

Fig. 4. Projections parallèlement à l'axe Oz du repère D . Les dessins ont été obtenus à l'aide du programme *ORTEP*, les ellipsoïdes d'agitation thermique étant à 50% de probabilité. (a) Molécule *A*. (b) Molécule *B*.

fait superposables, particulièrement au niveau des cycles *A* et *B*. La molécule *A*, la plus courbée, adopte la conformation de la canrenone (Weeks, Hazel &

Duax, 1976). D'autre part, la molécule *B*, plus plane, se superpose à la spironolactone (Dideberg & Dupont, 1972). Le squelette de ces molécules possède donc une certaine souplesse. La Fig. 3 illustre ces remarques. Sur la Fig. 4, on constate que les ellipsoïdes d'agitation thermique pour les molécules *A* et *B* ont des orientations tout à fait semblables.

Un calcul d'énergie intermoléculaire prenant en compte les interactions de van der Waals et les termes prépondérants de l'énergie électrostatique, conduit à une énergie d'interaction moyenne de l'ordre de $-0,8$ kcal/atome (C,H,O) pour les deux molécules. La principale différence de répartition d'énergie se situe au niveau du cycle *B*.

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10-Methyl-2,2'-bis(trifluoromethyl)-7,10'-biphenothiazine

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Abstract. $C_{27}H_{16}F_6N_2S_2$, monoclinic, $P2_1/c$, $a = 7.60$ (1), $b = 26.76$ (3), $c = 13.13$ (2) Å, $\beta = 91.2$ (9)°; $Z = 4$, $D_x = 1.48$, $D_m = 1.46$ g cm $^{-3}$ (by flotation). This study has established that the two phenothiazines dimerize in a 7,10' link rather than a 3,10' link as suggested in a previous study by NMR.

Introduction. 10-Methyl-2,2'-bis(trifluoromethyl)-7,10'-biphenothiazine was obtained as a dimeric product from the alkylation of 2-trifluoromethylphenothiazine with methyl iodide (Nagarajan, David & Gould, 1974) and was tentatively assigned a structure based on the proton NMR spectra. We have under-

Table 1. *Fractional coordinates* ($\times 10^4$)

	<i>x</i>	<i>y</i>	<i>z</i>
S(5)	173 (2)	1608 (0)	7934 (1)
S(5')	-5236 (3)	3239 (0)	11419 (2)
N(10)	3461 (5)	1464 (1)	9265 (3)
N(10')	-1885 (5)	2657 (1)	10927 (3)
C(1)	4138 (7)	651 (1)	8578 (4)
C(2)	3654 (9)	264 (2)	7871 (5)
C(3)	2133 (8)	265 (2)	7309 (5)
C(4)	995 (8)	665 (2)	7392 (4)
C(6)	-829 (8)	2134 (1)	9587 (3)
C(7)	-491 (6)	2346 (1)	10517 (4)
C(8)	1071 (6)	2274 (1)	11093 (4)
C(9)	2384 (7)	1977 (1)	10674 (4)
C(11)	3030 (6)	1058 (2)	8608 (4)
C(12)	1470 (7)	1067 (2)	8026 (4)
C(13)	552 (6)	1853 (1)	9199 (3)
C(14)	2105 (5)	1755 (1)	9718 (3)
C(15)	4917 (13)	-161 (2)	7775 (7)
C(16)	5268 (6)	1474 (2)	9726 (5)
C(1')	-461 (7)	3351 (2)	10173 (3)
C(2')	-482 (7)	3862 (2)	9878 (4)
C(3')	-1947 (7)	4183 (2)	10102 (4)
C(4')	-3307 (8)	3977 (2)	10602 (4)
C(6')	-5375 (8)	2533 (2)	12880 (4)
C(7')	-4939 (8)	2086 (2)	13348 (4)
C(8')	-3438 (8)	1826 (2)	12997 (5)
C(9')	-2441 (8)	2012 (2)	12206 (4)
C(11')	-1899 (6)	3175 (1)	10662 (3)
C(12')	-3299 (6)	3479 (1)	10879 (3)
C(13')	-4399 (7)	2714 (2)	12066 (4)
C(14')	-2886 (6)	2466 (2)	11743 (4)
C(15')	1037 (11)	4057 (3)	9320 (6)
F(1)	5403 (11)	-376 (2)	8633 (6)
F(2)	4313 (17)	-525 (3)	7275 (11)
F(3)	6428 (10)	-20 (2)	7426 (8)
F(1')	2494 (7)	3952 (4)	9661 (7)
F(2')	1111 (10)	4546 (2)	9251 (10)
F(3')	1042 (14)	3917 (5)	8397 (6)
SOLV(1)	0 (20)	0 (5)	0 (16)
SOLV(2)	-1891 (20)	542 (6)	-345 (15)
SOLV(3)	-526 (23)	410 (9)	345 (13)
SOLV(4)	-136 (24)	749 (6)	987 (10)

taken the X-ray crystallographic investigation of the crystalline product to establish its structural assignment and obtain the conformational details. A preliminary report was recently presented (Go & Kartha, 1976).

