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

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The crystal structure of the hydrobromide of *dl*-betaprodine (beta *dl*-1, 3-dimethyl-4-phenyl-4-propionoxypiperidine) has been determined by the heavy-atom method from three-dimensional intensity data collected with a scintillation-counter diffractometer. The structure has been refined by three cycles of differential syntheses to an *R*-factor of 0·10, and the hydrogen atoms of the molecule of betaprodine have been located from a three-dimensional difference synthesis. In the betaprodine molecule 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) now is axial, instead of equatorial, and is *cis* to the phenyl ring on C(4).

Introduction

An X-ray analysis of the crystal structure of *dl*-alphaprodine (alpha *dl*-1,3-dimethyl-4-phenyl-4-propionoxypiperidine) hydrochloride has been reported (Ahmed, Barnes & Kartha, 1959; Kartha, Ahmed & Barnes, 1960, 1961). The four possible steric arrangements of the substituents on C(3) and C(4) of the piperidine ring, assuming that CH_3 on N always is equatorial (Dauben & Pitzer, 1956) and that the piperidine ring has the chair form, are illustrated in Fig. 1 (compare Table 1 and Fig. 1 of Kartha, Ahmed & Barnes, 1960); it will be observed that II and IV may be derived from purely conformational inversions of I and III, respectively, followed, however, by a return of CH_3 on N from the resulting axial to an equatorial position. Thus, although the *cis–trans* relationships of the substituents on C(3) and C(4) remain unchanged by these inversions, those between CH_3 on N and the various substituents on C(3) and C(4) are reversed in going from I to II, and from III to IV. The hydrochloride and hydrobromide of alphaprodine are isostructural and the alphaprodine molecule in crystals of these salts has the configuration and conformation represented by III in Fig. 1; this is in agreement with the conclusions of Beckett and co-workers (1954, 1955, 1957, 1959) and of Archer (1958) regarding the alphaprodine molecule in solution. Of the other three models represented in Fig. 1, IV has been suggested for betaprodine by Ziering, Motchane & Lee (1957), I by Beckett *et al.* (1954, 1955, 1957, 1959), and II by Archer (1958).

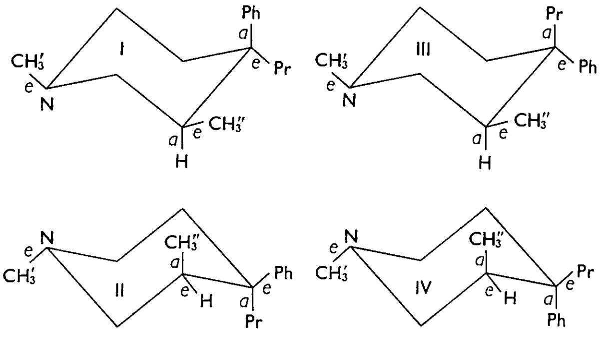

Fig. 1. Possible stereoisomers of 1,3-dimethyl-4-phenyl-4-propionoxypiperidine (prodine). Ph, phenyl; Pr, propionoxy.

Unlike the hydrochloride and hydrobromide of alphaprodine, the corresponding salts of betaprodine are not isomorphous. Crystals of betaprodine hydrochloride, like those of both the hydrochloride and hydrobromide of alphaprodine, are monoclinic (S.G. $P2_1/c$), whereas crystals of betaprodine hydrobromide are orthorhombic. An analysis of the crystal structure of *dl*-betaprodine hydrobromide is described in the present paper; a study of the hydrochloride will be presented later.

Crystal data

Suitable single crystals of *dl*-betaprodine hydrobromide were difficult to prepare but finally were obtained by very slow evaporation of an acetone solution containing a few drops of chloroform. The prismatic crystal selected for the present study had dimensions of $0{\cdot}12 \times 0{\cdot}20$ mm. in cross-section and 0·20 mm. in length. The space group was established from precession photographs, and the systematic absences later were confirmed with a scintillation-counter diffractometer.

The crystal was mounted on the diffractometer with the prism axis (corresponding to *a*) along the φ-axis of the goniostat (Furnas, 1957). The unit-cell dimensions were calculated from the arithmetical means of individual measurements of the 2θ values of the Cu $K\alpha_1$ (λ = 1·54050 Å) and Cu $K\alpha_2$ (λ = 1·54434 Å) peaks for the medium and high-order axial reflections obtained with a narrow (0·02°) slit and a take-off angle of 1°.

