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The Antischizophrenic Agent Sulpiride: Structures of the *S*(−) Enantiomer and the Racemate*

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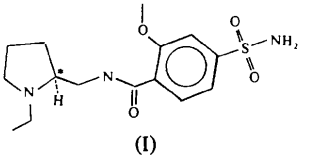
Abstract

The crystal and molecular structures of racemic and the active *S*(−) enantiomer of sulpiride, $C_{15}H_{23}N_3O_4S$ (M_r = 341), a potent antischizophrenic agent, were determined. The racemate crystallizes in space group $P\bar{1}$ with a = 9·067 (4), b = 9·372 (4), c = 11·175 (5) Å and α = 65·66 (9), β = 79·83 (9), γ = 76·79 (9)°, with V = 838·7 Å^3, D_x = 1·35 g cm^{-3}, Z = 2, and $\mu_{CuK\alpha}$ = 18·5 cm^{-1}. The structure was refined to a final R index of 7·38% for 1536 reflections and the positional coordinates were then used to solve the crystal structure of the *S*(−) enantiomer, which contains two molecules in the asymmetric unit in space group $P2_12_12_1$, with a = 12·037 (6), b = 24·163 (4), c = 11·536 (6) Å, V = 3355·3 Å^3, Z = 8 and D_x, $\mu_{CuK\alpha}$ values as for the racemate. The final discrepancy index for the *S*(−) enantiomer is 6·53% for 1401 reflections. The absolute configuration was confirmed using Hamilton's $\mathcal{R}$ test. Conformational similarities and differences between the racemate and the two independent molecules of the *S*(−) enantiomer are discussed.

Introduction

Sulpiride is the best known among the benzamide group of antipsychotic drugs. It has a mode of action for antischizophrenic efficacy that is different from most classical neuroleptics such as chlorpromazine and haloperidol in that it is relatively free from extrapyramidal side effects and tardive dyskinesia (Cassano, Castrogiovanni, Conti & Bonollo, 1977; Mielke, Gallant & Kessler, 1977; Mielke, Gallant, Roniger, Kessler & Kessler, 1977), and does not produce catalepsy. However, sulpiride does exhibit some effects of the classical neuroleptics, such as inhibition of apomorphine-induced behaviour in animals (Elliot, Jenner, Huizing, Marsden & Miller, 1977), inhibition of ^{3}H-haloperidol binding to dopamine receptors in homogenates of rat caudate (Seeman, 1977), elevation of prolactin secretion (Mielke, Gallant, Roniger, Kessler & Kessler, 1977; Macleod & Robyn, 1977) and increase in dopamine turnover (Elliot *et al.*, 1977; Scatton, Dedek & Kort, 1977). It has been shown that the neuroleptic efficacy of sulpiride is stereospecific and is primarily associated with the *S*(−) enantiomer (Andrews, Davis, Freeman, McDermed, Poat & Woodruff, 1978; Goldberg, Kohli, Litinsky & McDermed, 1979; Garau, Govoni, Stefanini, Trabucchi & Spano, 1978). We have determined the structure of *S*(−)-sulpiride (I) as part of an investigation of the stereochemical features of antipsychotic agents. In the course of the investigation, the crystal structure of racemic sulpiride was also determined as a step towards the solution for the structure of the *S*(−) enantiomer.



(I)

Experimental

S(−)-*Sulpiride*

Samples of both compounds (Ravizza Pharmaceutical Co., Italy) were obtained from Dr P. Seeman, Pharmacology Department, University of Toronto. A colourless crystal of dimensions 0·21 × 0·20 × 0·05 mm obtained from methanol was mounted along **a** for data collection on an automated four-circle

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diffractometer, and Ni-filtered Cu $K\alpha$ radiation was employed to collect data ($\theta/2\theta$ scan) to $2\theta = 110°$. An empirical absorption correction utilizing φ-scan curves at $\chi = 90°$ for reflections 400 and 200 ($2\theta = 29{\cdot}67$ and $14{\cdot}71°$ respectively) was applied to the intensity data, which were then reduced in the usual way. A total of 1401 reflections, out of 2327 independent reflections measured, were considered to be observed ($I > 3\sigma_I$), and were used in the structure refinement.

