The Structure of Thiothixene

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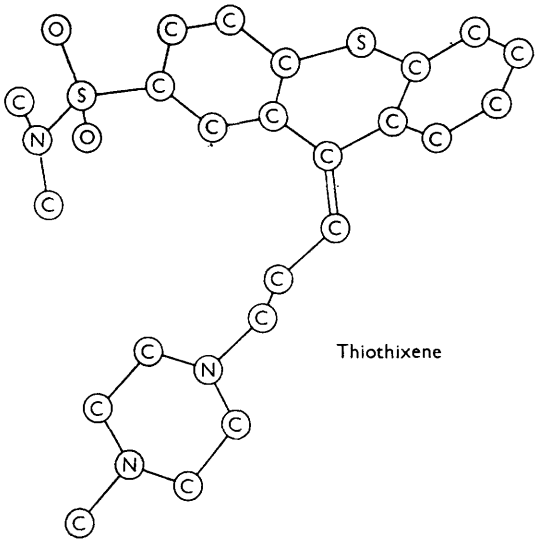
RECENT clinical studies[1] have shown that thiothixene (I) (*NN*-dimethyl-9-[3-(4-methyl-1-piperazinyl)propylidene]thioxanthrene-2-sulphonamide, *cis*-isomer) is an effective psychotropic drug with a broad therapeutic index and is particularly effective against schizophrenia. It has been found to be specifically active in combatting disorders of perception, thought content and processes, insight, and judgement in schizophrenics.

During the preparation of (I), two products are formed which are *cis*- and *trans*-isomers and of these only one exhibits therapeutic activity. Although the inactive isomer could readily be isomerized to (I), no unambiguous stereochemical assignment could be made on the basis of the available spectroscopic data for the two isomers. To clarify this detail of the structure, the crystal structure has been determined. The crystals are monoclinic; $a = 10{\cdot}13$, $b = 8{\cdot}77$, $c = 19{\cdot}99$ Å, $\beta = 139{\cdot}8°$; space group $P2_1$, $Z = 2$; $D_m = 1{\cdot}294$, $D_c = 1{\cdot}285$ for $2(C_{23}H_{29}N_3O_2S_2)$. Data were collected for $0k\bar{l}$–$5k\bar{l}$ and $h0l$–$h3l$ and the intensities of 2131 reflections were measured visually from equi-inclination Weissenberg photographs.

The positions of the two sulphur atoms were established by inspection of a three-dimensional sharpened Patterson map and phasing based on these atoms revealed the positions of the remaining atoms. The trial structure was refined using individual anisotropic thermal parameters by successive differential syntheses and the R factor is now 13·8%; refinement is being continued. The molecular structure (Figure) clearly shows that thiothixene should be formulated as the *cis*-isomer.



FIGURE

Interatomic distances for all atoms lie within the range of normally accepted values and average values (Å) are as follows: C–C (aromatic), 1·414; C–C (single bond), 1·545; C–C (vinyl), 1·514; C–C (vinyl-phenyl), 1·456; C=C, 1·401; C–N, 1·465; C–S, 1·740; S–O, 1·453. Least-squares planes through the aromatic rings were calculated and the maximum separation of an atom from the surface of the plane was 0·01 Å; the two planes intersect at an angle of 141·5°.

Although no specific interaction between the dimethylsulphonamide group and the piperazine ring occurs in the solid state, it is evident that the proximity of these functionalities is the most critical factor in determining the efficacy of the drug and this should provide a valuable clue toward understanding its mode of action from a biochemical viewpoint and aid in designing the synthesis of new compounds for use as psychotherapeutic agents.

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[1] D. M. Gallant, M. P. Bishop, and W. Shelton, *Amer. J. Psychiatry*, 1966, **123**, 345; G. M. Simpson and J. Iqbal, *Current Therapeut. Res.*, 1965, **7**, 697; A. A. Sugarman, A. A. Stolberg, and J. Herrmann, *ibid.*, p. 310; D. M. Gallant, M. P. Bishop, E. Timmons, and A. R. Gould, *ibid.*, 1966, **8**, 153; J. Simeon, A. Keskiner, D. Ponce, T. Itil, and M. Fink, *ibid.*, 1967, **9**, 10.