MOLECULAR PHARMACOLOGY, 21:409–414

Chlorpromazine, Methotrimeprazine, and Metabolites

Structural Changes Accompanying the Loss of Neuroleptic Potency by Ring Sulfoxidation

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Received June 25, 1981; Accepted October 7, 1981

SUMMARY

The 3-dimensional molecular structures of methotrimeprazine, methotrimeprazine sulfoxide, and chlorpromazine sulfoxide were examined by X-ray crystallography. Previous studies of their dopamine receptor binding affinities have indicated that both chlorpromazine sulfoxide and methotrimeprazine sulfoxide lack neuroleptic potency. The crystal structures of methotrimeprazine and its sulfoxide were similar to the previously published structure of chlorpromazine. The sulfoxide metabolite of chlorpromazine, on the other hand, had a different conformation of the side chain. A boat axial conformation of the sulfoxy group was found for both metabolites. The crystal structures suggest that the apparent loss of neuroleptic potency by biotransformation of the phenothiazine drugs to their ring sulfoxides is caused by the introduction of the sulfoxide group itself, and not by concurrent conformational changes in the rest of the molecule.

INTRODUCTION

Since the crystal structure of chlorpromazine was published in 1969 (1), there have been a number of reports on the molecular conformations and structure-activity relationships of neuroleptic drugs, and different molecular moieties have been proposed to be responsible for their antipsychotic effects (2, 3).

The phenothiazines are often mentioned as the prototype class of drugs which have a large number of different metabolites, and the impact of active metabolites on their effect in man has been the subject of several recent studies (4). It has been demonstrated that the 7-hydroxy metabolite of chlorpromazine has an antipsychotic effect in psychiatric patients (5), and the crystal structure of this metabolite has been reported (6). The ring sulfoxides are among the major metabolites of the phenothiazine drugs in man and in other species, but as these metabolites generally have low pharmacological activity (4), their molecular conformations seem to have received little attention.

The binding affinity of chlorpromazine, methotrimeprazine (levomepromazine), and their sulfoxides to central $alpha_1$-adrenergic and dopaminergic receptors in the rat have been examined by radioreceptor binding techniques (7). As shown in Table 1, methotrimeprazine sulfoxide had relatively low affinity in the dopamine receptor binding test but had a certain potency in the $alpha_1$-adrenergic binding test, whereas chlorpromazine sulfoxide had low affinity in both systems.

Since the sulfoxides of chlorpromazine and methotrimeprazine thus appeared to have pharmacological profiles largely different from those of their parent drugs, in spite of the minor differences in their chemical structures (Fig. 1), we examined their 3-dimensional molecular structures in the solid state in order to obtain information about any possible conformational changes accompanying the sulfoxidation process. The crystal structure of methotrimeprazine had not previously been reported, and was therefore also examined for comparison.

METHODS

Methotrimeprazine hydrochloride and methotrimeprazine sulfoxide (base) were donated by AB Leo (Helsingborg, Sweden) and chlorpromazine sulfoxide (base) by Rhône-Poulenc Industries (Paris, France). Crystals of the free bases of the three compounds were grown from hexane solutions, by slowly cooling in sealed glass capillaries.

The densities were determined by the flotation method, and the space groups and dimensions of the unit cells were found by the Weissenberg film technique.

The reflection intensities were recorded with a com-

Some of the findings described in this paper were presented at the XVI Scandinavian Congress of Physiology and Pharmacology (Oulu, July 1979) and at the 4th International Symposium on Phenothiazines and Structurally Related Drugs (Zürich, September 1979).

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0026-895X/82/020409-06$02.00/0

TABLE 1

Relative receptor binding affinity (chlorpromazine = 1) of methotrimeprazine, chlorpromazine, and their sulfoxides in the rat brain

Data are from Dahl and Hall (7).

	Relative potencies: receptor type, brain region, ligand	
	Dopaminergic, striatum, [^{3}H]spiroperidol	*Alpha*$_1$-adrenergic, cortex, [^{3}H]WB4101
Chlorpromazine	1.00	1.00
Chlorpromazine sulfoxide	0.02	0.07
Methotrimeprazine	0.63	1.96
Methotrimeprazine sulfoxide	0.03	0.47

puter-controlled automatic diffractometer (CAD 4), using monochromatic CuKα radiation. The intensities were measured both at room temperature and at −152° for the sulfoxides, and only at −152° for methotrimeprazine.