Racemic sulpiride

A crystal of dimensions $0{\cdot}20 \times 0{\cdot}10 \times 0{\cdot}08$ mm was mounted along **a*** and intensity data were collected as described above to $2\theta = 115°$. A total of 2295 independent reflections were measured. An empirical φ absorption curve (reflection 200, $2\theta = 20{\cdot}12°$) was employed and after data reduction 1536 reflections were classified as observed ($I > 3\sigma_I$).

Structure solutions and refinements

Data for *S*(−)-sulpiride were input to *MULTAN* 78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); one solution had significantly better agreement indices than any other, and the *E* map calculated with these phases showed that the two independent molecules constituting the asymmetric unit were related by a pseudo centre of symmetry. Atomic positions, related by the pseudo centre, could be chosen for 16 atoms of each molecule, *i.e.* for all but the five-membered rings and substituents. Since both molecules have the same absolute configuration the five-membered rings cannot be related by the symmetry, and the *E* map was extremely poorly resolved in those areas. Several attempts were made to break the pseudosymmetry and solve the structure, *e.g.* structure factor calculations and refinements using various possible interpretations by trial and error, partial molecular fragment used as input to rerun *MULTAN* 78 and *MULTAN* 80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), trial solutions using space group *Pbca* initially and then changing to $P2_12_12_1$, *etc.*, but none of these succeeded. The best *R* value obtained in the various trials was 0·135 (with anisotropic thermal parameters for non-hydrogen atoms) and was accompanied by poor bond parameters. We then decided to elucidate the crystal structure of the racemate as a means of obtaining crucial information on the orientation and relative location of the five-membered ring.

MULTAN 78 was used to derive the structure of the racemate. An *E* map from one of the two 'best' solutions revealed 22 of the 23 non-hydrogen atoms of the sulpiride molecule. A structure factor calculation using the 22 atoms gave $R = 0{\cdot}28$ and a Fourier electron density map showed the position of the remaining non-hydrogen atom. Full-matrix least-squares refinement and difference electron density distributions gave positions for all 23 H atoms and resulted in a final discrepancy index $R = 0{\cdot}074$.

The results of the structure determination of the racemate were utilized to solve the structure of the enantiomer in the following manner: the coordinates of a 12-atom 'backbone' fragment of a molecule of the racemate [Fig. 2; S, C(1)–C(7), O(15), O(17), N(8),

Table 1. *Final positional parameters* ($\times 10^4$) *and* B_{eq} ($=\frac{4}{3}\sum_i\sum_j \beta_{ij}\,\mathbf{a}_i\cdot\mathbf{a}_j$) *for S*(−)*-sulpiride*