Crystals are yellow thin needles with *c* parallel to the needle axis. Three-dimensional data were collected on a General Electric XRD-3 manual diffractometer to $2\theta = 120^\circ$ from a crystal approximately $0.1 \times 0.2 \times 0.5$ mm in size; Ni-filtered Cu *K* α radiation ($\lambda = 1.5418 \text{ \AA}$) was used with the stationary-crystal stationary-counter method (Furnas & Harker, 1955). The measured intensities were converted to structure amplitudes in the usual manner and corrected for Lorentz-polarization, as well as for empirical absorption and α_1, α_2 -splitting (Tulinsky, Worthington & Pignataro, 1959). Of 4098 independent reflections measured, 2926 had $I > 2\sigma(I)$ and were used for least-squares refinement [$\sigma(I)$ was determined from counting statistics].

The structure was solved by direct statistical methods (Karle & Karle, 1966) using the weighted multiresolution tangent refinement program *MULTAN* (Germain, Main & Woolfson, 1971). The density map corresponding to the highest figure of merit was computed and the map revealed the positions of the two S atoms and the rest of the 35 non-hydrogen-atom positions of the biphenothiazine molecule. A sharpened Patterson map confirmed the S positions. 2926 observed reflections were used in block-diagonal least-squares refinements with anisotropic thermal parameters for all non-hydrogen atoms and the weighting $1/[\sigma(F)]^2$ gave a final index of 0.129. The refinements took into consideration the unresolved solvent molecules as revealed in the difference Fourier map. As the solvent density was still unresolved and its specific nature unclear, and in view of the large thermal motions of the trifluoro group and poor-quality data, further refinement was considered unwarranted. Fractional coordinates are given in Table 1.*

Discussion. A stereoscopic view of the molecule is shown in Fig. 1 and its bond distances (\AA) and bond angles ($^\circ$) with atomic numbering in Fig. 2. The biphenothiazine is a dimer having the two phenothiazine planes nearly perpendicular to each other. The butterfly angles for each of the phenothiazines are 149° and 156° , which are in the range of reported values (Malmstrom & Cordes, 1972; Chu & van der Helm, 1975; McDowell, 1976). There has been much speculation and many attempts to correlate these angles with the pharmacological potency of the drug and the electron affinity of the substituted atoms (Malmstrom & Cordes, 1973). Clinically, the substitution in position 2 was found to alter mg potency and the length of the alkyl side chain seems to be more important in determining antipsychotic efficacy (Domino, 1967). Of the substituents in the 2 position, CF_3 shows greatest potency compared to H or CH_3 (Zirkle & Kaiser, 1970) but the dihedral angles for these compounds have been found to be nearly the same, showing very little correlation of the butterfly angles with potency or substituents. While in the different phenothiazines studied so far the angles do vary over a range of 25° or more, it seems more likely that much of this variation is attributable to crystal-packing effects as well as to the size and conformations of the alkyl substituents. This is seen from the crystal structure studies of phenothiazines (Bell, Blount, Briscoe & Freeman, 1968; McDowell, 1976) and triflupromazine (Phelps & Cordes, 1974) where the

* The thermal parameters and observed and calculated structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32869 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CHI 1NZ, England.

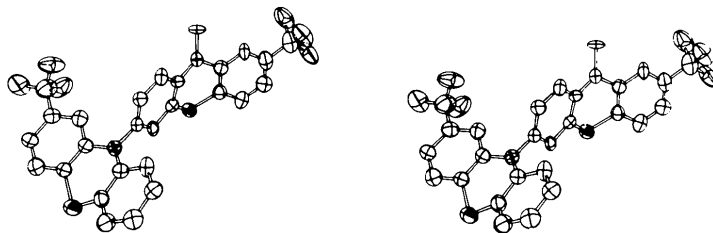


Fig. 1. Stereoscopic view of the molecule.

