

Fig. 3. Projection de la structure sur le plan  $xOz$  parallèlement à  $Oy$ .

(TMTTF)<sub>2</sub>X. Le paramètre  $c$  correspondant sensiblement au sens d'allongement de la molécule de TMCHDT est le seul qui soit profondément modifié.

Les distances interplanaires sont très voisines: 3,54 et 3,55 Å, mais cependant l'empilement ne peut être considéré comme régulier, les molécules de TMCHDT successives dans une même colonne se correspondant par inversion et non par translation.

Le décalage des molécules est longitudinal; sa valeur correspond à 1,33 Å, c'est à dire légèrement inférieur à la longueur d'une double liaison.

L'anion  $ClO_4^-$  se trouve dans une cavité centrosymétrique (Fig. 3); le désordre constaté rétablit le centre de symétrie. Un deuxième type de désordre, à caractère dynamique, existe probablement.

Le remplacement, dans la molécule de TMTTF, de la double liaison centrale par un cycle quinonique n'a pas apporté de modifications profondes dans l'édifice structural et dans les propriétés conductrices.

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*Acta Cryst.* (1980). **B36**, 1113–1117

## Crystal Structure and Absolute Configuration of the Hydrochloride of a Dopamine-Receptor-Blocking Rigid Spiro Amine: (1*S*,4*R*)-3'-Chloro-*N,N*-dimethylspiro[2-cyclohexene-1,5'-[5*H*]dibenzo[*a,d*]cyclohepten]-4-amine\*

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(Received 17 August 1979; accepted 26 November 1979)

### Abstract

The crystal structure and absolute configuration of (1*S*,4*R*)-3'-chloro-*N,N*-dimethylspiro[2-cyclohexene-1,5'-[5*H*]dibenzo[*a,d*]cyclohepten]-4-amine (A31472) hydrochloride have been determined. The compound, C<sub>22</sub>H<sub>23</sub>ClN<sup>+</sup>.Cl<sup>-</sup>, crystallizes in space group  $P2_12_12_1$  with  $a = 14.755$  (5),  $b = 12.389$  (3),  $c = 10.682$  (5) Å and  $Z = 4$ . The structure was refined to  $R = 0.047$  for 1064 reflections. The e.s.d.'s in bond lengths vary between 0.008 and 0.016 Å. A comparison between

the present and other structurally related rigid spiro amines is presented.

### Introduction

It has been shown that a novel series of tetracyclic spiro compounds (Carnmalm *et al.*, 1974), structurally related to the tricyclic antidepressants, block the apomorphine syndrome in rats (Carnmalm, Johansson, Råmsby, Stjernström, Ross & Ögren, 1976). The introduction of a Cl atom in the tricyclic moiety alters the pharmacological properties from antidepressant (*i.e.* noradrenaline-uptake inhibition) to neuroleptic (*i.e.* dopamine-receptor blockade). The isomer mixture of 3'-chloro-*N,N*-dimethylspiro[2-cyclohexene-1,5'-[5*H*]dibenzo[*a,d*]cyclohepten]-4-amine was resolved

\* IUPAC recommended nomenclature. Author's original nomenclature: 3-chloro-*N,N*-dimethylspiro[5*H*-dibenzo[*a,d*]cycloheptene-5,1'(*S*)-cyclohex-2'-ene]-4'(*R*)-amine.

into its four enantiomers (Carmalm, Johansson, Räsby & Stjernström, 1979). It was shown that the activity resides mainly in the  $\alpha(-)$  enantiomer, in the following denoted A31472,\* which has approximately the same potency as chlorpromazine (Ögren, Hall & Köhler, 1978). Since this compound shows stereoselective dopamine-receptor-blocking capability, it was of interest to determine its absolute configuration. This has been done by an X-ray crystallographic technique. The crystal structure of A31472 has been determined as the hydrochloride salt.

### Experimental

Crystals grown from ethanol solution were supplied by Dr N. E. Stjernström, Astra Läkemedel AB, Sweden. The cell dimensions were obtained from Guinier-Hägg powder data, collected by a film-scanner system described by Malmros & Werner (1973), using strictly monochromatized Cu  $K\alpha_1$  radiation ( $\lambda = 1.54056 \text{ \AA}$ ) and KCl as the internal standard ( $a = 6.2930 \text{ \AA}$ ). Crystal data are given in Table 1.