	Molecule (1)				Molecule (2)			
	x	*y*	*z*	B_{eq} (Å²)	*x*	*y*	*z*	B_{eq} (Å²)
C(1)	−2090 (14)	−202 (7)	483 (11)	2·3 (9)	−2102 (20)	5253 (8)	5480 (18)	4·7 (1·2)
C(2)	−2205 (20)	112 (9)	−515 (19)	5·5 (1·3)	−2131 (28)	4951 (9)	4455 (16)	2·7 (1·6)
C(3)	−1487 (17)	547 (7)	−661 (14)	3·2 (9)	−1550 (20)	4474 (11)	4308 (14)	4·8 (1·2)
C(4)	−781 (16)	685 (7)	322 (13)	2·5 (9)	−740 (18)	4295 (8)	5058 (15)	3·3 (1·0)
C(5)	−675 (16)	376 (8)	1339 (13)	2·8 (9)	−709 (17)	4583 (9)	6156 (13)	3·2 (1·0)
C(6)	−1407 (19)	−92 (8)	1438 (14)	2·8 (9)	−1348 (19)	5049 (9)	6328 (15)	3·3 (1·0)
C(7)	69 (18)	525 (9)	2402 (14)	3·1 (1·0)	−39 (18)	4473 (9)	7178 (12)	3·0 (1·0)
N(8)	798 (14)	909 (7)	2213 (12)	3·6 (9)	839 (15)	4090 (8)	7071 (10)	3·5 (9)
C(9)	1642 (17)	1033 (8)	3072 (16)	3·6 (1·0)	1557 (23)	3892 (9)	8051 (19)	5·2 (1·3)
C(10)	1374 (21)	1622 (8)	3573 (17)	4·4 (1·1)	1438 (17)	3298 (7)	8322 (17)	2·4 (8)
N(11)	2064 (14)	1735 (6)	4537 (13)	4·5 (8)	2358 (17)	3125 (8)	9082 (18)	6·5 (1·1)
C(12)	2565 (19)	2277 (8)	4433 (16)	6·2 (1·1)	1823 (27)	2933 (13)	10119 (23)	10·2 (1·6)
C(13)	2827 (22)	2288 (11)	3080 (20)	7·9 (1·5)	794 (25)	3178 (12)	10229 (19)	9·5 (1·8)
C(14)	1769 (20)	2055 (8)	2687 (15)	6·6 (1·2)	378 (16)	3183 (7)	8951 (18)	6·1 (1·2)
O(15)	−92 (10)	1135 (6)	154 (8)	3·3 (6)	−38 (11)	3847 (6)	4970 (10)	4·0 (0·8)
C(16)	−89 (25)	1428 (11)	−936 (15)	9·4 (1·7)	−38 (14)	3558 (6)	3944 (16)	3·8 (0·9)
C(17)	−177 (11)	302 (6)	3195 (10)	4·7 (8)	−109 (12)	4713 (5)	8181 (11)	4·9 (0·8)
C(18)	1496 (19)	1667 (8)	5694 (15)	5·6 (1·1)	3019 (30)	2686 (12)	8597 (35)	11·4 (1·4)
C(19)	521 (20)	2037 (8)	5926 (16)	7·1 (1·3)	3615 (24)	2784 (20)	7648 (26)	6·9 (3·0)
N(20)	−4222 (14)	−641 (7)	481 (12)	4·6 (9)	−4174 (17)	5641 (7)	5554 (12)	4·6 (1·0)
O(21)	−2677 (13)	−1189 (5)	−258 (11)	4·6 (7)	−2690 (12)	6170 (6)	4622 (9)	4·6 (7)
O(22)	−2744 (11)	−1027 (5)	1815 (8)	5·8 (7)	−2756 (13)	6013 (6)	6787 (12)	5·8 (9)
S	−2929 (6)	−837 (2)	682 (4)	3·8 (3)	−2915 (6)	5819 (2)	5602 (4)	3·8 (7)

C(9)], and its centrosymmetrically related equivalent were fit in turn by a least-squares procedure to each of the two independent $S(-)$-sulpiride molecules in the best ($R = 0{\cdot}135$) previously obtained trial structure. Two of the four molecular fits were significantly better than the others; for these two cases, the previously obtained enantiomeric structure coordinates (16 atoms of each molecule) were augmented by the coordinates of the five-membered ring system of the racemate molecule which had been fit to one of the enantiomer molecules. Structure factors and difference Fourier syntheses were then calculated; one of the two sets ($R = 0{\cdot}21$) displayed clearly the remaining five-membered ring system, with the same absolute configuration as the five-membered ring used as input to the calculation. Further refinement confirmed the correctness of this assignment. Full-matrix least-squares refinement and difference Fourier calculations allowed positions of all 46 H atoms to be obtained, and resulted in a final $R = 0{\cdot}065$.

A Hamilton's test (Hamilton, 1964) on the ratio of R_w's (7·45/7·34) for the R and S enantiomers, using anomalous-scattering factors of S, C, N, O atoms, confirmed that the structure determined is the $S(-)$ enantiomer to a significance level of 0·005.

