

The Structure of *N,N*-Dimethyl-2-phenylcyclopropylamine Hydrochloride

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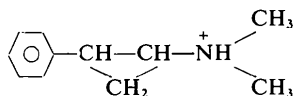
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The crystal structure of the hydrochloride of the drug *N,N*-dimethyl-2-phenylcyclopropylamine, $C_{11}H_{15}N \cdot HCl$, has been determined from three-dimensional X-ray diffractometer data. The orthorhombic unit cell, space group $Pna2_1$ has the dimensions $a = 11.17$, $b = 6.00$ and $c = 34.72$ Å and contains two formula units in the asymmetric unit ($Z = 8$). The structure was solved by the heavy-atom method and refined by full-matrix least-squares calculations to $R = 0.057$ for 897 observed reflexions. The two independent molecules having the amino nitrogen in *trans* position are nearly mirror images of one another. Their conformation in relation to biological monoamines is discussed. Each of the two molecules is bound to a chloride ion by a short $N \cdots Cl$ hydrogen bond (3.00 and 3.04 Å). The crystal packing is otherwise rather loose.

Introduction

The title compound, hereinafter referred to as SKF 556, is a monoamine oxidase (MAO) inhibitor (Shore & Cohn, 1960), a property possessed to an even higher degree by its unmethylated parent compound, trancylpromine. From the latter it was not possible to obtain crystals large enough for single-crystal analysis. The structure determination was hence carried out on SKF 556 which has a conformation characteristic of a *trans*-phenylcyclopropylamine. These compounds are drugs of steric interest as they contain the phenethylamine skeleton common to many neurotropic compounds but with a rigid ethylamine side chain locked by a cyclopropane ring:



In binding to MAO the phenylcyclopropylamines impair the normal metabolism of monoamines which are serving as neurotransmitters in the body.

Experimental

The hydrochloride of SKF 556 was kindly supplied by Smith, Kline & French Laboratories, Pennsylvania, U.S.A. The crystals were thin, orthorhombic diamond-shaped plates with the c axis perpendicular to the plane of the plates. A large number of crystals were investigated by oscillation and Weissenberg photographs before a crystal free from twinning and pronounced distortions was found. This crystal was trimmed to the dimensions $0.30 \times 0.25 \times 0.10$ mm, the latter figure corresponding to the initial thickness of the plate. Preliminary unit-cell dimensions and systematic absences were determined from Weissenberg photographs while accurate cell data were derived from measurements on an automatic diffractometer (Pailred) which was also used for collecting the three-dimensional intensity data.

Crystal data

N,N-Dimethyl-2-phenylcyclopropylamine hydrochloride, $C_{11}H_{15}N \cdot HCl$, M.W. 197.71, orthorhombic, $a = 11.174$ (5), $b = 5.997$ (3), $c = 34.719$ (12) Å $V = 2326.5$ Å³, $D_x(Z = 8) = 1.129$ g cm⁻³, $\mu(Mo K\alpha) = 2.88$ cm⁻¹. Absent spectra: $0kl$ when $k + l$ is odd, $h0l$ when h is odd. Space group $Pna2_1$ or $Pnam$. The structure was solved successfully assuming the non-centrosymmetric $Pna2_1$ which was indicated both by the distribution of the Cl-Cl vectors in the Patterson maps and the E -value statistics.

For the intensity measurements the crystal was mounted about its b axis and reflexions on levels $h0l$ through $h6l$ were recorded within $\sin \theta/\lambda \leq 0.55$ using graphite monochromatized $Mo K\alpha$ radiation and a scintillation counter with pulse-height discrimination. In all, 897 independent reflexions significantly differing from the background were recorded. The low number of reflexions above threshold intensity was partly caused by the rapid fall-off at higher angles partly due to the recording strategy. Preliminary measurements had shown that the crystals were not perfectly stable and to save time each reflexion was accordingly scanned only once rendering weak reflexions statistically uncertain. The intensities were corrected for Lorentz and polarization factors but not for extinction or absorption. By Wilson statistics the structure factors were put on an approximately absolute scale but the different layers were, in the subsequent refinement, given individual scale factors.

