

CRYSTAL AND MOLECULAR STRUCTURE OF 2-DIMETHYLAMINOMETHYL-3'-HYDROXYDIPHENYL SULPHIDE MALEATE

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The crystal and molecular structure of the title compound, $C_{19}H_{21}NO_5S$, $M = 375.44$, was solved by X-ray structure analysis using diffractometer intensity measurement with CuK_{α} radiation. The space group is $P\bar{1}$, with lattice parameters $a = 555.7(3)$, $b = 1697.0(8)$, $c = 1035.4(4)$ pm, $\alpha = 106.77(4)^{\circ}$, $\beta = 98.19(4)^{\circ}$, $\gamma = 90.64(4)^{\circ}$, $V = 923.9(8) \cdot 10^6$ pm³, $Z = 2$, $\rho_{calc} = 1.349$ g/cm³, $\rho_m = 1.32$ g/cm³. Anisotropic refinement of all nonhydrogen and isotropic refinement of eight hydrogen atoms converged to $R = 0.056$ and $wR = 0.114$ for 2481 observed reflections. Hydrogen bonds $O18-H181 \cdots O25$ and $N9-H91 \cdots O24^i$ join neighbouring diphenyl sulphide and maleate molecules to linear chains. The parallel chains interact through van der Waals contacts only. Molecules of maleic acid are nearly planar keeping π -electron delocalization. An angle between phenyl rings of the diphenyl sulphide molecule is $80.9(1)^{\circ}$ and torsion angles around S-C bonds are $23.2(3)^{\circ}$ and $73.6(3)^{\circ}$.

Recently, 2-(phenylthio)benzylamines have been found to be potentially antidepressive^{1,2}. Up to now, the most promising compound is 2-dimethylaminomethyl-3'-hydroxydiphenyl sulphide (in the form of maleate). This compound shows a very high affinity to both imipramine and desipramine binding sites in the rat brain and a very high selectivity of inhibition of 5-hydroxytryptamine re-uptake in the rat brain structures. It is undergoing preclinical studies.

Determination of three-dimensional structure of the title compound and its congeners may thus be of importance for understanding and further improving of relations between structure and biological activity of these compounds. This is why we began to study possible three-dimensional structures of substituted diphenyl sulphides³ and to solve crystal and molecular structures of biologically important derivatives⁴ by X-ray structure analysis. In the present paper, the three-dimensional structure of 2-dimethylaminomethyl-3'-hydroxydiphenyl sulphide is reported.

EXPERIMENTAL

Colorless well-developed crystals of the title complex¹ ($M = 375.44$) were grown from ethyl alcohol-heptane solution (9 : 1) by slow evaporation at a room temperature ($\rho_{calc} = 1.349$ g/cm³,

$\rho_m = 1.32 \text{ g/cm}^3$). The single crystal with dimensions of $0.66 \times 0.48 \times 0.41 \text{ mm}$ was employed for the intensity measurement on the Syntex P2₁ diffractometer using graphite-monochromated CuK_α radiation ($\lambda = 154.2 \text{ pm}$). Cell constants were refined by least squares using 15 reflections in the 2θ range $\langle 5^\circ; 33^\circ \rangle$. A space group was independently determined also by the Weissberg and oscillation techniques. Intensity data were collected by $\theta/2\theta$ scan in the range $2\theta \in \langle 0^\circ; 116^\circ \rangle$, $-6 \leq h \leq 5$; $-18 \leq k \leq 17$; $0 \leq l \leq 11$. A total of 2 515 unique reflections [2 481 from them with $F > 3.92\sigma(F)$] was measured. The stability of the crystal was checked up by measurement of three standard reflections (200; 060; 005) which were measured after every 47 reflections. No significant variation in their intensities was observed. No absorption correction was applied ($\mu r = 0.89$).