The structure of chlorpromazine sulfoxide was solved by Patterson analysis, and the structures of methotrimeprazine and methotrimeprazine sulfoxide were solved using MULTAN, a multiple tangent-formula direct method (8). Full crystallographic data will be published elsewhere.

RESULTS

Pertinent crystallographic data for the three compounds are given in Table 2. In both cases the sulfoxides crystallized in the same space group as their parent drug, and the unit cell volume increased by an amount which approximates to the Van der Waals volume of the inserted oxygen atoms.

The atomic coordinates are given in Table 3, and the symbols used to identify the atoms are shown in Fig. 2. ORTEP plots of the compounds, viewed from two different angles, are shown in Fig. 3 and Fig. 4. The sulfoxy group showed a boat axial conformation in both sulfoxides. As shown in Figs. 3 and 4, the rest of the methotrimeprazine sulfoxide molecule and methotrimeprazine itself had the same conformation as chlorpromazine. Chlorpromazine sulfoxide, on the other hand, showed another conformation of the side chain, with the terminal nitrogen atom appearing on the opposite side of the ring system (Fig. 4) and at a distance from the center of the two benzene rings which was different from that of chlorpromazine (Table 4). Chlorpromazine sulfoxide also showed a wider angle between the two benzene rings of the phenothiazine nucleus than the other compounds examined, as shown in Table 4.

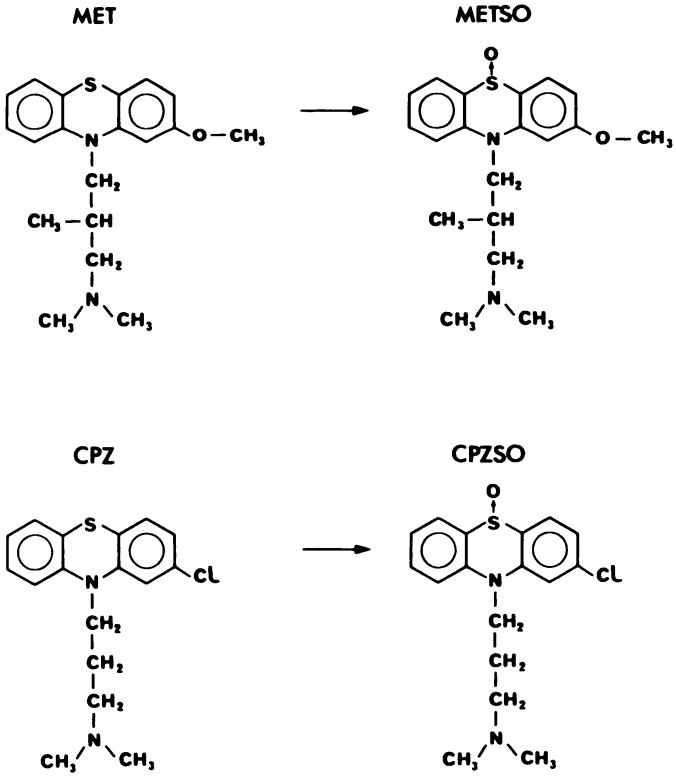

FIG. 1. *Chemical structures of methotrimeprazine (MET), chlorpromazine (CPZ), and their sulfoxides (METSO, CPZSO)*

DISCUSSION

Potential energy calculations and NMR analysis have demonstrated that the phenothiazine drugs must be regarded as flexible molecules, and it has been emphasized that crystal structural data therefore should be supplemented with information about their conformation in solution, in order to arrive at their most plausible conformation at the receptor site (9). However, comparison of the known molecular and crystal structures of different psychoactive phenothiazines has revealed that they have certain geometrical characteristics in common. One of their common features is that the side chain seems always to be tilted toward the substituted benzene ring (10, 11). It has been proposed that a similar deviation of the side chain of thioxanthene drug molecules would enable the 2-substituent to enter into Van der Waal's attractive forces with the side chain, which could account for the greater potency of the *cis* than of the *trans* forms of the thioxanthenes (2). As shown in Fig. 4 and Table 1, the side chain was also tilted toward the substituted benzene ring in chlorpromazine sulfoxide and methotrimeprazine sulfoxide, both of which have low dopamine receptor binding affinity and may, therefore, be presumed to lack neuroleptic potency. This demonstrates that such deviation of the side chain, although possibly essential for the neuroleptic potency, is not uniquely observed for the psychoactive phenothiazine derivatives.