A crystal of approximate dimensions  $0.375 \times 0.125 \times 0.100 \text{ mm}$  was used for both the data collection and the measurement of the Bijvoet differences. Intensity data were collected on a single-crystal computer-controlled diffractometer (Philips PW 1100) using graphite-monochromatized Cu  $K\alpha$  radiation. A total of 2100 reflections were collected up to  $2\theta = 140^\circ$ , with  $\theta-2\theta$  scans using a scan width of  $1.74^\circ$  and a speed of  $0.025^\circ \text{ s}^{-1}$ . Backgrounds were measured by stationary counts on each side of the peaks. 1064 reflections had  $I_{\text{net}} \geq 3\sigma(I)$  and were used in the subsequent calculations. Lorentz and polarization factors were applied but no corrections were made for extinction or absorption ( $\mu = 2.99 \text{ mm}^{-1}$ ).

### Structure determination and refinement

The structure was solved by the *MULTAN* program system (Germain, Main & Woolfson, 1970) using 250  $E$  values having  $|E| \geq 1.5$ . An  $E$  map based on the set

\* Internal code number, Astra Läkemedel AB, Sweden.

Table 1. *Crystal data*

|   |   |
|---|---|
| Molecular formula: $\text{C}_{22}\text{H}_{23}\text{ClN}^+ \cdot \text{Cl}^-$ , $M_r = 372.3$ |   |
| Orthorhombic, $P2_12_12_1$  | $Z = 4$   |
| $a = 14.755 (5) \text{ \AA}$  | $F(000) = 784$                                  |
| $b = 12.389 (3)$  | $D_c = 1.27 \text{ Mg m}^{-3}$                  |
| $c = 10.682 (5)$  | $\lambda = 1.5418 \text{ \AA}$ for Cu $K\alpha$ |
| $\mu = 2.99 \text{ mm}^{-1}$  | $V = 1952.8 \text{ \AA}^3$                      |
| Systematic absences: $h00$ for $h = 2n + 1$ ;   |   |
| $0k0$ for $k = 2n + 1$ ; $00l$ for $l = 2n + 1$   |   |

of phases for the solution with the highest combined consistency index yielded 20 of the 25 non-hydrogen atomic positions. The remaining five atoms were located from a difference Fourier synthesis, and three cycles of full-matrix least-squares isotropic refinement, using the *SHELX* program (Sheldrick, 1976), gave  $R = 0.14$ . Two further cycles with anisotropic thermal parameters reduced  $R$  to 0.074. At this stage the H atomic positions were calculated from geometrical considerations. The calculated H atoms were then included in the refinement, with the methyls treated as rigid groups and the C-H and N-H vectors held constant in magnitude and direction during the refinement, *i.e.* the H atoms riding on their respective mother atoms at a constant distance of  $1.08 \text{ \AA}$ . An overall isotropic temperature factor of  $0.05 \text{ \AA}^2$  was assigned to the H atoms and refined to  $0.058 \text{ \AA}^2$ .

After three more cycles, the refinement was terminated at  $R = 0.047^*$  and  $R_w = 0.045$  for 1064 reflections. During the final stage of the refinement a weighting scheme was introduced as  $w = K/[\sigma^2(F) + GF^2]$ , and the function minimized was  $\sum w(|F_o| - |F_c|)^2$ . The weighted discrepancy index is defined as  $R_w$ .

\* Lists of structure factors, anisotropic thermal parameters, and hydrogen coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35017 (5 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Positional parameters ( $\times 10^4$ ) for the non-hydrogen atoms*

E.s.d.'s are given in parentheses.

|       | $x$       | $y$       | $z$        |
|-------|-----------|-----------|------------|
| C(1)  | 9893 (6)  | 4274 (11) | -3722 (10) |
| C(2)  | 9163 (6)  | 3822 (8)  | -3105 (8)  |
| C(3)  | 8670 (5)  | 4397 (7)  | -2209 (8)  |
| C(4)  | 7898 (5)  | 3871 (5)  | -1481 (6)  |
| C(5)  | 8137 (5)  | 3844 (5)  | -67 (6)    |
| C(6)  | 7505 (5)  | 3110 (4)  | 680 (6)    |
| C(7)  | 7687 (5)  | 1949 (5)  | 283 (6)    |
| C(8)  | 7668 (5)  | 1871 (5)  | -1123 (7)  |
| C(9)  | 7761 (5)  | 2683 (5)  | -1891 (7)  |
| C(10) | 7017 (6)  | 4483 (5)  | -1737 (6)  |
| C(11) | 6290 (5)  | 4002 (7)  | -2367 (7)  |
| C(12) | 5488 (6)  | 4544 (8)  | -2532 (9)  |
| C(13) | 5352 (7)  | 5562 (9)  | -2086 (9)  |
| C(14) | 6057 (8)  | 6052 (8)  | -1493 (8)  |
| C(15) | 6900 (7)  | 5563 (6)  | -1336 (7)  |
| C(16) | 7623 (9)  | 6245 (6)  | -809 (8)   |
| C(17) | 8498 (9)  | 6192 (8)  | -1067 (10) |
| C(18) | 8945 (7)  | 5473 (8)  | -1937 (9)  |
| C(19) | 9684 (8)  | 5866 (11) | -2550 (13) |
| C(20) | 10171 (7) | 5306 (13) | -3479 (13) |
| C(21) | 7071 (6)  | 1157 (6)  | 2244 (6)   |
| C(22) | 6083 (5)  | 1286 (7)  | 400 (9)    |
| Cl(1) | 4619 (2)  | 3899 (3)  | -3346 (3)  |
| Cl(2) | 7810 (2)  | -1018 (2) | 438 (2)    |
| N     | 7029 (4)  | 1158 (4)  | 843 (5)    |