Determination of the structure

The x and y coordinates of the two chlorine atoms in the asymmetric unit were determined from three-dimensional Patterson maps. However, the y coordinates were quite uncertain as the strongest maximum in $P(xy0)$ was found to be a double peak. A three-dimensional Fourier synthesis was performed with the signs of structure factors calculated on the chlorine-

atom contributions. When the chlorine positions in this way had been accurately determined a renewed Fourier synthesis revealed all the missing 24 non-hydrogen atoms of the asymmetric unit. A final Fourier synthesis based on the 26 non-hydrogen atoms yielded an R value of 0.21 ($R = \sum ||F_o| - |F_c|| / \sum |F_o|$).

Refinement of the structural parameters was carried out by full-matrix least-squares calculations using all observed reflexions. With the exception of the chlorine atoms, which were refined anisotropically, isotropic refinement was preferred as the number of available reflexions was small. The function minimized was $\sum w(|F_o| - |F_c|)^2$, w being equal to $1/(a + |F_o| + b|F_c|)^2$ with $a = 10.0$ and $b = 0.01$. A few cycles of refinement lowered the R index to 0.074. At this stage a difference synthesis revealed the positions of all hydrogen atoms. The hydrogen atoms were given the B value of the atoms to which they were bound and although not refined they were included in the last cycles of refinement. The refinement procedure was terminated at an R index of 0.057 when the shifts of the positional coordinates were less than 20% of their e.s.d.'s. The final positional and thermal parameters of the non-hydrogen atoms and the thermal parameters of the hydrogen atoms as determined

from difference maps are given in Table 1.* The scattering factors for chlorine, carbon and nitrogen were those of *International Tables for X-ray Crystallography* (1962) while that for the hydrogen atoms was taken from Stewart, Davidson & Simpson (1965). All com-

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30995 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

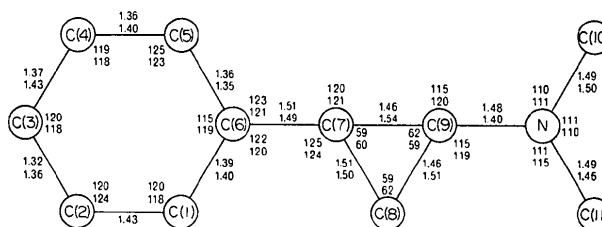


Fig. 1. Schematic drawing of the SKF 556 molecule showing the numbering of the atoms. Distances in Å, angles in degrees. The upper and lower figures refer to the *A* and *B* molecules respectively.

Table 1. Fractional atomic coordinates and thermal parameters

Standard deviations are in parentheses.

The β_{ij} of the chlorine atoms are coefficients in the expression $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$.

	<i>x</i>	<i>y</i>	<i>z</i>	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl(A)	0.7281 (2)	0.4056 (5)	0.0600 (-)	0.0073 (2)	0.0224 (11)	0.0012 (0)	0.0013 (8)	0.0005 (2)	-0.0009 (4)
Cl(B)	0.4656 (2)	0.4005 (5)	0.4381 (1)	0.0069 (2)	0.0221 (12)	0.0013 (0)	0.0041 (8)	-0.0009 (2)	0.0005 (4)