Another common feature of the phenothiazine drug molecules is that the two planar benzene rings of the phenothiazine nucleus are folded about the central S-N axis. In the unsubstituted phenothiazine molecule, the angle between the two planes is 153° (12), whereas the corresponding angle usually is between 134° and 146° in the psychoactive phenothiazine derivatives (10, 11, 13). In methoxypromazine maleate, which is considered a relatively weak neuroleptic, the ring system was more flat, with an angle of 157° between the two planes (14).

As may be noted from Table 4, the ring system in chlorpromazine sulfoxide was also relatively flat, with an

TABLE 2

Crystal structural data for chlorpromazine, methotrimeprazine, and their sulfoxides

	Space group	Molecules in unit cell	Density at 20°		Cell dimensions			Cell volume
			Observed	Calculated	a	b	c	
			g/cm^3			Å		$Å^3$
Chlorpromazine[a]	$Pbca$	8	1.29	1.285	9.23	15.20	23.50	3297
Chlorpromazine sulfoxide	$Pbca$	8	1.29	1.292	10.357	14.090	23.585	3442
Methotrimeprazine	$P2_12_12_1$	4	1.25	1.253	7.447	12.641	18.494	1741[b]
Methotrimeprazine sulfoxide	$P2_12_12_1$	4	1.23	1.239	7.636	12.783	18.317	1788[b]

[a] The data for chlorpromazine are from McDowell (1).

[b] Data measured at −152°.

angle of 159.5° between the planes of the two benzene rings. This angle is larger than in any other phenothiazine derivative for which the crystal structure has been determined. On the other hand, the corresponding angles in both methotrimeprazine sulfoxide and methotrimeprazine were within the range of the values that previously have been observed for the psychoactive phenothiazine derivatives. However, it appears that the angle between the planes of the two benzene rings is very much dependent on the crystal packing. It has been found that both thioridazine (13) and trifluopromazine hydrochloride (15) crystallize with two molecules in the asymmetrical unit, and that the angle between the planes of the two benzene rings is different in the two molecules in the asymmetrical unit, the difference being 11.4° for thioridazine and 6.6° for trifluopromazine hydrochloride. Therefore, too much emphasis should not be attached to the fact that the ring system in chlorpromazine sulfoxide is relatively flat.

In view of their molecular conformations in the solid state (Figs. 3 and 4), it is interesting to note that methotrimeprazine sulfoxide had a certain affinity for the $alpha_1$-adrenergic receptor, while this was not found for chlorpromazine sulfoxide (Table 1). With the limitations inherent in molecular structural data which have been obtained in the solid state only, the results of the present study would indicate that different conformations of the side chain might be the reason for the difference between the affinities of chlorpromazine sulfoxide and, on the other hand, of methotrimeprazine sulfoxide, methotrimeprazine, and chlorpromazine, for central $alpha_1$-adrenergic receptors. This would imply that central $alpha_1$-adrenergic receptors bind to parts of the phenothiazine

TABLE 3

Fractional atomic coordinates of methotrimeprazine sulfoxide (METSO), methotrimeprazine (MET), and chlorpromazine sulfoxide (CPZSO), determined at −152°

Estimated standard deviations are given in parentheses (axis length times 10^{-4}). The atoms are numbered as shown in Fig. 2.

