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The Crystal and Molecular Structure of *dl*-Betaprodine Hydrochloride

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The crystal structure of the hydrochloride of *dl*-betaprodine (*β*-*dl*-1,3-dimethyl-4-phenyl-4-propionoxypiperidine) has been determined from a three-dimensional vector convergence map. The atomic parameters have been refined by Fourier and differential syntheses to an R index of $0\cdot09_6$ for 2108 observed reflections, and all the hydrogen atoms in the structure have been located from a difference map. The betaprodine molecule in the monoclinic crystals of the hydrochloride has the same configuration and conformation as in the orthorhombic crystals of the hydrobromide. In both cases, the piperidine ring has the chair form with the phenyl ring equatorial and the propionoxy chain axial as in the alpha isomer, but the methyl group on C(3) is axial and is *cis* to the phenyl ring on C(4) in the betaprodine molecule.

Introduction

Crystals of *dl*-betaprodine (*β*-*dl*-1,3-dimethyl-4-phenyl-4-propionoxypiperidine) hydrochloride are monoclinic, space group $P2_1/c$, as are those of the hydrochloride and hydrobromide of *dl*-alphaprodine, whereas *dl*-betaprodine hydrobromide is orthorhombic, space group *Pbca* (Ahmed, Barnes & Masironi, 1963). The present investigation of the crystal structure of *dl*-betaprodine hydrochloride was undertaken because of the importance of the configuration and conformation of the betaprodine molecule (Kartha, Ahmed & Barnes, 1960; Ahmed, Barnes & Masironi, 1963), and to be certain that no molecular changes occur when HBr is replaced by HCl in the crystals of the hydrohalide salt. It was also hoped that it might be possible to locate the hydrogen atom of the hydrohalide in the hydrochloride because it did not appear unequivocally in the final difference maps of the hydrobromide.

Crystal data

dl-Betaprodine hydrochloride ($C_{16}H_{23}NO_2.HCl$; F.W. 297·83) is monoclinic with space group $P2_1/c$ (C_{2h}^5), $a=12\cdot07$ ($\sigma=0\cdot007$), $b=11\cdot84$ ($\sigma=0\cdot01$), $c=12\cdot25$ ($\sigma=0\cdot02$) Å, $\beta=112°\,15'$ ($\sigma=8'$), $U=1620\cdot3$ Å^3, $D_o=1\cdot214$ g.cm^{-3} (Barnes & Forsyth, 1954), $Z=4$, $D_c=1\cdot221$ g.cm^{-3}.

Tabular crystals were obtained by crystallization from acetone (Barnes & Forsyth, 1954); the one selected for data collection had dimensions 0·10, 0·17, and 0·33 mm along the c, a^*, and b axes, respectively. The unit cell parameters were measured on a scintillation-counter spectrogoniometer with Cu radiation, a take-off angle of 1° and a slit of 0·05°; the crystal was mounted with b along the φ-axis of the goniostat.

Intensity data

For Cu radiation, there are 3515 non-equivalent reciprocal lattice sites (excluding those prohibited by the space group symmetry) within the range of the single-crystal orienter, $0° < 2\theta \leq 160°$. The integrated intensities and background at each site were measured in the same way as for *dl*-betaprodine hydrobromide (Ahmed, Barnes & Masironi, 1963), and 2108 reflections (60%) were observed. The intensities were corrected by the appropriate $1/Lp$ factors, but no absorption corrections were considered necessary.