The density was determined by flotation of several

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clear crystals in carbon tetrachloride-benzene solutions.

dl-Betaprodine hydrobromide ($C_{16}H_{23}NO_2 . HBr$; F.W. = 342·29) is orthorhombic with space group $Pbca(D_{2h}^{15})$,

$$a = 10{\cdot}320\ (\sigma = 0{\cdot}012)\ \text{Å},\ b = 24{\cdot}202\ (\sigma = 0{\cdot}005)\ \text{Å},$$
$$c = 13{\cdot}415\ (\sigma = 0{\cdot}003)\ \text{Å};\ U = 3350{\cdot}6\ \text{Å}^3;$$
$$D_o = 1{\cdot}358\ \text{g.ml.}^{-1}\ (20\ ^\circ\text{C.});\ Z = 8;\ D_c = 1{\cdot}357\ \text{g.ml.}^{-1}.$$

Intensity data

The crystal and scintillation-counter settings (2θ, φ, χ) for each of the possible reflections were computed, and integrated intensities were measured at a take-off angle of 2° by the moving-crystal moving-counter method (Furnas, 1957). The range of the 2θ scans varied from 1·5° to 3·0° depending upon the mean 2θ value of the $K\alpha_1$ and $K\alpha_2$ peaks for each reflection. The background count for each reflection, the relative scales of the measured intensities and an approximate absorption correction in terms of an empirical function of φ (1·0 for $\varphi = 0°$ to 1·1 for $\varphi = 90°$) were recorded as described elsewhere (Bachmann, Ahmed & Barnes, 1960). Of 3658 possible non-equivalent reflections (excluding those prohibited by the space-group symmetry) within the Cu sphere of reflection and the instrumental limits ($0° < 2\theta < 160°$), 2330 (about 64%) were observed. The measured intensities were reduced to the same scale, corrected for absorption, and the appropriate $1/Lp$ factors for normal beam were applied.

Structure determination and refinement

The structure was established directly from the observed three-dimensional data by the heavy-atom method. The co-ordinates of the bromine atom were determined without ambiguity from a sharpened 3-D Patterson synthesis. Structure factors calculated from the contributions of the bromine atoms alone, with a temperature-factor constant of 2·5 Å², showed an R-factor of 0·49. A 3-D Fourier synthesis, computed after giving the signs of the bromine-atom contributions to 1904 of the observed structure amplitudes, revealed 19 locations with electron-density maxima of 3 to 8 e.Å^{-3} which corresponded to a plausible arrangement of the 19 atoms (excluding H) of the betaprodine molecule; the electron densities of all other low regions were $< 2{\cdot}5$ e.Å^{-3}. Structure factors calculated with the co-ordinates of these 19 sites for the light atoms with $B = 3{\cdot}5$ Å², together with the co-ordinates of the bromine atom with $B = 2{\cdot}5$ Å², gave $R = 0{\cdot}27$. A second Fourier synthesis, evaluated with 2180 observed structure factors, confirmed the locations of the light atoms with electron-density maxima of 6 to 13 e.Å^{-3} compared with a background density in the range $\pm 1{\cdot}0$ e.Å^{-3}. The R-factor, after application of the co-ordinate shifts indicated by this synthesis and modification of B to 3·3 Å² for bromine and 4·0 to 5·0 Å² for the light atoms, was 0·20, thus indicating that the trial structure probably was correct.

Refinement was then carried out by three cycles of differential syntheses, with the observed and calculated data, in which Booth's backshift method was employed for the correction of finite-summation errors. After each cycle the temperature factors for the individual atoms were refined by comparison of the observed and calculated electron densities and their curvatures at the atomic positions, and by taking into account the overall temperature-factor correction indicated by a plot of $\log_e (\Sigma|F_c|/\Sigma|F_o|)$ against $\sin^2\theta$. The last also served as a basis for modification of the scale factor applied to the observed data. As indicated by the electron-density distribution around the site of the bromine atom, an anisotropic temperature factor was adopted for Br while the other atoms were treated as isotropic. The scattering factor curves

Table 1. *Fractional atomic co-ordinates, with e.s.d.'s (in* Å)