Atom no.	METSO			MET			CPZSO		
	X	Y	Z	X	Y	Z	X	Y	Z
C-1	0.4509 (3)	0.3047 (2)	0.3581 (1)	1.0404 (6)	0.6977 (3)	0.8604 (2)	0.4241 (3)	0.7245 (3)	0.8636 (2)
C-2	0.5223 (3)	0.2095 (2)	0.3795 (1)	0.9657 (5)	0.7942 (3)	0.8811 (2)	0.5201 (4)	0.7705 (3)	0.8951 (2)
C-3	0.6288 (3)	0.2009 (2)	0.4413 (1)	0.8686 (5)	0.8051 (3)	0.9446 (2)	0.6106 (4)	0.8334 (3)	0.8715 (2)
C-4	0.6547 (3)	0.2895 (2)	0.4829 (1)	0.8528 (5)	0.7158 (3)	0.9892 (2)	0.6010 (4)	0.8507 (3)	0.8133 (2)
C-5	0.5853 (1)	0.4877 (1)	0.5275 (1)	0.9393 (1)	0.5148 (1)	1.0337 (1)	0.4969 (1)	0.8481 (1)	0.7093 (1)
C-6	0.6912 (3)	0.6795 (2)	0.4820 (1)	0.8171 (5)	0.3195 (3)	0.9892 (2)	0.4296 (4)	0.7364 (3)	0.6213 (2)
C-7	0.6998 (4)	0.7631 (2)	0.4354 (1)	0.7985 (5)	0.2385 (3)	0.9390 (2)	0.3586 (4)	0.6673 (3)	0.5925 (2)
C-8	0.6144 (4)	0.7564 (2)	0.3684 (1)	0.8731 (6)	0.2492 (3)	0.8700 (2)	0.2736 (4)	0.6092 (3)	0.6237 (2)
C-9	0.5184 (4)	0.6683 (2)	0.3489 (1)	0.9701 (5)	0.3399 (3)	0.8520 (2)	0.2594 (4)	0.6185 (3)	0.6828 (1)
N-10	0.4201 (2)	0.4914 (1)	0.3762 (1)	1.0996 (4)	0.5113 (2)	0.8877 (2)	0.3207 (3)	0.6957 (2)	0.7716 (1)
C-11	0.4823 (3)	0.3946 (2)	0.3969 (1)	1.0250 (5)	0.6103 (3)	0.9048 (2)	0.4147 (3)	0.7430 (3)	0.8042 (1)
C-12	0.5813 (3)	0.3853 (2)	0.4636 (1)	0.9327 (5)	0.6216 (3)	0.9717 (2)	0.5050 (3)	0.8078 (2)	0.7798 (1)
C-13	0.5972 (3)	0.5897 (2)	0.4629 (1)	0.9165 (5)	0.4097 (3)	0.9711 (2)	0.4162 (3)	0.7475 (3)	0.6812 (2)
C-14	0.5073 (3)	0.5831 (2)	0.3963 (1)	0.9970 (5)	0.4195 (3)	0.9036 (2)	0.3326 (3)	0.6876 (3)	0.7125 (1)
O-15	0.4065 (2)	0.4936 (1)	0.5619 (1)	—	—	—	0.4032 (2)	0.9304 (2)	0.7074 (1)
Cl-16	—	—	—	—	—	—	0.5314 (1)	0.7431 (1)	0.9671 (1)
O-16	0.4798 (2)	0.1281 (1)	0.3447 (1)	0.9963 (4)	0.8752 (2)	0.8329 (1)	—	—	—
C-17	0.5303 (3)	0.0253 (2)	0.3574 (1)	0.9557 (7)	0.9806 (3)	0.8568 (2)	—	—	—
C-18	0.2687 (3)	0.4934 (2)	0.3266 (1)	1.2427 (5)	0.5079 (3)	0.8330 (2)	0.2246 (3)	0.6346 (3)	0.8008 (1)
C-19	0.1052 (3)	0.4477 (2)	0.3634 (1)	1.4117 (5)	0.5601 (3)	0.8641 (2)	0.2747 (3)	0.5329 (3)	0.8128 (1)
C-20	0.0324 (3)	0.5238 (2)	0.4998 (1)	1.5005 (5)	0.4863 (3)	0.9193 (2)	—	—	—
C-21	−0.0329 (3)	0.4188 (2)	0.3063 (1)	1.5451 (6)	0.5889 (3)	0.8037 (2)	0.2048 (4)	0.4890 (3)	0.8638 (2)
N-22	0.0241 (3)	0.3318 (2)	0.2600 (1)	1.4763 (5)	0.6724 (2)	0.7557 (2)	0.2470 (3)	0.5322 (2)	0.9180 (1)
C-23	0.0009 (4)	0.2321 (2)	0.2965 (1)	1.4843 (6)	0.7772 (3)	0.7894 (2)	0.3725 (4)	0.4925 (3)	0.9369 (2)
C-24	−0.0754 (4)	0.3311 (2)	0.1919 (1)	1.5793 (7)	0.6748 (3)	0.6887 (2)	0.1491 (5)	0.5153 (4)	0.9624 (2)