Structure determination and refinement

The molecular structure (excluding the hydrogen atoms) was determined directly from a three-dimensional vector convergence map. The positional parameters of the chlorine atom ($x=0\cdot0292$, $y=-0\cdot0917$, $z=0\cdot2000$) were derived from the Cl–Cl vectors in the Patterson function evaluated with the intensities (modified by $1/Lp$ for normal beam as a sharpening function) for all the observed reflections. Four superpositions of this Patterson function with its origin placed at the four equivalent sites of the chlorine atom resulted in a Fourier map which showed a plausible structure for the molecule. With this trial structure, and assuming $B=3\cdot5$ Å^2 for all atoms, the R index for the observed data was 0·27. A three-dimensional Fourier synthesis computed with 96% of the observed data showed electron-density maxima of 25, 10 to 11, 9, and 6 to 8 e.Å^{-3} in the neighbourhood of the assumed positions for the Cl, O, N, and C atoms, respectively, and a background within $\pm1\cdot0$ e.Å^{-3}. The atomic coordinates taken from this map, assuming $B=3\cdot4$ to $4\cdot5$ Å^2 depending on the observed electron densities, reduced the R index to $0\cdot17_7$.

Two cycles of refinement by differential syntheses further reduced the overall R index to 0·13, assuming the temperature factors to be isotropic for all the light atoms and anisotropic for the chlorine. A difference map which was computed at this stage showed clearly all the hydrogen atoms in the structure including those of the three methyl groups and one

Table 1. *Fractional atomic coordinates, with e.s.d.'s* (Å)

An atom with anisotropic thermal motion was represented in the structure factor calculation by two halves separated from the mean position by the fractional coordinates given in parentheses (Kartha & Ahmed, 1960)

Atom	x	$\sigma(x)$	y	$\sigma(y)$	z	$\sigma(z)$
N(1)	0·0202	0·003	0·2232	0·003	0·0279	0·004
C(2)	0·1165	0·005	0·1982	0·004	0·1447	0·005
C(3)	0·2406	0·005	0·2086	0·004	0·1420	0·005
C(4)	0·2592	0·004	0·3272	0·004	0·0986	0·004
C(5)	0·1584	0·004	0·3515	0·004	−0·0192	0·004
C(6)	0·0362	0·004	0·3396	0·004	−0·0119	0·005
C(7)	0·3844	0·004	0·3411	0·004	0·0996	0·005
C(8)	0·4074	0·005	0·3488	0·005	−0·0033	0·006
C(9)	0·5231	0·005	0·3601	0·006	−0·0007	0·008
C(10)	0·6172	0·005	0·3633	0·006	0·1065	0·010
	(±0·0043)				(±0·0144)	
C(11)	0·5992	0·006	0·3552	0·006	0·2081	0·010
					(±0·0125)	
C(12)	0·4818	0·005	0·3441	0·005	0·2049	0·006
C(13)	0·2550	0·004	0·5147	0·004	0·1845	0·005
C(14)	0·2485	0·005	0·5688	0·005	0·2910	0·006
CH_3'	−0·1003	0·004	0·2105	0·005	0·0343	0·006
	(±0·0034)		(±0·0031)		(±0·0089)	
CH_3''	0·2679	0·006	0·1139	0·005	0·0722	0·007
	(±0·0035)		(±0·0035)		(∓0·0076)	
CH_3'''	0·3680	0·008	0·5620	0·007	0·3943	0·007
O′	0·2465	0·003	0·4005	0·003	0·1906	0·003
O″	0·2669	0·003	0·5620	0·003	0·1034	0·004
	(±0·0064)				(±0·0059)	
Cl	−0·0275	0·001	0·0917	0·001	−0·2003	0·001
	(±0·0081)				(±0·0036)	

close to the nitrogen atom. The electron density maxima at the hydrogen positions were between 0·4 and 0·7 e.Å^{-3} while the remainder of the map was flat (within ±0·2 e.Å^{-3}) with the exception of some regions between ±0·8 e.Å^{-3} close to the chlorine position, and between ±0·5 e.Å^{-3} near the sites of some other atoms, in the usual pattern indicative of thermal anisotropy. Assuming $B=6{\cdot}0$ Å^2 for the hydrogen atoms and adding their contributions to the calculated structure factors, the R index was reduced to $0{\cdot}10_5$. A final cycle of refinement gave the atomic coordinates shown in Table 1, and the electron densities, mean curvatures and the assumed temperature parameters listed in Table 2. The coordinates of the

