A Structure and Conformation Study of DL-*threo*-3,4-Dihydroxyphenylserine and its Hydrochloride Trihydrate

ARVID MOSTAD, CHRISTIAN RØMMING and MAGNE STRØMME

Chemistry Department, University of Oslo, Oslo 3, Norway

The crystal structures of the title compounds have been studied by X-ray diffraction methods. The crystals of the hydrochloride trihydrate (DOPS.HCl.3H$_2$O) are monoclinic, space group $P2_1/c$ with unit cell dimensions $a = 12.153(5)$ Å; $b = 7.065(3)$ Å; $c = 18.779(8)$ Å; $\beta = 123.15(2)°$. The structure was solved using Patterson methods and refined to a conventional R-factor of 0.038. Estimated standard deviations are $0.003-0.004$ Å in bond lengths and $0.2-0.3°$ in bond angles not involving hydrogen atoms.

The crystals of DL-*threo*-3,4-dihydroxyphenylserine (DOPS) are orthorhombic, space group $P2_12_12_1$, with unit cell dimensions $a = 6.046(1)$ Å; $b = 5.590(1)$ Å and $c = 25.999(4)$ Å; the structure was solved by direct methods. Disorder is indicated in Weissenberg films, and the structure could, presumably for this reason, not be refined to R-factors below 0.14.

The molecular structures were found to be similar to those found for 3,4-dihydroxyphenylalanine (DOPA) and the corresponding hydrochloride. The packings of the molecules in the crystals of DOPS and DOPA are found to be related.

L-*threo*-3,4-Di-hydroxyphenylserine (L-DOPS) has the (αS, βR) configuration and differs from L-3,4-dihydroxyphenylalanine (L-DOPA) only by the hydroxyl group in the β position. The compound is a substrate of mammalian aromatic L-amino acid decarboxylase[1,2] and may thus act as a direct precursor of noradrenaline. In order to study the effect of the β-OH group on the conformation of the molecule as well as to obtain data for the study of the structure and conformation of aromatic amino acids in general, the crystal structure of the title compounds has been carried out.

EXPERIMENTAL

Plate-shaped yellowish crystals of the hydrochloride trihydrate were formed by the addition of concentrated hydrochloric acid to an aqueous solution of DL-*threo*-dihydroxyphenylserine. The specimen used for the X-ray experiments had approximate dimensions 0.1 × 0.05 × 0.02 mm. Oscillation and Weissenberg photographs indicated monoclinic symmetry and systematic absent reflections proved the space group to be $P2_1/c$. Unit cell dimensions were determined from diffractometer settings of 16 general reflections using CuKα radiation ($\lambda = 1.5418$ Å). The intensity data were recorded on a SYNTEX $P1$ diffractometer using graphite crystal monochromated MoKα radiation ($\lambda = 0.71069$ Å). 2514 independent reflections with $\sin \theta/\lambda < 0.7$ Å^{-1} were measured using the $\theta/2\theta$ scanning mode with a scan speed (2θ) from 2 to 8° min^{-1} depending on the intensity. The scan range was from 0.8° below $2\theta(\alpha_1)$ to 0.8° above $2\theta(\alpha_2)$; background counts were taken for 0.35 times the scan time at each end of the scan range limits. Three standard reflections were measured at intervals of 72 reflections; they showed no systematic variations during the data collection. The standard deviation of the intensity was taken as $\sigma(I) = [C_T + (0.02 \, C_N)^2]^{\frac{1}{2}}$ where C_T is the total number of counts and C_N the scan count minus background count. Of the total number of recorded reflections 1616 were found to have intensities larger than $2.5\sigma(I)$ and subsequently used for the structure analysis.

Yellow plate-shaped crystals of DL-*threo*-dihydroxyphenylserine precipitated by slow diffusion of ethanol into an aqueous solution of the compound; a specimen with dimensions 0.28 × 0.24 × 0.12 mm was used for the X-ray experiments. Oscillation and Weissenberg photographs showed systematic absences of reflections corresponding to space group $P2_12_12_1$ and indicated also a disorder in the crystals; streaks of intensity connecting reflections in

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Table 1. Fractional atomic coordinate and thermal parameters ($\times 10^5$) with estimated standard deviations for non-hydrogen atoms in LD-threo-DOPS.HCl.3H$_2$O. The temperature factor is given by exp $- (B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)$.