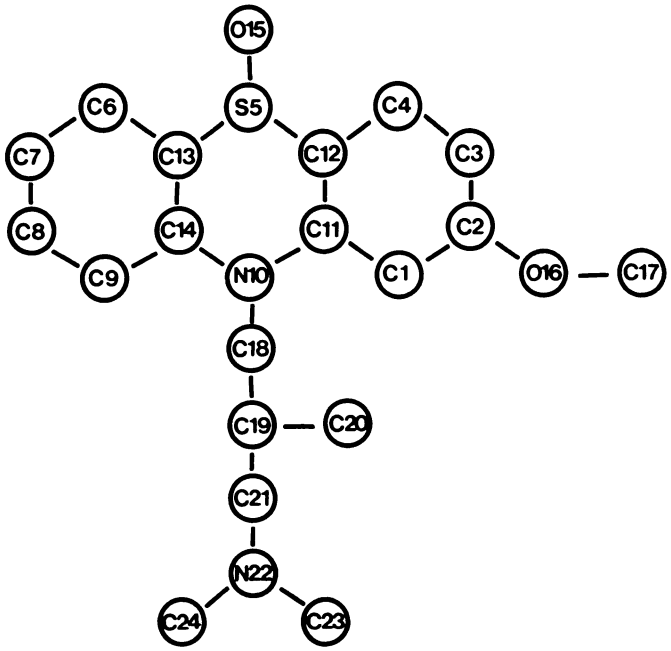

FIG. 2. *Identification of the atoms which are referred to in Table 3*
The chlorine atom in chlorpromazine sulfoxide has the same position as atom O-16 in this figure.

drug molecules other than the moiety containing the sulfur atom. Firmer conclusions about the importance of the conformation of the side chain for *alpha*$_1$-adrenergic binding, however, require experimental data on the molecular structure of other analogues with low *alpha*$_1$-adrenergic binding affinity, and information about the energies of different conformers of each analogue and the energy barriers between them.

Various attempts have been made to explain the dopamine receptor blocking properties of neuroleptic drugs in terms of their ability to mimic the 3-dimensional molecular structure of dopamine (2, 10, 16), but others have challenged this hypothesis (9). It has also been suggested that, because of their conformational flexibility, phenothiazine drug molecules may exist in different conformations in which either the sulfur atom or the 2-substituent on the phenothiazine nucleus can interact with a dopaminergic receptor (17).

The observation that methotrimeprazine sulfoxide, possessing relatively low affinity for central dopaminergic receptors (Table 1), has the same molecular conformation in the solid state as chlorpromazine and methotrimeprazine suggests that the loss of neuroleptic potency by ring sulfoxidation of methotrimeprazine is caused by the introduction of the sulfoxide group itself, and not by concurrent conformational changes in the rest of the