In all refinement procedures, positional and anisotropic thermal parameters (non-hydrogen atoms) were varied; H-atom positions were not refined and they were assigned isotropic temperature factors of 6·6 and 7·1 Å^2 for the racemate and enantiomer respectively. The real atomic scattering factors used were those given by Cromer & Mann (1968), the imaginary part being from *International Tables for X-ray Crystallography* (1974), and those for the H atoms by Stewart, Davidson & Simpson (1965). Weights used throughout were $1/\sigma_F^2$, derived from counting statistics. The final $[\sum w(F_o - |F_c|)^2/(m - n)]^{1/2} = 1{\cdot}0$ in both determinations. The positional parameters (non-hydrogen atoms) are given in Table 1.*

Results and discussion

Fig. 1 illustrates the similarities and differences in the molecular conformations of sulpiride in the two crystal forms by comparing each of the two independent molecules of $S(-)$-sulpiride with the conformation of the S-configuration molecule in the racemic crystal structure. Fig. 1(*a*) shows that the conformations of the racemate and one of the enantiomers are very similar,

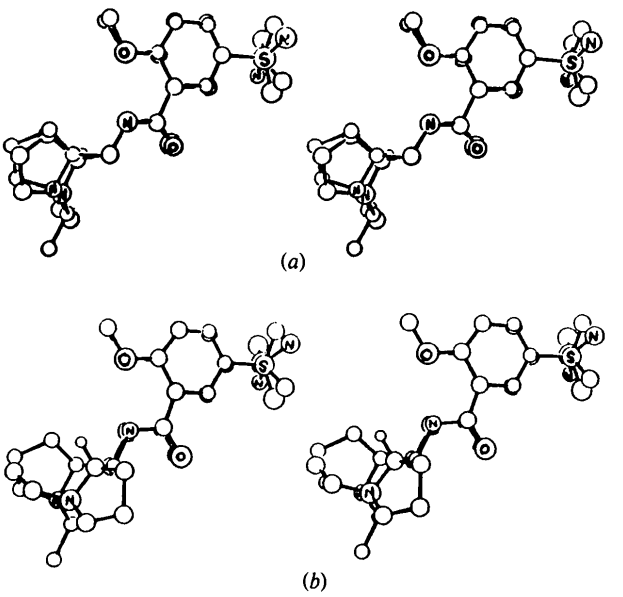

Fig. 1. Stereoscopic superposition of racemate sulpiride molecule (in smaller circles) with (*a*) molecule (1), (*b*) molecule (2) of the $S(-)$ enantiomer.

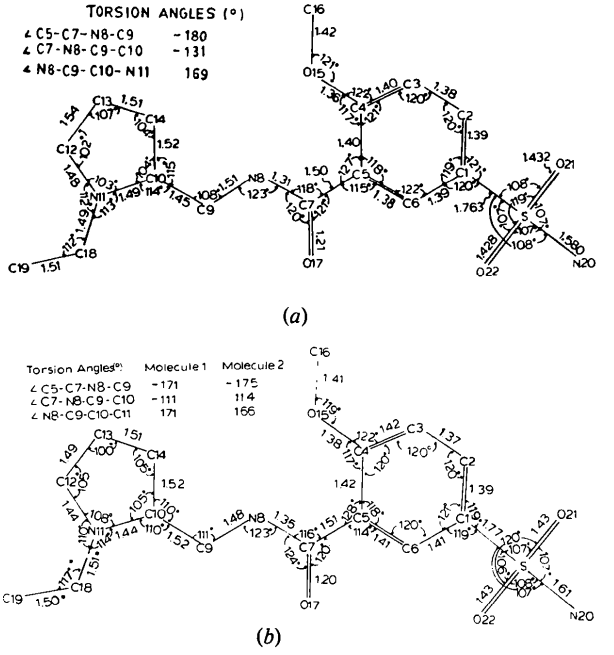

Fig. 2. Bond lengths (Å) and angles (°) of (*a*) racemic sulpiride and (*b*) averaged values of molecules (1) and (2) in $S(-)$-sulpiride. The standard errors are in (*a*) 0·01 Å for C–N, C–C and C–O bonds, 0·006 Å for S–C, S–N and S–O bonds, 1° for bond angles, and 2° for torsion angles, and in (*b*) 0·01 Å for S–O bonds, 0·02 Å for S–C, S–N, O–C bonds and 0·03 Å for C–C and C–N bonds and 1° for bond angles around S, 1·5° for bond angles around O and 2° for bond angles around N and C, and 2° for torsion angles. Asterisks indicate values from molecule (1) as high thermal motion for C(18) in molecule (2) makes the values unreliable.