Atom	X	Y	Z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl	29190(9)	6477(13)	15047(6)	871(10)	1724(22)	360(4)	210(25)	711(11)	−138(16)
O1	67100(19)	32397(31)	61907(13)	407(22)	1430(52)	165(9)	−362(54)	232(25)	−146(35)
O2	72364(20)	34560(33)	50059(14)	529(25)	1723(60)	222(11)	−431(57)	413(28)	−42(40)
O3	−10584(20)	21741(33)	29463(14)	466(23)	2226(64)	271(11)	−338(65)	214(27)	314(44)
O4	−1092(23)	12719(37)	42987(26)	607(26)	2786(75)	291(11)	−383(70)	433(28)	412(47)
O5	14776(21)	−631(32)	33948(13)	435(22)	1127(50)	304(11)	−72(58)	181(26)	−348(39)
O6	24239(27)	50529(50)	11888(20)	719(30)	1978(81)	407(15)	57(77)	565(36)	−328(56)
O7	58852(30)	20237(47)	22740(17)	699(32)	2186(79)	282(12)	−96(81)	488(33)	−129(51)
O8	4288(32)	19452(42)	16290(20)	749(32)	1846(70)	467(16)	376(79)	678(40)	511(55)
N	11174(29)	39861(44)	32500(20)	457(30)	1042(67)	320(15)	205(74)	389(36)	318(53)
C1	34971(26)	17437(39)	43258(18)	333(28)	736(66)	192(13)	40(70)	187(32)	−6(46)
C2	44636(27)	22343(42)	51562(19)	412(30)	919(67)	201(14)	148(74)	354(35)	70(50)
C3	56979(26)	28083(40)	53676(16)	378(29)	783(62)	138(12)	160(71)	149(32)	−30(46)
C4	59792(26)	29140(40)	47483(18)	357(29)	864(66)	209(13)	−47(73)	298(34)	−18(50)
C5	50240(29)	24453(44)	39202(19)	542(34)	1378(81)	176(14)	−49(81)	392(37)	−8(52)
C6	37894(30)	18637(44)	37105(19)	434(32)	1203(75)	135(13)	155(80)	89(35)	−94(53)
C7	21688(27)	11136(42)	41283(19)	346(29)	861(68)	190(13)	−195(71)	145(34)	−3(49)
C8	12378(27)	27844(44)	39363(19)	438(31)	968(68)	206(14)	−41(75)	316(35)	−27(52)
C9	−1202(29)	20549(44)	36691(21)	467(32)	1002(70)	289(16)	144(79)	413(39)	134(56)

the c^* direction told of an imperfect periodicity along the c axis. Unit cell dimensions were determined from the diffractometer settings of 15 general reflections using Mo$K\alpha$ radiation. 1278 independent reflections were recorded ($\theta/2\theta$ scan, scan speed $2-4°$ min^{-1}, scan range $\pm 1°$); of these 1061 had $I > 2.5\sigma(I)$ and were used for the structure determination.

The intensity data were corrected for Lorentz and polarization effects; no correction for absorption was made. Atomic form factors used were those of Doyle and Turner for Cl$^-$, O, N and C,[3] and of Stewart, Davidson and Simpson for H.[4] Descriptions of computer programs employed in the calculations are given in Refs. 5 and 6.

CRYSTAL DATA

DL-*threo*-3,4-Dihydroxyphenylserine hydrochloride trihydrate, $C_9H_{11}NO_5 \cdot HCl \cdot 3H_2O$, monoclinic, $a = 12.153(5)$ Å; $b = 7.065(3)$ Å; $c = 18.779(7)$ Å; $\beta = 123.15(2)°$ ($t = 18 \pm 1$ °C). $V = 1350.0$ Å^3; $F(000) = 640$; $Z = 4$; $M = 303.70$; $D_{obs} = 1.50$ g cm^{-3}; $D_x = 1.494$ g cm^{-3}. Absent reflections: ($0k0$) for k odd, ($h0l$) for l odd. Space group $P2_1/c$ (No. 14).