The structure was solved by direct methods using the MULTAN program⁵ in the space group $P7_1$. Solution yielded a set of coordinates of all non-hydrogen atoms. The structure was refined with the SHELX76 program⁶. An isotropic refinement based on 2 481 observed $|F|$ magnitudes including all non-hydrogen atoms gave $R = 0.16$. Anisotropic refinement of non-hydrogen atoms and isotropic one of hydrogens converged to $R = 0.064$. Hydrogen atoms were put to their geometrically ideal positions and 13 of them had to be kept in these positions to the end of refinement. The positions of fixed hydrogen atoms are not tabulated in Table I. In the following refinement cycles, the scalar extinction coefficient g (Eq. (1)):

$$F_{\text{CNEW}} = F_o(1 - gF_c^2/\sin \theta) \quad (1)$$

was refined to $g = 6.5 \cdot 10^{-6}$ lowering thus R factor from 0.064 to the final value of 0.056 for 270 refined parameters (final $R_w = 0.114$ and $s = 3.6$). Final difference Fourier map did not contain any peak higher than 0.29 and lower than -0.32 e/\AA^3 . $(\Delta/\sigma)_{\text{max}} = 0.17$.

RESULTS AND DISCUSSION

The final fractional coordinates and equivalent isotropic temperature factors with their estimated standard deviations are listed in Table I. *PLUTO drawing⁷ of a single molecule of the title compound is depicted in Fig. 1 and a packing diagram is shown in Fig. 2. Intra- and intermolecular geometrical parameters were computed by the PARST program⁸.

The pivotal crystal packing forces are hydrogen bonds $\text{O18} \cdots \text{H181} \cdots \text{O25}$ [the $\text{O18} \cdots \text{O25}$ length is $266.9(3) \text{ pm}$ and the $\text{O18} \cdots \text{H181} \cdots \text{O25}$ angle is $155.8(3)^\circ$] and $\text{N9} \cdots \text{H91} \cdots \text{O24}^i$ [$\text{N9} \cdots \text{O24}^i = 278.6(3) \text{ pm}$, $\text{N9} \cdots \text{H91} \cdots \text{O24}^i = 165(2)^\circ$]. These bonds join neighbouring diphenyl sulphide and maleate molecules to a linear chains (Fig. 2). The parallel chains interact through van der Waals contacts only. Other important intermolecular contacts are $\text{C8} \cdots \text{H82} \cdots \text{O18}^i$, $\text{C21} \cdots \text{H211} \cdots \text{O26}^{ii}$ and $\text{C22} \cdots \text{H221} \cdots \text{O25}^{ii}$ (i and ii are equivalent positions: $i \equiv x, y, z - 1$; $ii \equiv x - 1, y, z$).

The principal bond lengths, angles and torsion angles are listed in Table II. All atoms of maleic acid lie almost in one plane. The H261 hydrogen atom of maleic

* Lists of observed and calculated structure factors, anisotropic thermal parameters and details of refinement are available upon request from authors.

TABLE I

Fractional atomic coordinates of 2-dimethylaminomethyl-3'-hydroxydiphenyl sulphide maleate and equivalent isotropic temperature parameters U_{eq} [pm^2] of non-hydrogen atoms and isotropic temperature parameters of hydrogen atoms with their e.s.d.'s in parentheses. Only non-restrained hydrogen atom parameters are given. $U_{\text{eq}} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$

Atom	$(x/a) \cdot 10^4$	$(y/b) \cdot 10^4$	$(z/c) \cdot 10^4$	U_{eq}
S1	9285(1)	2915·0(4)	3304·5(6)	610(3)
C2	6801(4)	3382(1)	2574(2)	476(8)
C3	5849(5)	4099(1)	3325(2)	560(9)
C4	3981(6)	4458(2)	2735(3)	683(11)
C5	3019(6)	4118(2)	1376(3)	740(11)
C6	3961(6)	3419(2)	621(3)	684(10)
C7	5855(4)	3037(1)	1190(2)	496(8)
C8	6862(4)	2275(1)	330(2)	497(8)
N9	4990(3)	1584(1)	— 314(2)	448(7)
C10	3652(5)	1357(2)	694(3)	607(11)
C11	6167(5)	847(1)	— 1118(3)	588(9)
C12	9157(4)	3276(1)	5084(2)	514(9)
C13	10975(5)	3819(2)	5927(3)	607(10)
C14	10949(5)	4053(2)	7330(3)	654(10)
C15	9210(5)	3734(2)	7870(3)	609(9)
C16	7387(4)	3179(1)	7002(2)	526(8)
C17	7352(4)	2961(1)	5612(2)	503(9)
O18	5740(4)	2861(1)	7601(2)	740(8)
O19	— 831(4)	494(1)	1874(2)	740(8)
C20	32(4)	750(2)	3075(3)	556(10)
C21	— 1549(4)	806(1)	4135(3)	521(8)
C22	— 1127(4)	1071(2)	5495(3)	536(10)
C23	1142(4)	1422(1)	6452(2)	498(9)
O24	1078(3)	1595(1)	7684(2)	630(7)
O25	3050(3)	1545(1)	5958(2)	707(8)
O26	2331(3)	989(2)	3450(2)	758(9)