* Lists of structure factors, heavy-atom anisotropic thermal parameters, and H-atom positional parameters for both structures, and heavy-atom coordinates for the racemate have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36991 (29 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

and indicates why the molecular-fitting procedure we adopted was successful in solving the structure of the *S*(−) crystal. Both molecules have extended, rather flattened conformations (angles between normals to mean planes through the five- and six-membered rings are 13 and 29°) and differ only in orientations of (freely rotatable) substituent groups at both ends. Fig. 1(*b*) illustrates that the second enantiomeric molecule differs greatly from the other molecules in the conformational relationship of the five-membered heterocyclic ring to the rest of the molecule; the C(7)–N(8)–C(9)–C(10) torsion angle (Fig. 2) of +114 (2)° [*vs* −111 (2) and −131 (2)° in the other molecule of the enantiomeric crystal and the racemate *S* configuration respectively] results in a ring orientation almost perpendicular to those of the other molecules. (The angle between normals to the mean ring planes in this molecule is 124°.)

The phenyl ring and amide linkage in all three molecules are roughly planar, as expected; the five-membered ring is not, and exhibits conformational flexibility. Least-squares planes calculated through all combinations of four atoms at a time show that in the racemate structure atom N(11) lies 0·633 (6) Å from the plane of the other four [maximum deviation 0·002 (9) Å], while in one of the *S*(−) structure molecules C(13) is 0·57 (3) Å from the plane of the others [maximum deviation 0·009 (18) Å] and in the other equally good planes can be described omitting either C(12) or C(13) [0·65 (2) Å] from the plane of the remaining four [maximum deviation 0·09 (2) Å].

Bond lengths and angles (and numbering scheme) for the two compounds are shown in Fig. 2. The values agree moderately well for the two compounds, considering the rather high standard deviations, and fall within expected ranges. The configuration at the ring N atom is tetrahedral, with the lone pair of electrons occupying the fourth position; the N is a hydrogen-bond acceptor in the racemic structure but not in the crystal of *S*(−)-sulpiride. In both structures there is an intramolecular hydrogen bond from N(8) to O(15); the H···O distances are 1·88 and 2·10 Å (racemate and averaged enantiomeric structures) and the N–H···O angles are 132 and 117°.

The intermolecular bonding scheme in the *S*(−)-sulpiride crystal involves the carbonyl O of each independent molecule as an H-bond acceptor from the terminal SO_2NH_2 group of two others (one of each type of molecule); O···N distances range from 2·86 (2)–3·00 (2) Å. In the racemate structure each SO_2NH_2 is also the donor in two hydrogen bonds, one to the carbonyl O [O···N = 2·88 (3) Å] and the other to the heterocycle N [N···N = 2·94 (3) Å] of two different molecules. Hydrogen-bond angles are in the range 140–162°.

After this work was completed a paper on the structure of racemic sulpiride appeared (Houttemane, Boivin, Nowogrocki & Thomas, 1981). They chose a triclinic cell different from ours, but the structural results are extremely similar, with insignificant differences in bond lengths and angles. Houttemane *et al.* noted large thermal motion for atoms N(8) and C(9) and ascribed this to positional disorder; we encountered the same situation, but to a lesser degree (B_{eq} = 8·6 and 9·2 Å^2 respectively; *vs* their findings of 12·6 and 12·4 Å^2). Difference electron density maps showed small residual density around N(8) and C(9), but bond parameters calculated for these positions were so poor that their inclusion at very low weights was not warranted.