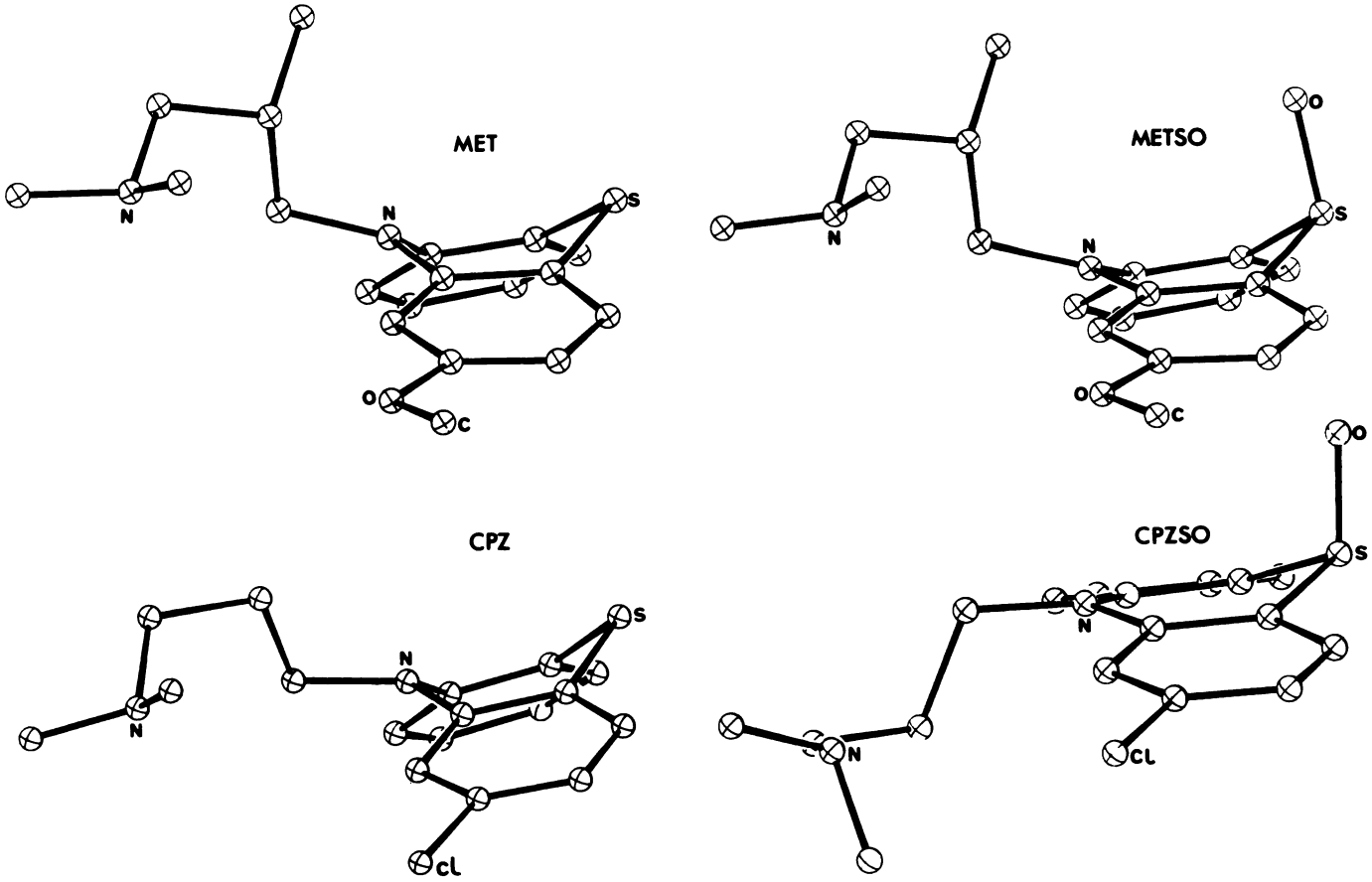

FIG. 3. *ORTEP plots of methotrimeprazine (MET), methotrimeprazine sulfoxide (METSO), chlorpromazine (CPZ), and chlorpromazine sulfoxide (CPZSO), viewed perpendicular to the S-N axis of the phenothiazine nucleus*
The hydrogen atoms are not drawn. Atomic coordinates published by McDowell (1) and a fixed isotropic temperature factor were used for chlorpromazine.