L-*threo*-3,4-Dihydroxyphenylserine, $C_9H_{11}NO_5$, orthorhombic, $a = 6.046(1)$ Å; $b = 5.590(1)$ Å; $c = 25.999(4)$ Å, ($t = 18 \pm 1$ °C). $V = 878.7$ Å^3; $F(000) = 448$; $Z = 4$; $M = 213.19$; $D_{obs} = 1.55$ g cm^{-3}; $D_x = 1.611$ g cm^{-3}. Absent reflections: ($h00$) for h odd, ($0k0$) for k odd, ($00l$) for l odd. Space group $P2_12_12_1$ (No. 19).

STRUCTURE DETERMINATIONS

DL-threo-*DOPS.HCl.3H₂O*. The structure was solved by Patterson methods and refined by Fourier and least-squares calculations. Hydrogen atoms were introduced from stereochemical considerations and all positional parameters, anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms were refined. The final conventional R-factor was 0.038, $R_w = 0.035$ and $S = [\sum w(\Delta F)^2/(n-m)]^{\frac{1}{2}} = 1.3$. Corresponding parameters for non-hydrogen atoms are listed in Table 1 and for hydrogen atoms in Table 2.

DL-threo-*DOPS*. This structure was solved by direct methods using the program assembly MULTAN.[6] Refinements of the positional parameters and anisotropic parameters of all non-hydrogen atoms terminated at a conventional

Table 2. Fractional atomic coordinates ($\times 10^3$) and B-value with estimated standard deviations for hydrogen atoms in DL-*threo*-DOPS.HCl.3H₂O.

Atom	X	Y	Z	B
H2	429(2)	216(4)	557(2)	1.5(0.6)
H5	524(2)	247(4)	353(2)	1.4(0.6)
H6	317(3)	157(4)	316(2)	2.2(0.7)
H7	226(2)	45(3)	463(1)	6(0.5)
H8	160(2)	354(4)	446(2)	1.6(0.6)
HN1	55(3)	480(5)	313(2)	3.6(0.9)
HN2	92(4)	335(6)	276(2)	6.0(1.2)
HN3	199(4)	469(6)	344(2)	6.8(1.0)
HO1	636(3)	321(5)	646(2)	4.7(1.1)
HO2	733(3)	375(5)	460(2)	3.4(1.0)
HO4	−98(5)	81(8)	413(3)	10.7(1.6)
HO5	203(4)	−103(6)	347(2)	6.4(1.1)
H1O6	260(5)	384(8)	126(3)	9.2(1.8)
H2O6	291(4)	545(6)	166(3)	5.1(1.3)
H1O7	511(4)	188(6)	207(2)	5.7(1.3)
H2O7	605(4)	305(6)	248(3)	6.0(1.5)
H1O8	−8(4)	244(6)	125(3)	6.9(1.3)
H2O8	106(5)	167(7)	154(3)	8.6(1.6)

R-factor of 0.14 ($R_w = 0.16$). None of the hydrogen atoms could be located from difference Fourier maps and introduction of such atoms from stereochemical considerations did not improve the R-factor. The difficulties in refining the structure are believed to be caused by the disorder indicated in the Weissenberg films. Final parameters are listed in Table 3.
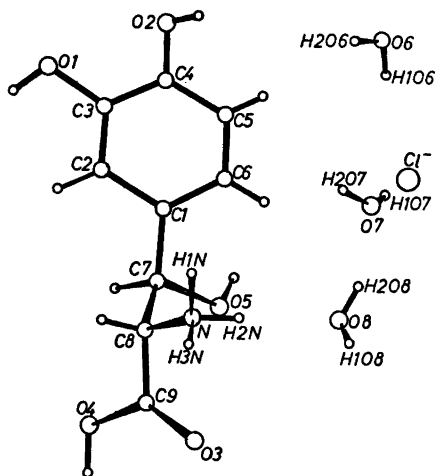

Fig. 1. The numbering of the atoms in the structure of DOPS.HCl.3H₂O.

