these metabolites varies widely, even for compounds which differ only slightly in their chemical structures.

Levomepromazine is used in Europe mainly as a neuroleptic with pronounced sedative properties, and in the United States as an analgesic. Ten of its metabolites have been identified in the urine (Dahl & Garle, 1977; Johnsen & Dahl, 1982), and five of these have also been identified in the blood (Dahl & Garle, 1977; Dahl, Johnsen & Lee, 1982) of patients treated with this drug. Pharmacokinetic studies have shown that the sulphoxide metabolite of levomepromazine (LMSO) occurs in a considerably higher concentration than the parent drug in the urine (Dahl & Garle, 1977), and indeed that the plasma from psychiatric patients contains LMSO in concentrations two to four times as high as that of the parent drug after treatment with oral doses of levomepromazine (Dahl, 1976). Studies with isolated rat atria (Dahl & Refsum, 1976) and α-adrenergic receptors in brain membranes (Dahl & Hall, 1981) have shown that LMSO exhibits a certain pharmacological activity. The sulphoxide of chlorpromazine (part II of this series) is virtually inactive in both these systems, and shows no significant neuroleptic activity (Dahl, 1981).

Experimental

LMSO [(VI) $R^1 = OCH_3$, $R^2 = CH_3$] obtained from Leo AB, Helsingborg, Sweden, was recrystallized by slow cooling of a hexane solution in a sealed glass ampoule. The compound crystallized as needle prisms with the *a* axis parallel to the needle axis. The crystallographic parameters are given in the *Abstract* and some of the experimental parameters in Table 1.

Initial data collection was carried out at 293 K on an Enraf–Nonius CAD-4 diffractometer using graphite-monochromated Mo $K\alpha$ radiation. Out of a possible 2229 reflections, 933 were classified as observed, using a 2σ cutoff. The crystal remained stable under data collection. No correction for absorption effects was carried out ($\mu = 1{\cdot}89$ cm^{-1}).

The structure was solved using the *MULTAN* program package (Germain, Main & Woolfson, 1971), to give 16 chemically sensible atoms in the *E* map calculated using the 300 reflections with $|E| > 1{\cdot}1$. A

Table 1. *Experimental parameters*

Temperature (K)	293	120
2θ range (°)	4–56	4–65
Number of measured reflections	2229	3226
Number of reflections classified as observed	933	2529
Exclusion criterion	$I < 2\sigma(I)$	$I < 3\sigma(I)$
R	0·098	0·037
$R_w[w = 1/\sigma^2(F)]$	0·087	0·030

Table 2. *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)	0·4509 (3)	0·3047 (2)	0·3581 (1)	17
C(2)	0·5223 (3)	0·2095 (2)	0·3795 (1)	18
C(3)	0·6288 (3)	0·2009 (2)	0·4413 (1)	19
C(4)	0·6547 (3)	0·2895 (2)	0·4829 (1)	18
S(5)	0·5853 (1)	0·4877 (1)	0·5275 (1)	17
C(6)	0·6912 (3)	0·6795 (2)	0·4820 (1)	22
C(7)	0·6998 (3)	0·7631 (2)	0·4354 (1)	25
C(8)	0·6144 (4)	0·7564 (2)	0·3684 (1)	25
C(9)	0·5184 (3)	0·6683 (2)	0·3489 (1)	23
N(10)	0·4201 (2)	0·4914 (1)	0·3762 (1)	16
C(11)	0·4823 (3)	0·3946 (2)	0·3989 (1)	15
C(12)	0·5813 (3)	0·3853 (1)	0·4636 (1)	16
C(13)	0·5972 (3)	0·5897 (1)	0·4629 (1)	17
C(14)	0·5073 (3)	0·5831 (2)	0·3963 (1)	17
O(15)	0·4065 (2)	0·4936 (1)	0·5619 (1)	24
O(16)	0·4797 (2)	0·1281 (1)	0·3347 (1)	24
C(17)	0·5303 (3)	0·0253 (2)	0·3574 (1)	21
C(18)	0·2687 (3)	0·4934 (2)	0·3266 (1)	19
C(19)	0·1052 (3)	0·4477 (2)	0·3634 (1)	18
C(20)	0·0324 (3)	0·5238 (2)	0·4198 (1)	29
C(21)	−0·0329 (3)	0·4188 (2)	0·3063 (1)	22
N(22)	0·0241 (3)	0·3318 (1)	0·2600 (1)	23
C(23)	0·0009 (4)	0·2321 (2)	0·2965 (1)	31
C(24)	−0·0753 (4)	0·3311 (2)	0·1919 (1)	38

subsequent difference Fourier map revealed the positions of the rest of the non-hydrogen atoms.