Atom	$(x/a) \cdot 10^3$	$(y/b) \cdot 10^3$	$(z/c) \cdot 10^3$	$U_{\text{iso}} \cdot 10^{-1}$
H41	365(6)	504(2)	325(4)	83(9)
H51	194(7)	444(3)	98(4)	90(9)
H91	364(5)	169(1)	— 95(3)	42(5)
H141	1222(6)	446(2)	791(4)	74(8)
H171	596(5)	262(2)	508(3)	56(7)
H211	— 303(6)	58(2)	372(3)	74(9)
H221	— 261(5)	102(1)	598(3)	47(6)
H261	276(7)	117(2)	457(4)	95(11)

acid forms an intramolecular hydrogen bridge between O26 and O25 [$O25 \cdots O26 = 246.5(3)$ pm, $O26-H261 \cdots O25 = 167(3)^\circ$]. The atoms forming this hydrogen bridge have greatest deviations from a mean plane formed by the C and O atoms of the molecule [$O25: 6.8(3)$, $O26: -5.3(6)$ and $H261: -13(4)$ pm]. C—C—C valence

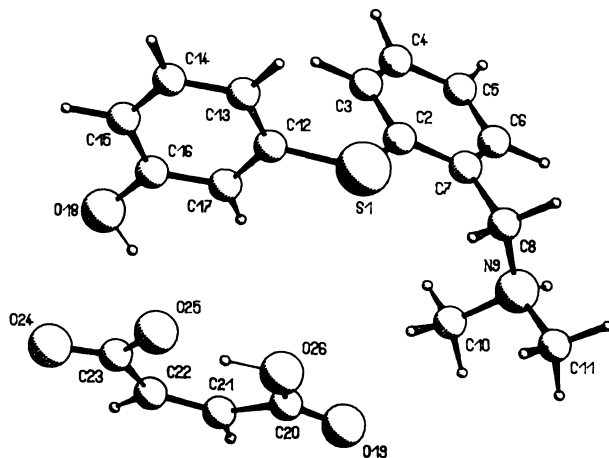


FIG. 1

A perspective view of 2-dimethylaminomethyl-3'-hydroxydiphenyl sulphide maleate with a labeling scheme

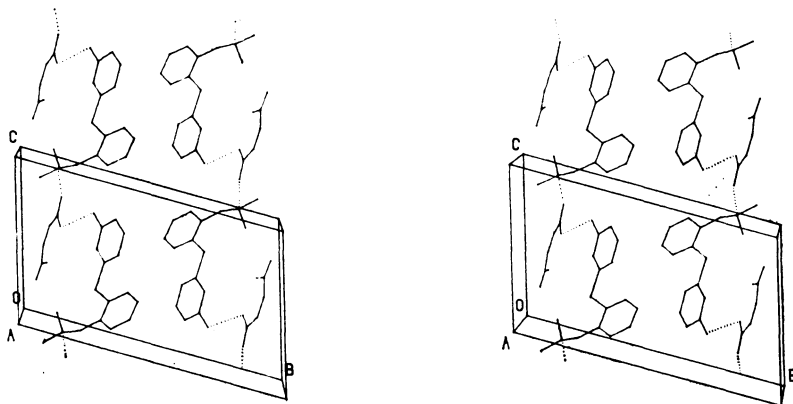


FIG. 2

Stereoscopic packing diagram. View down the *a* axis shows the content of two elementary cells. Hydrogens were omitted for clarity. Dotted lines are hydrogen bonds

angles of the carbon atoms bound by the double bond are enlarged (Table II). The deformation relieves too short contact of the carboxy groups and helps to hold the molecule planar. Planarity is probably energetically favorable due to π -electron delocalization.