Atom	x	$\sigma(x)$	y	$\sigma(y)$	z	$\sigma(z)$
N(1)	0·0726	0·004	0·1997	0·004	0·3851	0·005
C(2)	−0·0044	0·005	0·1575	0·006	0·4389	0·005
C(3)	0·0586	0·005	0·1001	0·005	0·4350	0·006
C(4)	0·1988	0·005	0·1029	0·005	0·4753	0·005
C(5)	0·2738	0·005	0·1465	0·005	0·4165	0·005
C(6)	0·2097	0·006	0·2030	0·005	0·4235	0·005
C(7)	0·2620	0·005	0·0457	0·005	0·4755	0·005
C(8)	0·3496	0·006	0·0294	0·006	0·4039	0·006
C(9)	0·4008	0·008	−0·0235	0·007	0·4044	0·010
C(10)	0·3675	0·007	−0·0608	0·006	0·4772	0·011
C(11)	0·2806	0·008	−0·0454	0·006	0·5479	0·011
C(12)	0·2226	0·006	0·0075	0·006	0·5470	0·008
C(13)	0·2786	0·005	0·1285	0·004	0·6396	0·005
C(14)	0·2259	0·007	0·1454	0·009	0·7413	0·008
C (of CH_3')	0·0070	0·008	0·2547	0·007	0·3914	0·007
C (of CH_3'')	0·0473	0·007	0·0744	0·007	0·3299	0·007
C (of CH_3''')	0·3339	0·011	0·1500	0·011	0·8184	0·008
O′	0·1775	0·003	0·1209	0·004	0·5781	0·004
O″	0·3897	0·004	0·1251	0·005	0·6173	0·005
Br	0·1388	0·001	0·2005	0·001	0·1514	0·001

Table 2. *Electron densities* (e.Å^{-3}), *mean curvatures* (e.Å^{-5}), *and temperature-factor constants* (Å^2)

Atom	ϱ_o	ϱ_c	ϱ_o''	ϱ_c''	B_1*	B_2*
N(1)	9·8	9·4	78	74	4·1	3·9
C(2)	7·9	7·6	64	61	4·0	3·8
C(3)	7·9	7·6	64	60	3·8	3·6
C(4)	8·2	7·8	67	62	3·8	3·6
C(5)	8·3	8·0	69	66	3·8	3·6
C(6)	7·8	7·7	63	62	4·0	3·8
C(7)	8·4	8·0	69	66	3·8	3·6
C(8)	7·0	6·9	54	53	4·6	4·5
C(9)	6·2	6·2	43	44	5·2	5·2
C(10)	6·4	6·2	45	46	5·4	5·3, 5·3, 6·2
C(11)	5·6	6·1	43	45	5·4	5·3, 5·3, 6·3
C(12)	6·4	6·8	51	51	5·0	5·2
C(13)	7·9	8·2	71	68	3·8	3·6
C(14)	6·0	6·1	43	42	5·2	5·2
C (of CH_3')	6·2	6·5	47	48	5·0	5·2
C (of CH_3'')	6·5	6·6	48	49	5·0	5·2
C (of CH_3''')	5·3	5·4	35	37	6·0	6·5, 6·8, 5·4
O′	11·9	11·6	98	93	3·7	3·6
O″	9·9	9·7	72	70	4·7	4·6
Br	57·9	61·3	494	524	5·6, 5·0, 3·6	5·9, 5·3, 3·5

* B_x, B_y, B_z are given for those atoms treated anisotropically.

employed were those given by Freeman (1959) for C, N, and O, and by Thomas & Umeda (1957) for Br.

A 3-D difference synthesis computed after the second set of differential syntheses showed a reasonably flat general background (within $\pm 0{\cdot}3$ e.Å^{-3}), residual electron densities within $\pm 0{\cdot}6$ e.Å^{-3} at the sites of C, N, and O and within $\pm 2{\cdot}0$ e.Å^{-3} at that of Br, together with positive electron densities of $0{\cdot}3_5$ to 0·7 e.Å^{-3} at positions where hydrogen atoms might reasonably be expected to occur. For the final set of calculated differential syntheses, therefore, the 23 hydrogen atoms of the betaprodine molecule were assumed to be in these positions, and their contributions were added to the calculated structure factors for all reflections for which $\sin^2\theta < 0{\cdot}3$. Final values of the atomic co-ordinates resulting from this synthesis are given in Table 1 where the e.s.d.'s have been calculated according to the equation of Cruickshank (1949). For all except the hydrogen atoms, the electron densities and the mean curvatures are shown in Table 2, where the values under B_1 are the temperature-factor constants employed in the evaluation of ϱ_c, and those under B_2 are those derived on the basis of the last set of differential syntheses. The fractional co-ordinates of the hydrogen atoms were not refined; they are listed in Table 3.