Molecule A					Molecule B				
	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>		<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
C(1)	0.3675 (12)	0.6373 (24)	0.1908 (5)	6.2 (3)	C(1)	0.0994 (11)	0.6918 (23)	0.3123 (4)	5.2 (3)
C(2)	0.2729 (15)	0.5813 (28)	0.2170 (5)	7.3 (4)	C(2)	0.0120 (13)	0.6520 (26)	0.2849 (5)	6.6 (4)
C(3)	0.2170 (13)	0.3884 (24)	0.2138 (4)	6.1 (3)	C(3)	-0.0539 (12)	0.4620 (24)	0.2835 (4)	5.6 (3)
C(4)	0.2419 (16)	0.2488 (31)	0.1838 (6)	7.7 (5)	C(4)	-0.0259 (15)	0.2891 (32)	0.3103 (6)	7.5 (5)
C(5)	0.3314 (14)	0.3036 (28)	0.1590 (5)	6.2 (3)	C(5)	0.0623 (14)	0.3320 (29)	0.3379 (5)	6.4 (3)
C(6)	0.3955 (10)	0.4963 (20)	0.1603 (4)	4.3 (3)	C(6)	0.1272 (10)	0.5216 (20)	0.3383 (4)	4.3 (3)
C(7)	0.4896 (11)	0.5544 (20)	0.1309 (4)	4.5 (3)	C(7)	0.2222 (12)	0.5555 (22)	0.3678 (4)	5.1 (3)
C(8)	0.5662 (15)	0.7616 (25)	0.1316 (7)	6.2 (4)	C(8)	0.3073 (15)	0.7484 (24)	0.3674 (6)	6.4 (4)
C(9)	0.4693 (10)	0.7375 (16)	0.1039 (4)	2.9 (3)	C(9)	0.2121 (11)	0.7407 (20)	0.3982 (6)	4.6 (4)
N	0.5093 (8)	0.6953 (15)	0.0638 (3)	3.3 (2)	N	0.2461 (8)	0.6995 (17)	0.4362 (3)	3.5 (2)
C(10)	0.4129 (10)	0.5781 (20)	0.0419 (4)	4.0 (2)	C(10)	0.1490 (11)	0.5785 (21)	0.4577 (4)	4.6 (3)
C(11)	0.5438 (10)	0.9087 (22)	0.0447 (4)	4.6 (3)	C(11)	0.2837 (11)	0.8965 (22)	0.4580 (4)	4.7 (3)

H(1)	0.415	0.787	0.193	H(1)	0.140	0.838	0.312
H(2)	0.249	0.683	0.238	H(2)	-0.005	0.767	0.266
H(3)	0.155	0.340	0.232	H(3)	-0.115	0.438	0.266
H(4)	0.200	0.097	0.181	H(4)	-0.080	0.145	0.311
H(5)	0.355	0.203	0.138	H(5)	0.080	0.208	0.359
H(7)	0.538	0.413	0.124	H(7)	0.260	0.412	0.382
H(8a)	0.542	0.881	0.144	H(8a)	0.290	0.843	0.350
H(8b)	0.662	0.722	0.125	H(8b)	0.401	0.736	0.376
H(9)	0.411	0.813	0.104	H(9)	0.142	0.810	0.400
H(N)	0.566	0.585	0.060	H(N)	0.312	0.590	0.440
H(10a)	0.342	0.692	0.039	H(10a)	0.087	0.687	0.460
H(10b)	0.429	0.550	0.018	H(10b)	0.144	0.439	0.447
H(10c)	0.394	0.445	0.052	H(10c)	0.173	0.547	0.482
H(11a)	0.472	1.025	0.043	H(11a)	0.343	0.961	0.438
H(11b)	0.612	0.949	0.062	H(11b)	0.215	1.000	0.470
H(11c)	0.552	0.834	0.022	H(11c)	0.331	0.817	0.477

putations were performed using the program system by Bergin (1971*a*) written for an IBM 360/75.

Molecular geometry

Bond lengths and angles found in the two independent left- and right-handed molecules are shown in Fig. 1.