Table 3. Fractional atomic coordinates and thermal parameters ($\times 10^4$) with estimated standard deviations for non-hydrogen atoms in DL-threo-DOPS. The temperature factor is given by $\exp-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)$.

Atom	X	Y	Z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
O1	8809(16)	−1688(14)	3385(3)	256(28)	162(24)	11(1)	155(46)	25(10)	−24(9)
O2	9483(16)	1391(15)	2636(3)	197(25)	224(25)	11(1)	−27(46)	29(9)	24(10)
O3	−31(17)	5142(24)	4995(3)	236(26)	437(35)	9(1)	−62(66)	47(9)	−6(13)
O4	−1770(14)	5632(20)	4238(4)	113(20)	425(41)	14(2)	−23(46)	35(9)	2(13)
O5	1520(19)	799(18)	4246(6)	253(30)	214(28)	25(2)	−107(49)	74(14)	−12(13)
N	3945(17)	4891(27)	4602(4)	143(24)	357(39)	10(1)	−58(64)	−15(9)	−27(15)
C1	4084(19)	2287(17)	3579(5)	136(27)	83(25)	12(2)	42(47)	26(12)	4(11)
C2	5521(17)	308(21)	3654(3)	132(28)	229(37)	6(1)	14(55)	−6(9)	7(12)
C3	7334(15)	86(21)	3333(4)	91(22)	139(26)	8(1)	−78(50)	−6(9)	−2(12)
C4	7741(22)	1766(26)	2932(4)	167(33)	374(50)	6(1)	−180(70)	4(11)	−33(14)
C5	6234(23)	3555(23)	2859(4)	221(35)	225(36)	7(1)	72(63)	6(12)	20(12)
C6	4447(22)	3956(20)	3174(4)	215(35)	180(33)	9(1)	183(61)	8(12)	−39(12)
C7	2035(21)	2588(21)	3912(4)	160(29)	170(32)	10(2)	−58(56)	13(12)	−15(12)
C8	2113(15)	4988(19)	4227(3)	112(22)	103(22)	5(1)	−24(48)	9(9)	−14(11)
C9	−97(17)	5189(23)	4525(4)	121(26)	190(34)	10(1)	27(56)	13(10)	−34(13)

Table 4. Bond lengths (Å), angles (°) and some torsional angles (°) in the DOPS molecules. Estimated standard deviations in parentheses.

Bond	DOPS.HCl.3H₂O	DOPS
C1−C2	1.389(4)	1.42(2)
C2−C3	1.386(4)	1.38(1)
C3−C4	1.382(4)	1.42(2)
C4−C5	1.379(4)	1.37(2)
C5−C6	1.389(4)	1.37(2)
C6−C1	1.385(4)	1.42(2)
C1−C7	1.512(4)	1.52(2)
C7−C8	1.535(4)	1.57(2)
C8−C9	1.524(4)	1.55(4)
C3−O1	1.384(3)	1.34(1)
C4−O2	1.381(3)	1.32(2)
C7−O5	1.424(3)	1.36(2)
C9−O4	1.316(4)	1.28(2)
C9−O3	1.186(3)	1.22(2)
C8−N	1.483(4)	1.48(1)
C−H	0.94	
N−H	0.93	
O−H	0.84	
Angle		
C1−C2−C3	120.9(3)	118(1)
C2−C3−C4	120.1(3)	121(1)
C3−C4−C5	119.5(3)	118(1)
C4−C5−C6	120.2(3)	124(1)
C5−C6−C1	120.8(3)	117(1)
C6−C1−C2	118.5(3)	121(1)
C6−C1−C7	122.7(3)	118(1)
C2−C1−C7	118.9(3)	120(1)
C1−C7−C8	112.5(2)	112(1)
C7−C8−C9	110.0(3)	107(1)
C1−C7−O5	113.3(2)	118(1)
C8−C7−O5	104.6(2)	108(1)
C7−C8−N	110.8(3)	110(1)
C9−C8−N	108.9(3)	109(1)
C2−C3−O1	123.1(3)	122(1)
C4−C3−O1	116.8(3)	117(1)
C3−C4−O2	117.1(3)	117(1)
C5−C4−O2	123.4(3)	125(1)
C8−C9−O4	111.2(3)	114(1)
C8−C9−O3	123.4(3)	118(1)
O3−C9−O4	125.4(3)	128(1)
Csp₂−Csp₂−H	120	
Csp₃−Csp₃−H	109	
C−N−H	112	
C−O−H	108	
H−N−H	107	
Torsion angle		
C2−C1−C7−C8	−86.4(3)	119(1)
C2−C1−C7−O5	155.2(3)	−6(2)
C1−C7−C8−C9	−174.5(3)	117(1)
O5−C7−C8−C9	−51.2(3)	−53(1)
C7−C8−C9−O3	109.2(4)	116(1)