Table 2. *Electron densities, mean principal curvatures, assumed isotropic B-values, and the anisotropic components ΔB in parentheses*

Atom	ϱ_o (e.Å^{-3})	ϱ_c (e.Å^{-3})	ϱ_o'' (e.Å^{-5})	ϱ_c'' (e.Å^{-5})	B (Å^2)
N(1)	8·88	8·91	68·8	68·6	4·1
C(2)	6·80	6·91	52·1	51·9	4·5
C(3)	6·75	6·77	49·4	49·8	4·4
C(4)	7·81	7·89	62·5	62·5	3·8
C(5)	7·33	7·31	58·0	58·2	4·0
C(6)	6·81	6·76	51·1	50·6	4·4
C(7)	7·23	7·20	55·5	55·2	4·5
C(8)	5·95	6·02	43·4	43·4	5·4
C(9)	5·26	5·48	36·4	37·3	6·3
C(10)	5·17	5·18	34·7	34·7	6·0 (2·3)
C(11)	5·31	5·19	33·7	33·7	6·3 (2·0)
C(12)	5·87	5·86	41·8	41·9	5·9
C(13)	7·24	7·47	59·0	59·2	4·1
C(14)	5·94	6·04	43·9	43·3	5·3
CH_3'	6·10	6·29	45·9	47·1	5·0 (1·0)
CH_3''	5·57	5·83	39·1	40·3	5·0 (1·3)
CH_3'''	5·00	5·13	31·3	32·5	6·7
O′	10·67	10·76	84·1	83·7	4·2
O″	8·96	9·32	67·9	69·4	4·9 (0·6)
Cl	24·06	24·86	197·9	205·2	4·5 (0·7)

Table 3. *Fractional coordinates of the hydrogen atoms*

Atom	x	y	z	Bonded to
H(1)	0·103	0·117	0·186	C(2)
H(2)	0·117	0·252	0·210	C(2)
H(3)	0·305	0·190	0·228	C(3)
H(4)	0·170	0·426	−0·060	C(5)
H(5)	0·156	0·290	−0·082	C(5)
H(6)	−0·029	0·353	−0·095	C(6)
H(7)	0·025	0·384	0·056	C(6)
H(8)	0·334	0·348	−0·090	C(8)
H(9)	0·533	0·357	−0·088	C(9)
H(10)	0·707	0·378	0·107	C(10)
H(11)	0·680	0·360	0·290	C(11)
H(12)	0·467	0·342	0·287	C(12)
H(13)	0·190	0·522	0·328	C(14)
H(14)	0·217	0·653	0·267	C(14)
H(15)	−0·100	0·127	0·065	C of CH_3'
H(16)	−0·110	0·254	0·100	C of CH_3'
H(17)	−0·164	0·230	−0·045	C of CH_3'
H(18)	0·230	0·048	0·103	C of CH_3''
H(19)	0·367	0·110	0·083	C of CH_3''
H(20)	0·207	0·117	−0·025	C of CH_3''
H(21)	0·393	0·480	0·418	C of CH_3'''
H(22)	0·440	0·602	0·370	C of CH_3'''
H(23)	0·360	0·602	0·471	C of CH_3'''
H(24)	0·020	0·162	−0·039	N(1)

Table 4. *Agreement summary*

2108 observed reflections ($1{\cdot}9 \le |F_o| \le 124{\cdot}4$)

Category	Limits	Number
1	$|\Delta F| \le 1{\cdot}0|F_{th}|$, or, $|\Delta F|/|F_o| \le 0{\cdot}2$	2048
2	$1{\cdot}0|F_{th}| < |\Delta F| \le 2{\cdot}0|F_{th}|$, or, $0{\cdot}2 < |\Delta F|/|F_o| \le 0{\cdot}3$	57
3	$2{\cdot}0|F_{th}| < |\Delta F| \le 3{\cdot}0|F_{th}|$, or, $0{\cdot}3 < |\Delta F|/|F_o| \le 0{\cdot}4$	3