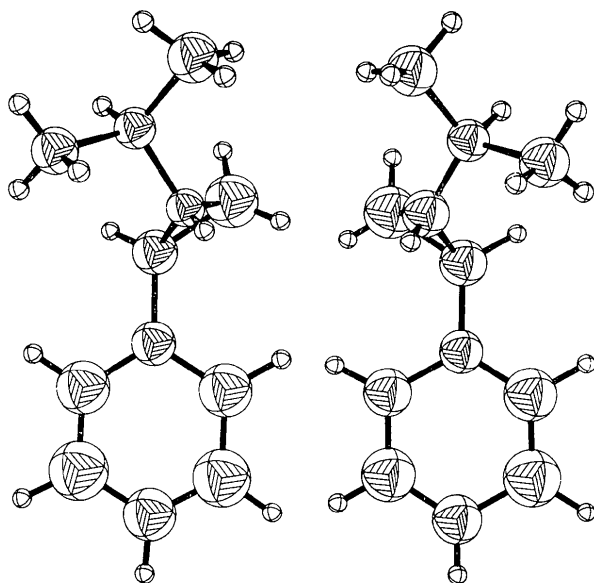


Fig. 2. Perspective drawings projected onto the plane of the phenyl ring of molecule *A* (left) and *B* (right) of SKF 556. Heavy atoms are represented by thermal spheres of 50% probability. Hydrogen atoms depicted as small spheres [program *ORTEP* by Johnson (1965)].

Owing to the limited number of reflexions, the high thermal movement and the mediocre quality of the crystal, the calculated e.s.d.'s are large: 0.02–0.03 Å in the C–C bonds and 1.0°–1.9° in the bond angles. The six-membered rings of the *A* and *B* molecules are both planar within ± 0.02 Å. The positions of the hydrogen atoms as determined from a difference synthesis also resulted in quite normal C–H and N–H bonds with lengths ranging from 0.8 to 1.1 Å. As is evident from Fig. 2 the *A* and *B* molecules are almost mirror images of one another. This is reflected in the torsion angles τ_1 and τ_2 : the τ_1 angle, C(5)–C(6)–C(7)–C(9), is $+111^\circ$ and -115° in the *A* and *B* molecules respectively and the τ_2 angle, C(6)–C(7)–C(9)–N, is -139° and $+139^\circ$. The conformations of the two molecules, where only the τ_1 angle has rotational freedom, are not far from what is normally found in crystal structure determinations of biologically active monoamines with a charged amino nitrogen atom (Carlström, Bergin & Falkenberg, 1973). These important compounds have usually an extended ethylamine side chain (τ_2 close to 180°), the plane of which is more or less perpendicular to the aromatic ring(s) (τ_1 around 90°). Although the molecule of SKF 556 has its ethylamine side chain locked in a *trans* position it is twisted 41° from the fully extended conformation. This deflexion of the chain is however counteracted by a larger τ_1 angle resulting in a position of the amino nitrogen atom with respect to the aromatic ring almost identical with that of an 'ideal' monoamine. The distance of the amino nitrogen from the centre of the phenyl ring is 5.09 Å and its distance from the phenyl plane is 1.63 Å in both the *A* and *B* molecules of SKF 556. These figures are