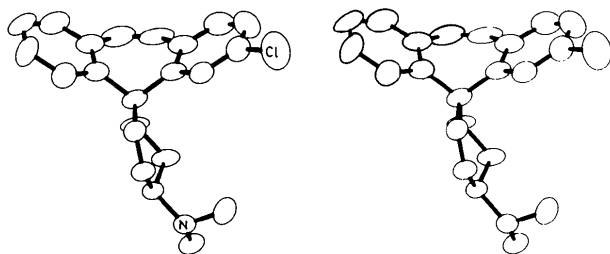


Fig. 4. Stereoview of A31472, showing the absolute configuration.

of the rings are given in Fig. 2. The e.s.d.'s in bond distances vary between 0.008 and 0.016 Å and in bond angles between 0.6 and 1.3°. The packing arrangement is shown in Fig. 3. Since the compound crystallizes as a hydrochloride, the N is positively charged and hydrogen bonded to the negative chloride ion at a distance of 2.964 (6) Å. All other contacts between the molecules correspond to normal van der Waals distances.

The compound A31472 has an (*S*) configuration at the spiro carbon atom (1,5') and an (*R*) configuration at the carbon atom (4) bearing the amino group. The absolute configuration is shown in Fig. 4. This compound, A31472, has the same absolute configuration as the related spiro amine (1*S*,4*R*)-3'-chloro-10',11'-dihydro-*N,N*-dimethylspiro[2-cyclohexene-1,5'-[5*H*]dibenzo[*a,d*]cyclohepten]-4-amine, A23887 (Wagner, 1980*a*), in which the tricyclic moiety is saturated. A discussion concerning the stereoselective effect of A31472, A23887 and related compounds

resulting in a topographical model of the neuroleptic receptor is presented elsewhere (Carnmalm, Johansson, Råmsby, Stjernström & Wägner, 1979; Råmsby, 1979).

Three parameters used for describing the tricyclic moiety have been calculated. These are: the bend angle, the twist angle and the skew distance (for definition see, for example, Corey, Corey & Glick, 1975). Further, some parameters which have been used with the neuroleptics (Horn, Post & Kennard, 1975) have also been calculated: (1) the distance between the centres of gravity of the benzene rings *A* and *B*, (2) the distances between these centres and the N atom and, finally, (3) the distance from the N to a mean plane through the four benzo C atoms in the cycloheptene ring. In Table 4 the above-mentioned parameters are given for the present compound A31472, for A23887 and for the structurally related antidepressant *N,N*-dimethylspiro[cyclohexane-1,5'-[5*H*]dibenzo[*a,d*]cyclohepten]-4-amine, A01866 (Rodgers, Horn & Kennard, 1975; Rodgers, Kennard, Sheldrick & Horn, 1976).

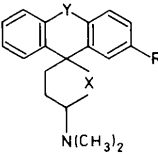
It can be seen from Table 4 that the two compounds A31472 and A01866 show the strongest resemblance between parameter sets. The third compound, A23887, differs from the others mainly in the twist angle and the distance from the N to the mean plane through the four benzo C atoms. Further, in A31472 and A23887 the Cl atom is in a *cis* configuration with respect to the N atom. The compound A01866 lacks the Cl atom, but shows the same kind of asymmetry, *i.e.* the N is in a 'cis-line' configuration with respect to one of the benzene rings (ring *A*). This can be seen by comparing the distances *A*–N and *B*–N in Table 4.