Refinement of the non-hydrogen atoms using the 933 reflections observed at room temperature converged to $R = 0{\cdot}098$ (anisotropic temperature factors), but the standard deviations in the bond lengths were about 0·03 Å, and it was not possible to locate any of the H atoms in a difference map. A new data collection was therefore carried out at 120 K using a Syntex $P\bar{1}$ diffractometer. Data were collected out to $\theta = 32{\cdot}5°$, again using graphite-monochromated Mo $K\alpha$ radiation. Out of a possible 3226 reflections, 2529 were classified as observed using a 3σ cutoff. Cooling of the crystal resulted in 3% contraction of the unit cell. The crystal was stable to X-rays and the data were not corrected for absorption effects.

Atomic coordinates from the room-temperature structure were used as the initial coordinates for the refinement with the low-temperature data. Refinement of non-hydrogen atoms converged to $R = 0{\cdot}058$ using anisotropic temperature factors. All 24 H atoms in the structure were located in a difference Fourier map and subsequent refinement (H atoms isotropic) converged to $R = 0{\cdot}037$, and $R_w = 0{\cdot}030$ using reciprocal weighting ($w = 1/\sigma_F^2$) (Table 1).

Table 2 contains the positional and thermal parameters for the structure. Table 3 contains details of several planes in the molecule, and torsion angles in the N(10) side chain are given in Table 4. The molecular structure is illustrated in Fig. 2. The bond lengths are

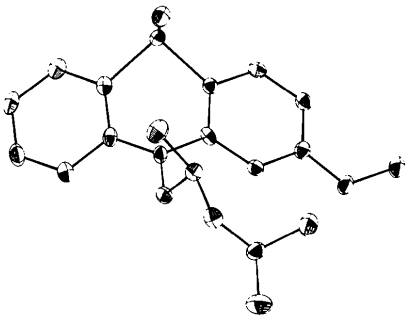
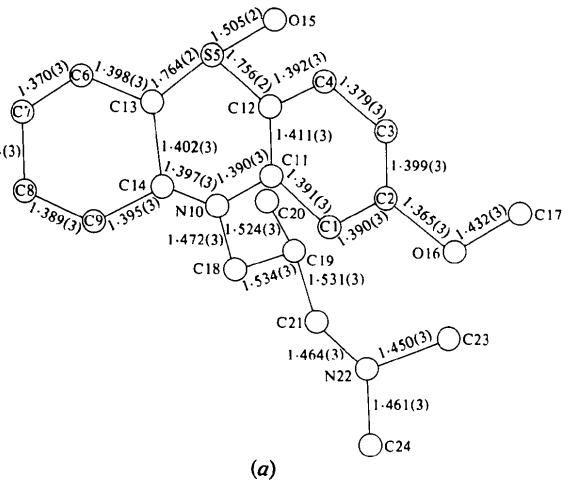
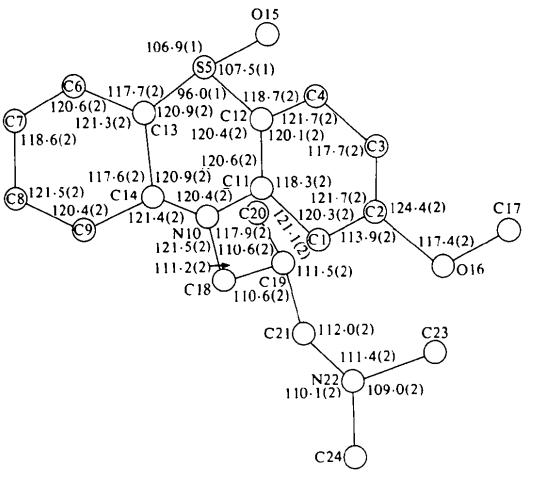


Fig. 2. *ORTEP* drawing (Johnson, 1971) of levomepromazine sulphoxide.



(*a*)



(*b*)

Fig. 3. (*a*) Bond lengths (Å) and atomic numbering scheme in levomepromazine sulphoxide. (*b*) Bond angles (°) in levomepromazine sulphoxide.

Table 3. *Least-squares planes in the structure*

The equation of the plane is $ax + by + cz = d$. Deviations from the planes (Å) are given in square brackets. E.s.d.'s on these values are 0·002 Å.