1407 unobserved reflections

Category	Limits	Number
1	$|F_c| \le 1{\cdot}0|F_{th}|$	1135
2	$1{\cdot}0|F_{th}| < |F_c| \le 2{\cdot}0|F_{th}|$	259
3	$2{\cdot}0|F_{th}| < |F_c| \le 3{\cdot}0|F_{th}|$	13

Note. $|F_{th}|$ = threshold amplitude = 1·0 to 3·3. All observed reflections have been classified into three categories according to selected limits for $|\Delta F| = ||F_o| - |F_c||$ and $|\Delta F|/|F_o|$. For 72% of the present data, each reflection falls into the same category on the basis of either criterion. For the rest of the data, each reflection falls into two categories on this basis, and it has been included in the total number for the lower category only. This makes allowance for the fact that $|\Delta F|$ may be large for a very strong reflection even when $|\Delta F|/|F_o|$ is satisfactorily low, while $|\Delta F|/|F_o|$ may be misleadingly high for a very weak reflection for which $|\Delta F|$ is, in fact, satisfactorily small.

hydrogen atoms, as derived from the difference map, are recorded in Table 3. With these final parameters the overall R index for the observed data is $0{\cdot}09_6$.

A summary of the agreement between the observed structure amplitudes and the calculated structure factors is given in Table 4, and a complete list of the data may be obtained from the authors on request. Of the 3515 reflections that were examined, only three of those observed, and thirteen of those unobserved, occur in categories which correspond to fairly high discrepancies.

Discussion

The estimated standard deviations listed in Table 1 were derived by Cruickshank's expressions (1949, 1954), taking into account the appropriate multiplicities for the observed reflections and neglecting those unobserved. The bond lengths with their e.s.d.'s (Ahmed & Cruickshank, 1953), and the bond angles are shown in Fig. 1 in the same diagrammatic form as by Kartha, Ahmed & Barnes (1960) and Ahmed, Barnes & Masironi (1963). The e.s.d.'s for the angles (*International Tables for X-ray Crystallography*, 1959) are between 0·4° and 0·8°.

Within the accuracy of the structure determination, the betaprodine molecule in crystals of the monoclinic hydrochloride is very similar to that previously reported for the orthorhombic hydrobromide (Ahmed, Barnes & Masironi, 1963). The Student's distribution $t=(l_1-l_2)/(s_1^2+s_2^2)^{\frac{1}{2}}$ (Cruickshank & Robertson, 1953) for the individual bonds in the two molecules shows that $P>5\%$ for 17 bonds, $5\%>P>1\%$ for C(3)–CH_3'' and O′–C(13), and $1\%>P>0{\cdot}1\%$ for C(13)–C(14) where the observed difference of 0·043 Å is significant statistically. The corresponding test for the angles shows that 19 angles have $P>5\%$, seven have $5\%>P\geq 1\%$, and only O′–C(13)–O″ and O′–C(13)–C(14) have $P<0{\cdot}1\%$ where the observed differences of 2·7° and 2·6°, respectively, are significant.

The mean plane through atoms N(1), C(3), C(4), C(6) of the piperidine ring, referred to the orthogonal axes, $x'=x+z\cos\beta$, $y'=y$, $z'=z\sin\beta$, is

$$0{\cdot}4438x'-0{\cdot}4006y'-0{\cdot}8016z'+1{\cdot}2732=0\,, \quad (1)$$

and all four atoms lie within ±0·012 Å of the mean plane, while C(2) and C(5) are at −0·656 Å and +0·669 Å, respectively, from it, thus demonstrating that the piperidine ring is in the chair form. The carbon atom of CH_3' and atom C(7) of the phenyl ring are both equatorial and lie at distances of −0·645 Å and +0·604 Å on opposite sides of plane (1), whereas the carbon atom of CH_3'' on C(3), and O′ of the propionoxy chain on C(4), are both axial and are at distances of +1·363 Å and −1·431 Å, respectively, from this plane. Hence, in this structure, as in that of *dl*-betaprodine hydrobromide, the methyl group on C(3) is *cis* to the phenyl ring on C(4). The six carbon atoms of the phenyl ring lie within ±0·003 Å of their mean plane,