Table 4. Continued.

N−C8−C9−O3	− 12.3(4)	− 3(1)
C6−C1−C7−C8	93.2(3)	− 65(1)
C6−C1−C7−O5	− 25.2(4)	170(1)
C1−C7−C8−N	− 54.1(3)	− 66(1)
O5−C7−C8−N	69.2(3)	65(1)
C7−C8−C9−O4	− 67.0(3)	− 71(1)
N−C8−C9−O4	168.5(3)	170(1)
C2−C3−O1−HO1	8	
C5−C4−O2−HO2	− 18	
C1−C7−O5−HO5	− 53	
C8−C7−O5−HO5	− 176	
O4−C9−O3−HO4	− 2	

DESCRIPTION AND DISCUSSION

DL-threo-*DOPS.HCl.3H₂O*. A drawing of one formula unit is presented in Fig. 1 where the numbering of the atoms may also be found. Bond lengths and angles are given in Table 4 together with selected torsion angles. These refer to the $(\alpha S, \beta R)$-configuration as depicted in Fig. 1. The crystal environment of the ions is illustrated by a stereoscopic drawing in Fig. 2; the data relevant to the hydrogen bonds are given in Table 5.

Table 5. Angles (°) and distances (Å) regarding the hydrogen bonds in DOPS.HCl.3H₂O. The position of the H-atoms are shown as indicated by the suggested hydrogen bond system.