Plane constants			
a	*b*	*c*	*d*
−6·2477	−2·5960	9·8524	−0·0843

[C(1) 0·0048, C(2) 0·0157, C(3) −0·0180, C(4) −0·0001, C(12) 0·0205, C(11) −0·0228]

−6·2504	5·0086	7·6946	2·7911

[C(6) 0·0009, C(7) 0·0076, C(8) −0·0085, C(9) 0·0008, C(14) 0·0076, C(13) −0·0086]

−6·5339	0·7546	9·4174	0·8803

[C(11) −0·0231, C(12) 0·0230, C(13) −0·0212, C(14) 0·0214]

Table 4. *Dihedral torsion angles* (°) *in the* N(10) *side chain*

E.s.d.'s are 0·2°.

C(11)–N(10)–C(18)–C(19)	63·9
C(14)–N(10)–C(18)–C(19)	−120·4
N(10)–C(18)–C(19)–C(20)	73·5
N(10)–C(18)–C(19)–C(21)	−162·5
C(20)–C(19)–C(21)–N(22)	−169·5
C(19)–C(21)–N(22)–C(23)	79·7
C(19)–C(21)–N(22)–C(24)	−159·3
C(18)–C(19)–C(21)–N(22)	67·0
C(17)–O(16)–C(2)–C(3)	7·7
C(17)–O(16)–C(2)–C(1)	−172·8

given in Fig. 3(*a*), and Fig. 3(*b*) shows the bond angles.*

Discussion

Molecular conformation

As may be seen from Figs. 2–3 and Table 4, LMSO has a conformation similar to that of chlorpromazine (McDowell, 1969) and most of the other psychoactive phenothiazines (Tollenaere, Moereels & Koch, 1977). In the substituted aromatic ring the deviations of the C atoms from the least-squares plane are within ±0·023 Å, and the deviations of the C atoms of the other aromatic ring from the least-squares plane are within ±0·009 Å (Table 3). The central thiazine ring is in the expected boat conformation and the sulphoxide oxygen atom O(15) is in an axial position with respect to this ring. Comparison with several thioxanthene sulphoxides in the literature (Chu, 1975) shows that the axial position is preferred, although Jacobs & Sundaralingam (1969) have reported one case where the sulphoxide oxygen atom is equatorial.

The dihedral angle between the least-squares planes of the phenyl rings (*A* and *B*) is 144·7° and follows the approximate correlation with the C(11)–N(10)–C(14) angle which is found by comparison of bond angles and dihedral angles in a series of phenothiazine derivatives, which were tabulated by Chu & van der Helm (1975). The methoxy group at C(2) is rotated 7·8° out of the plane of the substituted benzene ring.

The C(11)–N(10)–C(18)–C(19) dihedral angle (Table 4) is similar to the C(13)–N–C(15)–C(16) dihedral angle in *N*-ethylphenothiazine (63°) (Chu & van der Helm, 1975). This conformation is, with the exception of methoxypromazine maleate (Marsau & Gauthier, 1973), normal for the N-substituted phenothiazine derivatives. The torsion angles in LMSO (Table 4) show that the side-chain backbone is approximately 'all-staggered', but is not 'all-*trans*' since the torsion angle about the C(19)–C(21) bond is 67° (180° for all-*trans*). As a consequence of this, N(22) approaches ring *A*, a situation which is similar to that in chlorpromazine (McDowell, 1969). Several authors [see, for example, Horn, Post & Kennard (1975)] have suggested that this feature may have pharmacological significance.

Bond lengths and angles

With the exception of the C(6)–C(7) bond (1·370 Å), all the aromatic C–C bonds are of normal length to within the accuracy of this determination. The two bridgehead bonds, C(11)–C(12) and C(13)–C(14), are, as is usual for phenothiazines, the longest of the aromatic C–C bonds. Comparison of the bond lengths and angles involving S(5) with the mean values of those tabulated by Chu & van der Helm (1975) (C–S = 1·766 Å, C–S–C = 98·5°) suggests that sulphoxidation has reduced the lengths of the C–S bonds slightly, and has reduced the C–S–C angle by about 2·5° (Fig. 3). Both the S–O bond, the S–C bonds, the C–S–C angle and the two C–S–O angles are similar to those in the thioxanthene oxides (Chu, 1975), giving an approximately tetrahedral S atom with a lone pair equatorial to the thiazine ring.