TABLE II
Selected bond lengths (pm), angles ($^{\circ}$) and torsion angles ($^{\circ}$)

Bonds			
S1-C2	178.3(3)	S1-C12	177.8(3)
C7-C8	150.7(3)	C8-N9	149.1(3)
N9-C10	149.6(4)	N9-C11	150.3(3)
C16-O18	136.3(4)	O19-C20	121.6(3)
O26-C20	130.6(3)	O24-C23	123.0(3)
O25-C23	128.1(3)	C20-C21	148.4(4)
C21-C22	133.3(4)	C22-C23	148.8(3)

Valence angles			
C2-S1-C12	103.4(2)	C10-N9-C11	110.4(2)
S1-C2-C3	121.8(2)	C15-C16-C17	120.0(2)
S1-C3-C7	118.7(2)	C15-C16-O18	117.0(3)
S1-C12-C13	119.2(2)	O19-C20-O26	121.0(3)
D1-C12-C17	119.6(2)	O24-C23-O25	123.2(3)
C3-C2-C7	119.4(3)	O19-C20-C21	119.9(3)
C13-C12-C17	121.0(3)	O24-C23-C22	118.2(3)
C2-C7-C6	118.3(3)	C20-C32-C22	132.8(3)
C2-C7-C8	121.3(3)	C23-C22-C21	130.8(3)
C7-C8-N9	113.4(3)	C20-C21-H211	108(2)
C8-N9-C10	113.2(2)	C23-C22-H221	113(1)
C8-N9-C11	109.6(3)		

Torsion angles			
C12-S1-C2-C3	23.3(3)	C12-C1-C2-C7	-157.5(3)
C2-S1-C12-C13	-111.3(3)	C2-S1-C12-C17	73.4(3)
S1-C2-C7-C8	1.3(4)	C2-C7-C8-N9	122.6(3)
C7-C8-N9-C10	-54.9(3)	C7-C8-N9-C11	-178.6(2)
C7-C8-N9-H91	61(2)	C14-C15-C16-O18	178.1(3)
C15-C16-O18-H181	-180.0(3)	O19-C20-C21-C22	-178.5(4)
O26-C20-C21-C22	0.4(6)	O23-C23-C22-C21	-177.5(4)
O25-C23-C22-C21	3.9(5)	C20-C21-C22-C23	0.9(6)
C21-C20-O26-H261	4(2)	C20-C21-C22-H221	-178(2)
C23-C22-C21-H211	176(3)		

A diphenyl sulphide skeleton of the 2-dimethylaminomethyl-3'-hydroxydiphenyl sulphide molecule has all the characteristic features of diphenyl sulphide molecules³ as they were found by statistical analysis of geometries retrieved from the Cambridge Structural Database⁹. The angle between mean planes of the phenyl rings is 80.9(1)° and torsion angles around the S—C bonds are 23.2(3)° for C3—C2—S1—C12 and 73.6(3)° for C2—S1—C12—C17.

The phenyl ring C2···C7 inclusive, is almost planar [$\chi^2 = 8.7$, the greatest deviation has C3: 0.6(3) pm]. The S1 and C8 atoms lie in this plane, too [deviations are 4.2(2) and 2.3(3) pm]. The second phenyl ring, C12···C17 inclusive, is more deformed from planarity [$\chi^2 = 34.5$, greatest deviation has C17: 1.3(4) pm]. The O18 and H181 atoms are both close to the plane (Table II). The S1 atom do not lie in the plane [the distance is 14.9(2) pm].

The N9 cation is attracted to the atom O24ⁱ of maleic acid with which it forms the intermolecular hydrogen bond. Thus, the torsion angle C2—C7—C8—N9 differs from an expected value of 90° and is 122.6(3)°. The tetrahedral arrangement around N9 is not violated (Table II).

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