D	A		D−A	D−H	H−A	∠DHA
O1	O7	$(x, \frac{1}{2}-y, \frac{1}{2}+z)$	2.722	0.83	1.91	168
O2	Cl	$(1-x, \frac{1}{2}+y, \frac{1}{2}-z)$	3.146	0.78	2.40	161
O4	O6	$(-x, y-\frac{1}{2}, \frac{1}{2}-z)$	2.584	0.99	1.56	177
O5	O1	$(1-x, -y, 1-z)$	2.936	0.92	2.02	171
N	O8	$(-x, y-\frac{1}{2}, \frac{1}{2}-z)$	2.902	0.84	2.11	157
N	O8	(x, y, z)	3.043	0.93	2.11	178
N	O1	$(1-x, 1-y, 1-z)$	2.981	1.04	1.98	160
O6	Cl	(x, y, z)	3.164	0.87	2.29	174
O6	O7	$(1-x, \frac{1}{2}+y, \frac{1}{2}-z)$	2.830	0.79	2.05	167
O7	Cl	(x, y, z)	3.214	0.81	2.42	166
O7	Cl	$(1-x, \frac{1}{2}+y, \frac{1}{2}-z)$	3.207	0.79	2.44	162
O8	Cl	(x, y, z)	3.290	0.89	2.41	171
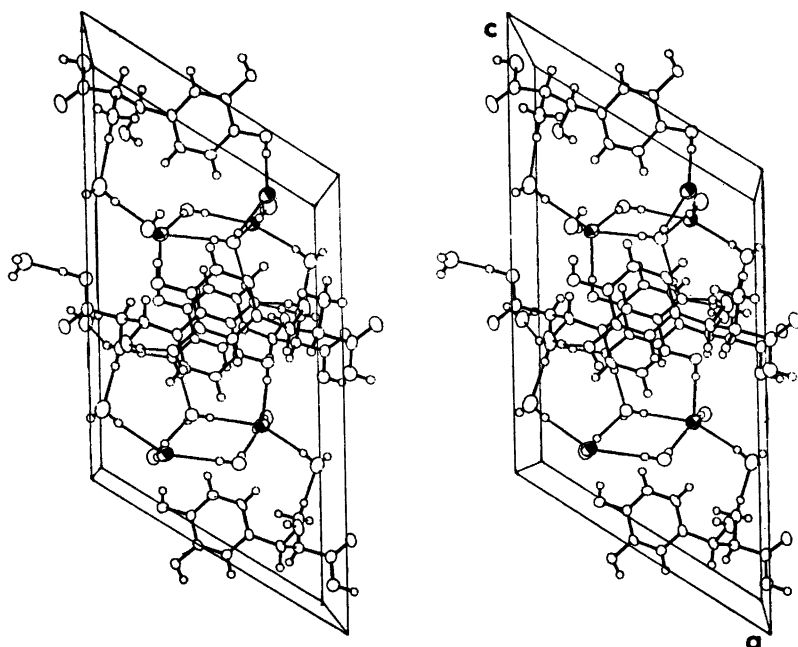
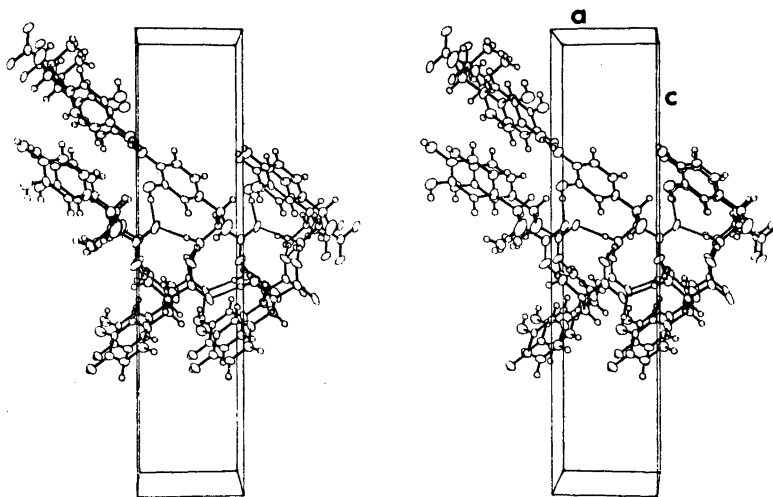*Fig. 2.* Stereoscopic drawing of the packing of molecules in the crystals of DOPS.HCl.3H₂O.

Fig. 3. Stereoscopic drawing of the packing of molecules in the crystals of DOPS.

The crystal structure may be described as stacks of centrosymmetrical pairs of molecules interconnected through two pairs of hydrogen bonds, $O5-HO5\cdots O1$ and $N-H3N\cdots O1$. The stacks, running parallel to the b-axis, appear to be separated from each other by water molecules and chloride ions. Each chloride ion is acceptor in five hydrogen bonds from five oxygen atoms, $O2(1-x,y-\frac{1}{2},\frac{1}{2}-z)$, $O6$, $O7$, $O7(1-x,y-\frac{1}{2},\frac{1}{2}-z)$ and $O8$, situated at the corners of a distorted trigonal bipyramid around the central chloride ion.