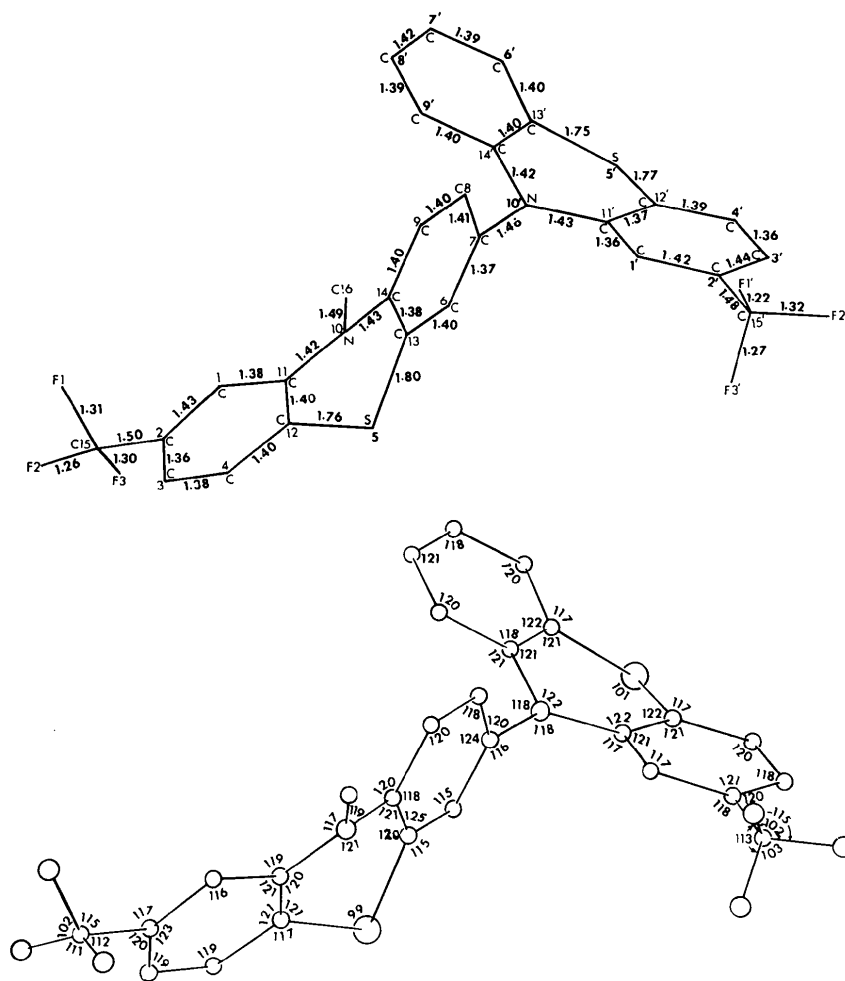


Fig. 2. Bond lengths in Å and bond angles in degrees. Standard deviations are 0.008 Å and 0.9° respectively.

angles for the same molecule showed significant differences depending on the crystal packing. It is interesting to note that some other tricyclic analogs, such as the dihydroanthracenes (Chu & Chung, 1976), in which S and N were replaced by O and C and which also act as antipsychotic drugs, appeared to have dihedral angles within the same range. The S—C bond, C—S—C angles, C—N bonds and C—N—C angles indi-

cated that there is some degree of partial double-bond character in the heterocyclic central ring. This may also be responsible for the variation of the dihedral angles.

Fig. 3 shows the packing of the molecules in a projection along **a**. There are some short intra-molecular contacts, such as C(7) to C(1') (2.73 Å), C(8) to C(9') (2.84 Å), C(3) to F(2) (2.69 Å), C(3') to F(2') (2.78 Å), and C(1) to F(1) (2.91 Å). In

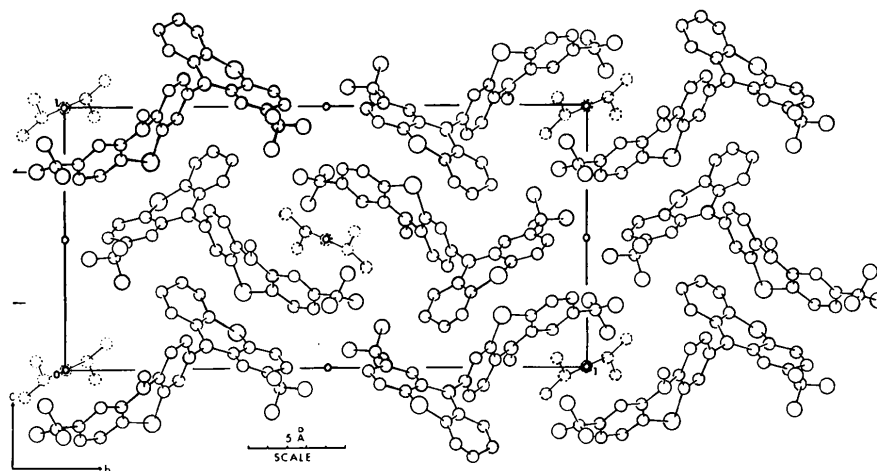


Fig. 3. Packing of molecules: projection along *a*. Disordered solvent molecules (dotted circles) are sandwiched between four sheets of tricyclic rings.

triflupromazine, Phelps & Cordes (1974) also found close contacts between C(3) and F(1) (2.73 Å), C(23) and F(6) (2.76 Å). This feature is evidently common among the trifluorophenothiazines. There are also some short intermolecular contacts involving solvent molecules, one to F(1') and another to C(11') (3.43 and 3.40 Å respectively).

This study has established that biphenothiazine as a dimer links at the 7,10' positions rather than the 3,10' as previously suggested by NMR data (Nagarajan *et al.*, 1974).

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