However, these three structurally related compounds show different pharmacological profiles. Due to the introduction of the Cl atom in the tricyclic moiety at the 3 position [corresponding to atom C(12)] (Carnmalm *et al.*, 1974), A31472 and A23887 show a neuroleptic effect, *i.e.* dopamine-receptor blockade, while A01866, which lacks the Cl atom, has antidepressant properties, *i.e.* potently inhibits the membrane uptake of noradrenaline (Carnmalm *et al.*, 1974). The two neuroleptic compounds are more or less equally potent with respect to the dopamine-receptor-blocking capability, but A23887 shows less extrapyramidal side effects (Ögren, 1979).

It is noteworthy that the calculated solid-state geometrical parameters (*cf.* Table 4) do not seem to be sufficient for the characterization of the pharmacological profiles of the three present compounds. This in turn leads to the suggestion that parameters other than strictly geometrical ones, *i.e.* electronic properties, charge distribution and  $\pi$ -electron systems, atomic polarizabilities and hydrophobic/hydrophilic properties, might be of importance for the characterization of the pharmacological profile. A further discussion of A31472, A23887 and related compounds acting on the

Table 4. Some molecular parameters for A31472, A23887 and A01866

E.s.d.'s are given in parentheses.



(1) Y = -CH=CH-  
X = -CH=CH-  
R = Cl

(2) Y = -CH<sub>2</sub>-CH<sub>2</sub>-  
X = -CH=CH-  
R = Cl

(3) Y = -CH=CH-  
X = -CH<sub>2</sub>-CH<sub>2</sub>-  
R = H

| Compound  | A31472 <sup>(1)</sup> | A23887 <sup>(2)*</sup> | A01866 <sup>(3)</sup> |
|---|-----------------------|------------------------|-----------------------|
| Bend angle (°)  | 123.5 (18)            | 131.1 (9), 143.5 (5)   | 120.8 (13)†           |
| Twist angle (°)   | -1.1 (5)              | 23.1 (5), 23.9 (5)     | 2.7 (10)†             |
| Skew distance (Å)   | 0.57 (2)              | 0.59 (1), 0.54 (1)     | 0.63 (2)†             |
| Distance (Å) between ring centres <i>A</i> and <i>B</i>                                       | 4.88 (2)              | 5.29 (1), 5.25 (1)     | 4.87 (3)†             |
| Distance (Å) from N to centre of ring <i>A</i>  | 5.78 (1)              | 5.83 (1), 5.73 (1)     | 5.54 (2)†             |
| Distance (Å) from N to centre of ring <i>B</i>  | 6.99 (1)              | 6.75 (1), 6.81 (1)     | 7.24 (2)†             |
| Distance (Å) from N to the mean plane through the four benzo C atoms in the cycloheptene ring | -3.72 (1)             | -1.96 (1), -1.94 (1)   | -3.84 (1)†            |

\* There are two molecules in the asymmetric unit (from Wagner, 1980*a*).

† Calculated from Rodgers, Kennard, Sheldrick & Horn (1976).

‡ From Rodgers, Horn & Kennard (1975) without e.s.d.'s. Recalculated from Rodgers, Kennard, Sheldrick & Horn (1976) to obtain e.s.d.'s.

dopaminergic system will be presented (Wägner, 1980b).

The author wishes to thank Professor Peder Kiergaard and Dr Per-Erik Werner for their kind interest in this work and for stimulating discussions and Dr Sven Westman for linguistic advice. This work has received financial support from the Swedish Natural Science Research Council. The author is also indebted to Stiftelsen Bengt Lundqvists Minne and P. E. Lindahls Stipendiefond for financial support.

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*Acta Cryst.* (1980). **B36**, 1117–1121

## Structure du [*N*-(Hydroxy-2 méthyl-1 phényl-2 éthyl) *N*-méthyl-amino]-2 Maléate de Diméthyle

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(Reçu le 22 février 1979, accepté le 4 décembre 1979)

### Abstract

The crystal structure of dimethyl 2-[*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylamino]maleate (C<sub>16</sub>H<sub>21</sub>NO<sub>5</sub>, *M<sub>r</sub>* = 307) has been determined from three-dimensional data collected with Cu *K*α radiation. The crystal structure is orthorhombic, space group

*P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, with *a* = 10.091 (4), *b* = 17.803 (7), *c* = 9.322 (4) Å [*Z* = 4, *V* = 1674.7 Å<sup>3</sup>, *d<sub>x</sub>* = 1.22 Mg m<sup>-3</sup>, *F*(000) = 656]. The structure was solved by direct methods with *MULTAN* 77; *R* = 6% for 989 observed reflexions. The chemical behaviour of the title compound has been discussed on the basis of its strong conjugation.

0567-7408/80/051117-05\$01.00

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