One water molecule ($O7$) is engaged as donor in hydrogen bonds to two chloride ions related by a screw axis. It is also acceptor in hydrogen bonds to $O1$ and $O6$. The arrangement of hydrogen bonds is nearly tetrahedral. $O6$ is engaged as acceptor in one and donor in two hydrogen bonds; $O8$ acts as acceptor in one and donor in one such bond. One of the water
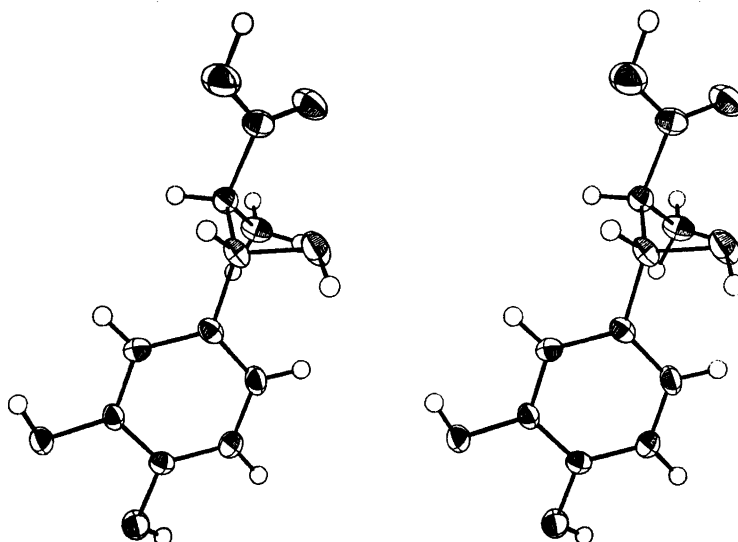

Fig. 4. The conformation of DOPS in the crystals of the hydrochloride.

Table 6. Distances (Å) in the suggested hydrogen bond system in DOPS as compared with those found in DOPA.

D	A		D-A (Å)
DOPS			
O2	O2	$(2-x,\ y-\frac{1}{2},\ \frac{1}{2}-z)$	2.95
O1	O4	$(x+1,\ y-1,\ z)$	2.70
N	O4	$(x+1,\ y,\ z)$	2.79
N	O3	$(x+\frac{1}{2},\ \frac{1}{2}-y,\ 1-z)$	3.07
N	O3	$(x-\frac{1}{2},\ 3/2-y,\ 1-z)$	3.03
DOPA			
O2	O2	$(-x,\ y-\frac{1}{2},\ -z)$	2.85
O1	O4	$(x,\ 1+y,\ z-1)$	2.74
N	O4	$(x,\ y,\ z-1)$	2.82
N	O3	$(1-x,\ y-\frac{1}{2},\ 2-z)$	2.87
N	O3	$(1-x,\ y+\frac{1}{2},\ 2-z)$	3.02

hydrogen atoms (H2O8) is thus not used in the hydrogen bond system.

The conformation of the DOPS molecule is described by the stereoscopic illustration in Fig. 4.

DL-threo-*3,4-Dihydroxyphenylserine*. The numbering of the atoms corresponds to that given in Fig. 1 for the hydrochloride; bond lengths and angles are given in Table 4. The packing of the molecules and the suggested hydrogen bond network in the crystal are illustrated in Fig. 3. The closest O---O and N---O separations, assumed to indicate hydrogen bonds, are given in Table 6.

The way the β-hydroxy oxygen atom (O5) participates in the hydrogen bond system appears obscure. The distance to O3′$(\frac{1}{2}+x,\frac{1}{2}-y, 1-z)$ is only 2.92 Å and the C7−O5−O3′ angle is 114°, both values being reasonable for a hydrogen bond. However, O3′ seems also to act as acceptor in hydrogen bonds from two nitrogen atoms and O5 is situated close to the plane defined by O3′ and the two nitrogen atoms. Another oxygen atom, O1, is separated by 3.10 Å from O5; the C7−O5−O1 angle is 89.4°, indicating another possibility of a weak hydrogen bond.

The conformation of the DOPS molecule is illustrated by the stereoscopic drawing in Fig. 5 and through the torsion angles in Table 4. It may be noticed that the main difference in conformation of DOPS and its hydrochloride is the rotation of about 180° of the aromatic moiety about the C1−C7 bond.