The benzamide type of neuroleptics differ considerably in structure from the phenothiazines and butyrophenones, but like many of the members of these categories of neuroleptics, sulpiride, as shown here, has some degree of conformational flexibility. Thus it may be useful to try to fit sulpiride conformationally to active and inactive isomers of other types of neuroleptic molecules, superposing various reactive centres and utilizing the allowable flexibilities, in order to delineate stereochemical features which may be common to the different classes. Such experiments are in progress in these laboratories.

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The Stereoconfiguration and Restrained Refinement of an Unsymmetric Trimer: 3,7,11-Tris(*p*-chlorophenyl)-2,3,6,7,10,11-hexahydro-2,2,6,6,10,10-hexaphenyltris[1,2,4]triazolo[1,5-*a*:1′,5′-*c*:1″,5″-*e*][1,3,5]triazine: $C_{60}H_{42}Cl_3N_9$

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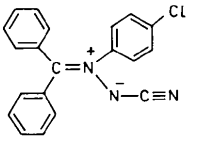
Abstract

C,C,N$^{\alpha}$-triaryl-N$^{\beta}$-cyanoazomethine imines trimerize on heating in solution or even in the crystalline state. An X-ray single-crystal analysis was performed on one of these trimers to determine whether or not the molecule has threefold symmetry. Results of the study showed the trimer to be unsymmetric. The compound ($C_{60}H_{42}Cl_3N_9$) crystallizes in the triclinic space group $I\bar{1}$ with a = 16·102 (10), b = 24·894 (20), c = 13·241 (9) Å, α = 96·7 (1), β = 91·2 (1), γ = 106·8 (1)°, Z = 4 [reduced Niggli cell: $P\bar{1}$, a = 13·242, b = 13·558, c = 16·103 Å, α = 108·5, β = 91·2, γ = 111·6°, Z = 2; transformation matrix: (001 $\bar{1}\bar{1}\bar{1}$ $\frac{1}{2}\frac{1}{2}\frac{1}{2}$ 100)], D_x = 1·312 g cm^{-3} and μ = 2·36 cm^{-1}. The structure was solved by direct methods and refined both by full-matrix and restrained least-squares procedures. A full-matrix refinement using 4003 reflections and only the non-hydrogen atoms gave a final R_w of 0·072. An anisotropic restrained least-squares refinement, using all the atoms and all 6053 reflections, gave a final R_w of 0·065.

Introduction

C,C,N$^{\alpha}$-triaryl-N$^{\beta}$-cyanoazomethine imines (*e.g.* I) trimerize on heating in solution or even in the crystalline state to give products such as (II) {3,7,-11-tris(*p*-chlorophenyl)-2,3,6,7,10,11-hexahydro-2,2,-6,6,10,10-hexaphenyltris[1,2,3]triazolo[1,5-*a*:1′,5′-*c*:1″,5″-*e*][1,3,5]triazine}. The tetracyclic heterosystem is formed by a sequence of three 1,3-dipolar cycloaddition reactions of the azomethine imine to the cyano group, the first two taking place intermolecularly and the third intramolecularly. The structural formula (II) was correctly predicted in 1962 (Eckell, 1962) and it was suggested that it would have threefold (C_3) molecular symmetry. Studies of spectroscopic data and chemical properties of the compound could not confirm this prediction (Huisgen, Fleischmann & Eckell, 1977). The X-ray study corroborated the structural formula and established the stereochemistry of the molecule. The results of this analysis revealed large departures from C_3 symmetry, with two *p*-chlorophenyl rings projecting away to one side of the average plane of the central heterocyclic ring system and the third $-C_6H_4Cl$ group directed towards the opposite side (Fig. 4).



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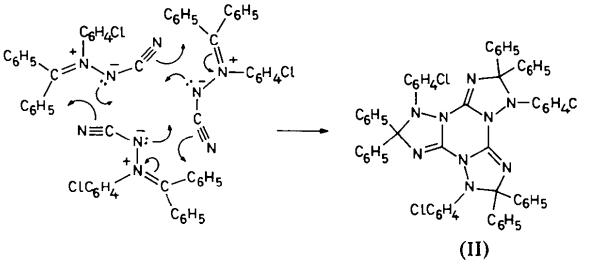

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