$$0{\cdot}0949x'-0{\cdot}9952y'-0{\cdot}0216z'+3{\cdot}6440=0\,. \quad (2)$$

The angle between the normals to planes (1) and (2) is about 63° which is nearly equal to the corresponding angle of 64° found in the hydrobromide derivative, but both are appreciably different from the corresponding angle of 84° in *dl*-alphaprodine. This difference in the orientation of the phenyl group relative to the piperidine ring in the alpha and beta isomers appears to be due mainly to the interchange of the substituents H and CH_3'' attached to atom C(3).

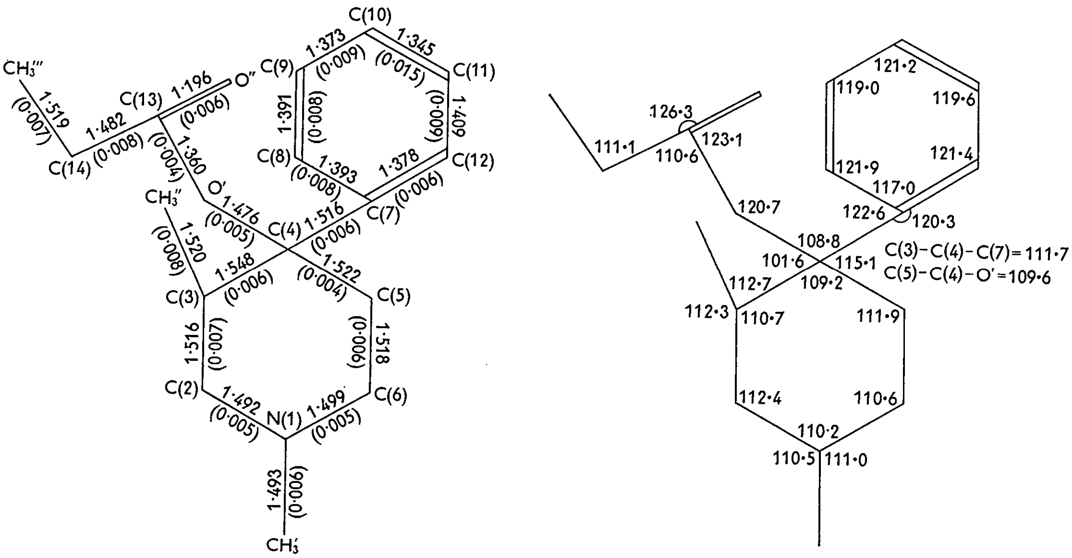

Fig. 1. Bond lengths (Å; e.s.d.'s in parentheses) and bond angles (°).

The only intermolecular contacts (excluding the hydrogen atoms) which are less than 3·5 Å are O″–C(9) = 3·358 Å, C(9)–C(9) = 3·361 Å, O″–CH_3' = 3·402 Å, and O″–C(10) = 3·475 Å. As expected, the intermolecular distances in this structure are significantly different from the corresponding values in that of *dl*-betaprodine hydrobromide.

The C–H bonds have a mean value of 1·08 Å and a standard deviation of 0·04 Å, and the angles involving a hydrogen bond have a mean value of 109·2° and a standard deviation of 5·7°. The only short Cl to N distance is 3·058 Å between Cl and N(1) with the coordinates listed in Table 1. This distance is in close agreement with the corresponding values of 3·026 Å found in the structure of alphaprodine hydrochloride (Kartha, Ahmed & Barnes, 1961), and 3·08 Å in the structure of piperidine hydrochloride (Rérat, 1960). In the difference map for the present structure, a hydrogen atom H(24) with $\varrho_o = 0\cdot6$ e.Å^{-3} was clearly identifiable at a distance of 1·09 Å from N(1) and 2·02 Å from Cl. The direction of the N(1)–H(24) bond is 14·3° from the N(1)–Cl vector, so that the angles between the N(1)–H(24) bond and the three N(1)–C(2), N(1)–C(6), and N(1)–CH_3' bonds are closer to the theoretical tetrahedral value than those between the N(1)–Cl vector and the same three N–C bonds as illustrated in Fig. 2. Hence, as in the structures of alphaprodine hydrochloride and piperidine hydrochloride, each chlorine atom appears to be hydrogen-bonded to a nitrogen atom.