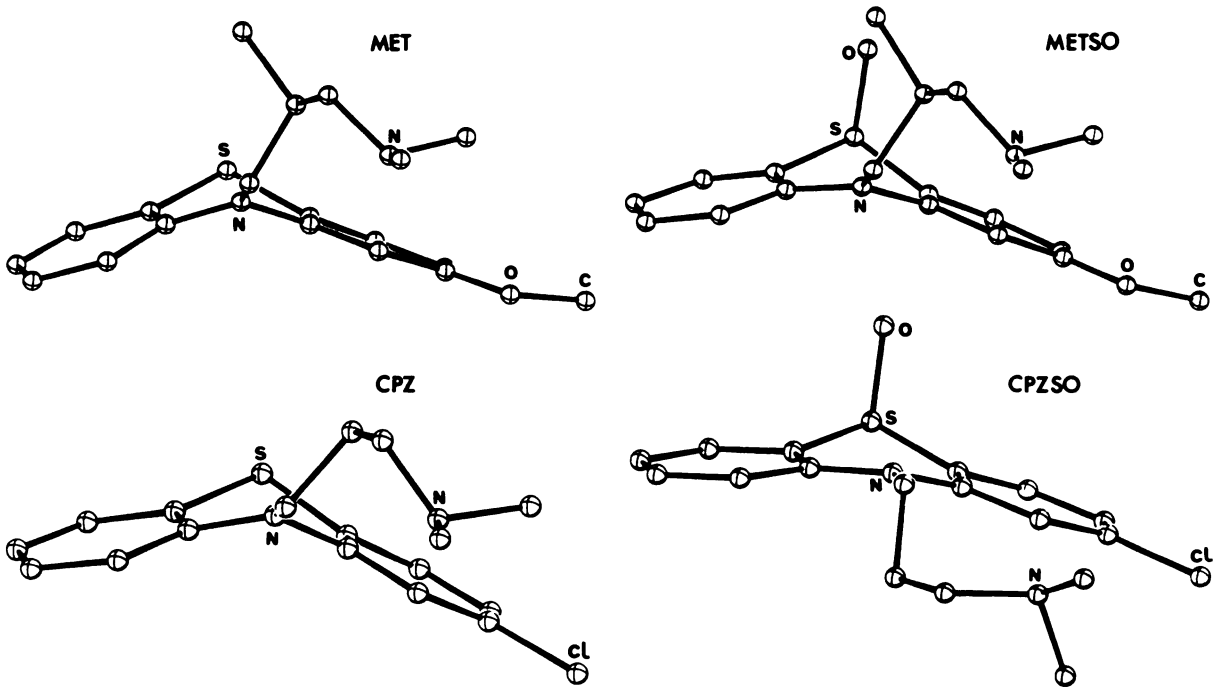

FIG. 4. *ORTEP plots of methotrimeprazine (MET), methotrimeprazine sulfoxide (METSO), chlorpromazine (CPZ), and chlorpromazine sulfoxide (CPZSO), viewed along the S-N axis of the phenothiazine nucleus*

The hydrogen atoms are not drawn. Atomic coordinates published by McDowell (1) and a fixed isotropic temperature factor were used for chlorpromazine.

molecule. This supports the hypothesis that it is the region of the phenothiazine nucleus containing the sulfur atom that binds to dopaminergic receptors. Steric hindrance of the binding to the dopamine receptor, caused by the sulfoxy group, could thus explain the low binding affinities of the ring sulfoxide metabolites of chlorpromazine and methotrimeprazine. However, the reduced affinity to dopamine receptors could also be due to the change in the electron density of the thiazine ring which takes place by sulfoxidation.

It has been demonstrated that psychoactive phenothiazine derivatives have a high binding affinity not only for dopamine receptors, but also for *alpha*$_1$-adrenergic, muscarinic cholinergic, histamine H_1, and serotonin receptors in brain membranes, and the hypothesis that their antipsychotic effects could be associated with actions at sites other than dopamine receptors has been examined (18). However, whether their binding affinity for different receptor types is due to their ability to attain different conformations or is caused by binding to different parts of the phenothiazine molecule is still unknown. We believe that the present work, and similar studies on the molecular conformations of chemically similar derivatives possessing highly different receptor binding affinities, should help to shed light upon the molecular pharmacology of the phenothiazine drugs.

TABLE 4

R-factors after structure refinement and some geometrical characteristics of the molecules

The data were derived from intensities measured at −152°: angle (φ) between the best planes of the benzene rings, and distances of the terminal nitrogen atom from the center of the substituted (N–A) and unsubstituted (N–B) benzene ring.

	R-Factors after structure refinement[a]	φ	Distances	
			N–A	N–B
			Å	
Chlorpromazine[b]	—	139.4°	5.12	6.81
Chlorpromazine sulfoxide	0.051	159.5	4.85	6.63
Methotrimeprazine	0.045	138.0	5.05	6.84
Methotrimeprazine sulfoxide	0.037	144.7	5.01	6.84

[a] Isotropic temperature factors were used for the hydrogen atoms and anisotropic temperature factors were used for other atoms.

[b] Data from McDowell (1), acquired at room temperature.

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