Comparison with the mean values (C–N = 1·415 Å, C–N–C = 118·4°) of the data tabulated by Chu & van der Helm (1975) suggests further that sulphoxidation has also resulted in a *ca* 0·02 Å contraction of the cyclic C–N bonds, and an opening of the endocyclic C–N–C angle by 2° (Fig. 3). The exocyclic C–N bond is of the normal length for an N_{sp^2}–C_{sp^3} bond, in spite of the fact that the endocyclic C–N bonds imply a higher degree of π–π interaction than is normal in phenothiazines. The cyclic nitrogen atom N(10) lies 0·3 Å out of the plane through C(11), C(14) and C(18), but the sum of the angles at N(10) is 359·8°, suggesting sp^2 hybridization of the N atom. Taken as a whole, the observed changes in the geometry of the thiazine ring suggest that sulphoxidation results in an increased involvement of π electrons from the S and N atoms.

The C–H bond lengths in the molecule lie between 0·94 and 1·05 Å, with estimated standard deviations of 0·02–0·03 Å. The angles and bond lengths between the non-hydrogen atoms in the 3-dimethylamino-2-methylpropyl side chain are also normal for a binding system of this type.

The crystal packing

Fig. 4 shows the crystal structure of LMSO. The molecules are packed to give layers of phenothiazine

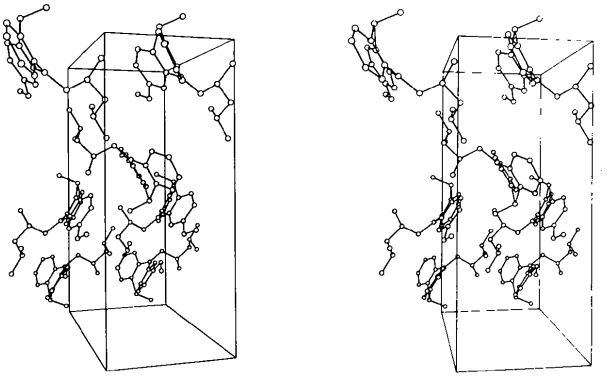


Fig. 4. Stereoscopic illustration of the molecular packing, viewed approximately down the *b* axis.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36869 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

nuclei perpendicular to the *c* axis. The 3-dimethylamino-2-methylpropyl side chains lie between these layers in a relatively empty environment, and do not seem to be subject to any severe conformational restraints.

None of the intermolecular contact distances are shorter than the sum of the appropriate van der Waals radii.

Levomepromazine sulphoxide was kindly supplied by Leo AB, Helsingborg, Sweden. We would also like to thank Dr B. Klewe at the Institute of Chemistry, University of Oslo, for collection of the low-temperature data.

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Structure of and Energy Calculations for 1,2,9,10,17,18-Hexadehydro[2.2.2]paracyclophane

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(*Received* 23 *November* 1981; *accepted* 3 *March* 1982)

Abstract

The crystal structure of 1,2,9,10,17,18-hexadehydro-[2.2.2]paracyclophane, $C_{24}H_{18}$, $M_r = 306{\cdot}41$, has been determined at 113 and 298 K. At low temperature, the space group is $P2_1/n$, with $Z = 4$, $a = 16{\cdot}914$ (7), $b = 10{\cdot}066$ (4), $c = 10{\cdot}292$ (3) Å and $\beta = 105{\cdot}90$ (3)°, $V = 1685$ Å^3, $D_x = 1{\cdot}208$ g cm^{-3}. At room temperature, the space group is $C2/c$, with $Z = 4$, $a = 17{\cdot}111$ (8), $b = 10{\cdot}132$ (6), $c = 10{\cdot}581$ (4) Å and $\beta = 106{\cdot}95$ (3)°, $V = 1755$ Å^3, $D_x = 1{\cdot}160$ g cm^{-3}. Intensity data were collected on a Syntex $P\bar{1}$ diffractometer with graphite-monochromatized Mo $K\alpha$ radiation. The low-temperature structure was determined with *MULTAN*; the room-temperature structure was deduced from that at low temperature. Each structure was refined by full-matrix least squares to $R = 0{\cdot}086$ (113 K) and $R = 0{\cdot}103$ (298 K), reflections with $F \geq 2\sigma(F)$ being used in the refinements (2325 at 113 K and 886 at 298 K). In the room-temperature structure, the molecule lies on a twofold axis of the crystal; in the low-temperature structure it is rotated approximately 4° (chiefly about the **c*** direction) from the room-temperature position, and has no symmetry, the individual rings having rotated an average of about 5° from their apparent positions at 298 K. Lattice-energy calculations with rigid molecules indicate that the room-temperature structure might be described by a 50:50 mixture of asymmetric molecules of the low-temperature geometry in two different positions; this hypothesis is supported by an examination of the Gaussian ellipsoids of the atoms at 298 K. Calculations suggest also that the apparent position found for the molecule at 298 K is not the most stable

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