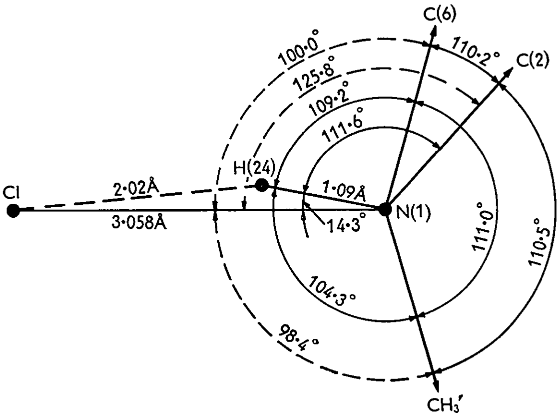

Fig. 2. Coordination angles (°) at the nitrogen atom.

The configuration and conformation of the betaprodine molecule is the same in crystals of both the orthorhombic hydrobromide (see Ahmed, Barnes & Masironi, 1963, Fig. 2) and the monoclinic hydrochloride. The only apparently significant numerical differences are in one bond length and two angles involving C(13) of the propionoxy chain. Although the shortest intermolecular contacts are not the same in both structures they do involve the same two atoms, O″ and C(9). The molecular volume decreases by 13·7 Å^3 in going from the orthorhombic crystals of the hydrobromide (418·8 Å^3) to the monoclinic crystals of the hydrochloride (405·1 Å^3) of betaprodine, while it decreases by 14·3 Å^3 in going from the hydrobromide (442·9 Å^3) to the hydrochloride (428·6 Å^3) of alphaprodine, both of which are monoclinic. The change of crystal class and space group in the case of the betaprodine salts is accompanied by a smaller change in molecular volume than is observed in the case of the corresponding salts of alphaprodine for which no change in either crystal class or space group occurs.

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References

Ahmed, F. R. (1961). *Crystallographic Computations for the IBM 650 Computer* (Reports No. 6333 and 6478). Ottawa: National Research Council.

Ahmed, F. R. (1962). *Crystallographic Programs for the IBM 1620 Computer* (Programs No. 369, 370). I.U.Cr. *World List of Crystallographic Computer Programs.*

Ahmed, F. R., Barnes, W. H. & Masironi, L. Di Marco (1963). *Acta Cryst.* **16**, 237.

Ahmed, F. R. & Cruickshank, D. W. J. (1953). *Acta Cryst.* **6**, 385.

Barnes, W. H. & Forsyth, W. J. (1954). *Canad. J. Chem.* **32**, 991.

Cruickshank, D. W. J. (1949). *Acta Cryst.* **2**, 65.

Cruickshank, D. W. J. (1954). *Acta Cryst.* **7**, 519.

Cruickshank, D. W. J. & Robertson, A. P. (1953). *Acta Cryst.* **6**, 698.

International Tables for X-ray Crystallography (1959). Vol. II, p. 331. Birmingham: Kynoch Press.

Kartha, G. & Ahmed, F. R. (1960). *Acta Cryst.* **13**, 532.

Kartha, G., Ahmed, F. R. & Barnes, W. H. (1960). *Acta Cryst.* **13**, 525.

Kartha, G., Ahmed, F. R. & Barnes, W. H. (1961). *Acta Cryst.* **14**, 93.

Rérat, C. (1960). *Acta Cryst.* **13**, 72.