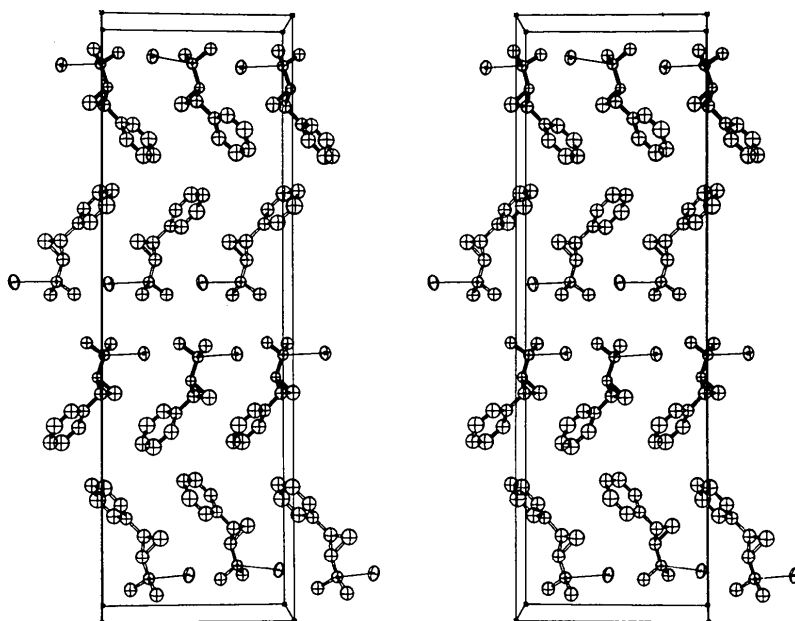


Fig. 3. Stereoscopic drawing of the unit cell of SKF 556 projected onto the *ac* plane. The *A* molecules are shown with filled bonds, the *B* molecules with open bonds. The N...Cl hydrogen bonds are represented by thin lines. Hydrogen atoms are omitted for clarity [program *ORTEP* by Johnson (1965)].

within 0.1 Å the same as those given by Bergin (1971*b*) for biologically active phenethylamines. The geometry of the SKF 556 molecule may explain its strong interaction with monoamine oxidase. No information, however, is available as to whether there is any difference in activity between the two stereoisomers of the *trans* form here investigated.

Crystal packing

Each of the two molecules in the asymmetric unit of the SKF 556 structure is connected to its neighbouring chlorine atom by an unusually short N-H...Cl hydrogen bond; the N...Cl distance being 3.00 Å and 3.04 Å for the *A* and *B* molecules respectively. The hydrogen atom on the amino nitrogen is in both cases pointing towards the chlorine atom with N-H...Cl angles of 163° and 168° respectively, resulting in H...Cl distances of 2.11 and 2.06 Å. The phenylcyclopropylamine cation and the chloride ion thus form a unit. In the structure these units are held together by van der Waals forces only. As can be seen in Fig. 3, which depicts the arrangement of the cations and the anions within a cell, the two independent molecules have virtually identical surroundings. It should be pointed out that the *A* and *B* molecules are related by a non-crystallographic glide translation along [100] at $z = \frac{1}{4}$. Thus, the symmetry operation: $x - \frac{1}{4}, y, \frac{1}{2} - z$ almost brings the *A* and *B* molecules into coincidence. This symmetry operation results in a non-crystallographic centre of symmetry at $x = \frac{1}{8}, y = 0, z = 0$.

The shortest intermolecular distances involving non-hydrogen atoms all exceed 3.59 Å (a Cl...Cl distance) which is well above the sum of van der Waals radii. The same is true for the C...H and N...H intermolecular distances which all are larger than 3.03 Å. The only

short contacts are between hydrogen atoms of neighbouring methyl groups (minimum H...H separation 2.34 Å) and between methyl hydrogen atoms and chloride ions with a shortest H...Cl distance of 2.34 Å. Since the positions of the hydrogen atoms were not accurately determined these figures may not be very reliable. The structure is quite loosely packed resulting in a relatively low density and allowance for high thermal movements which are especially pronounced in the phenyl rings. Since no intra- or intermolecular hydrogen bonds act upon the molecules and the packing is rather loose it is believed that the molecules have assumed a conformation corresponding to an energy minimum.

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Structure Cristalline et Moléculaire du Bromure d'*o*-Formyl Phénylsélénényle (C₇H₅OSeBr)

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The crystal and molecular structure of *o*-formylphenylselenenyl bromide has been determined by three-dimensional X-ray analysis. Crystals are orthorhombic, *Pc*2₁*n*, with $a = 15.632$, $b = 4.582$, $c = 11.084$ Å and $Z = 4$. The refinement led to a final *R* value of 0.060. The molecule has a planar *cis* conformation. The structure is compared with that of *o*-formylphenyltellurenyl bromide.

Introduction

La détermination de la structure cristalline et moléculaire du bromure d'*o*-formyl phénylsélénényle

(C₇H₅OSeBr) s'inscrit dans le cadre plus général de l'étude physico-chimique des benzaldéhydes *ortho*-substitués caractérisés sur la Fig. 1.

Des travaux récents ont été consacrés aux composés