The molecular conformation in the crystals of DOPS corresponds closely to that of L-DOPA.[7] Although the space groups are different (DOPS: $P2_12_12_1$, L-DOPA: $P2_1$), the molecular packings in the two structures are also found to be related, which is apparent from the two hydrogen bond systems, (see Table 6, in which the hydrogen bonds of L-DOPA are included for comparison). Actually, the *a*-axis of DOPS is of the same length as the *c*-axis of DOPA (6.046 and 6.049 Å, respectively) and the molecule marked by A in Fig. 6 is described almost as well by the coordinates given in Ref. 7 (except, of course, for the O5H
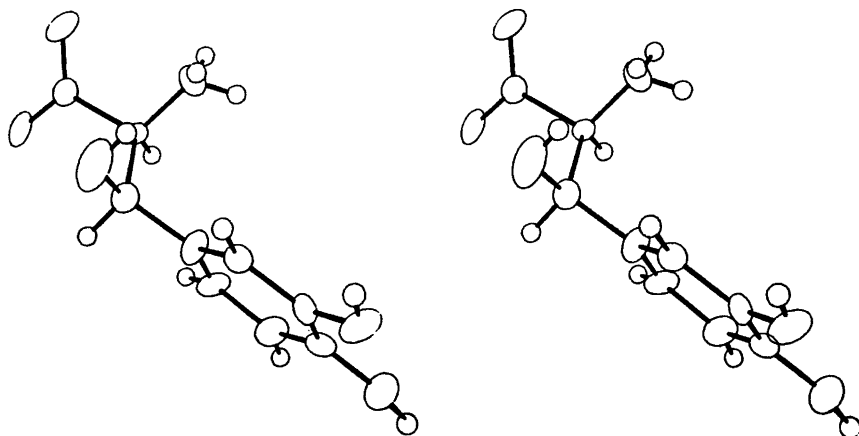

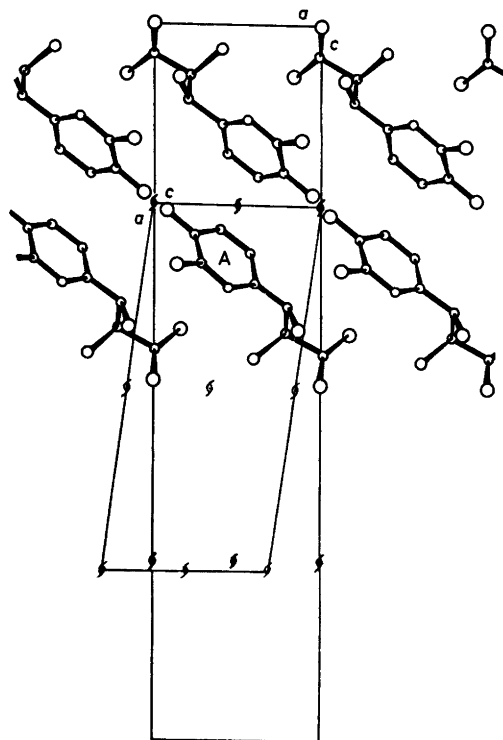*Fig. 5.* The conformation of DOPS in the crystals of the pure compound.

Fig. 6. Comparison of the space groups found in the crystals of DOPS $(P2_12_12_1)$ and L-DOPA $(P2_1)$ in the *b*-projection. The molecular packing in the layer shown in the figure is the same in both structures, but the layers are displaced differently according to the respective space group.

group) as by those given in Table 3 when the origins and axes are chosen as indicated in Fig. 6. It follows that the two crystal structures contain almost identical double molecular layers as depicted in Fig. 6. These layers are, however, differently packed in the two compounds according to the difference in space group symmetry. In DOPA the double layer in Fig. 6 is translated along the appropriate *a*-axis and thus all the molecules have the same orientation in the *b*-projection. On the other hand, the double layer in the DOPS structure is displaced by a screw axis in the *a*-direction of the DOPS unit cell, thereby changing the orientation of the molecules in such a way as to give the *b*-projection a zig-zag appearance. Nevertheless, the hydrogen bonds linking the double layers together in the two

structures are quite similar as may be seen from Table 6. It appears that if the DOPS molecules were to adopt the same packing as in the DOPA structure, the O5$\cdots$O3$(1-x,-y+\frac{1}{2},2-z)$ separation would be only about 2.45 Å. This may be the main reason why another packing is adopted for DOPS. However, occasional mistakes in the discrimination between the two packing modes may well explain the slight disorder in the direction of the *c* axis.

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