Based on the co-ordinates of Table 1, the temperature-factor constants (B_2) in the last column of Table 2, and application of the method of Kartha & Ahmed (1960) to the anisotropic atoms, $R = 0{\cdot}10_0$ for all the observed data. Assuming the co-ordinates for the hydrogen atoms given in Table 3, and with $B = 5{\cdot}4$ Å^2, inclusion of the hydrogen-atom contributions to F_c for the 570 observed reflections with $\sin^2\theta < 0{\cdot}3$ reduces R for these reflections from $0{\cdot}09_2$ to $0{\cdot}06_7$, and R for all the observed reflections to $0{\cdot}08_9$.

A summary of the agreement between $|F_o|$ and $|F_c|$ for all possible non-equivalent reflections is presented

Table 3. *Fractional co-ordinates of the hydrogen atoms*

Atom	x	y	z	Bonded to carbon atom
H(1)	−0·023	0·170	0·518	C(2)
H(2)	−0·100	0·157	0·405	C(2)
H(3)	0·003	0·075	0·490	C(3)
H(4)	0·372	0·151	0·440	C(5)
H(5)	0·282	0·133	0·338	C(5)
H(6)	0·205	0·216	0·502	C(6)
H(7)	0·263	0·232	0·375	C(6)
H(8)	0·380	0·059	0·348	C(8)
H(9)	0·477	−0·037	0·353	C(9)
H(10)	0·413	−0·101	0·473	C(10)
H(11)	0·252	−0·073	0·607	C(11)
H(12)	0·177	0·023	0·612	C(12)
H(13)	0·150	0·114	0·759	C(14)
H(14)	0·193	0·188	0·730	C(14)
H(15)	0·060	0·283	0·340	C (of CH_3')
H(16)	−0·003	0·268	0·469	C (of CH_3')
H(17)	−0·094	0·250	0·382	C (of CH_3')
H(18)	0·089	0·099	0·274	C (of CH_3'')
H(19)	0·085	0·030	0·332	C (of CH_3'')
H(20)	−0·053	0·068	0·318	C (of CH_3'')
H(21)	0·390	0·113	0·802	C (of CH_3''')
H(22)	0·400	0·185	0·803	C (of CH_3''')
H(23)	0·300	0·145	0·894	C (of CH_3''')

Table 4. *Agreement summary*

Category and limits	Reflections
Observed	
1. $\lvert\Delta F\rvert \le 4{\cdot}2$ or $\lvert\Delta F\rvert \le 0{\cdot}2\lvert F_o\rvert$	2145
2. $\lvert\Delta F\rvert \le 8{\cdot}4$ or $\lvert\Delta F\rvert \le 0{\cdot}4\lvert F_o\rvert$	176
3. $\lvert\Delta F\rvert \le 12{\cdot}6$ or $\lvert\Delta F\rvert \le 0{\cdot}6\lvert F_o\rvert$	9
	Σ 2330
Unobserved ($\lvert F_{th}\rvert$ = threshold amplitude)	
1. $\lvert F_c\rvert \le 1{\cdot}0\lvert F_{th}\rvert$	1221
2. $1{\cdot}0\lvert F_{th}\rvert < \lvert F_c\rvert \le 1{\cdot}5\lvert F_{th}\rvert$	102
3. $1{\cdot}5\lvert F_{th}\rvert < \lvert F_c\rvert \le 2{\cdot}0\lvert F_{th}\rvert$	5
	Σ 1328

in Table 4 according to categories similar to those of Hanson & Ahmed (1958, p. 726). These categories have been selected on the basis of $|F_o|_{\text{min.}}=4·2$, $|F_o|_{\text{max.}}=296·8$, and $R=0·1$ for the observed data. For the unobserved reflections with $\sin^2\theta<0·3$, the hydrogen contributions have been added to F_c as for the observed data. Of all possible 3658 reflections, only 14 occur in categories of high discrepancy, 9 observed (for which $|\Delta F|_{\text{max.}}<11·0$), and 5 unobserved (for which $|F_c|_{\text{max.}}=13·1$).

Results and discussion

The molecule of betaprodine is shown in perspective in Fig. 2. Bond lengths, with their e.s.d.'s calculated according to the equation of Ahmed & Cruickshank (1953), and bond angles are given in Fig. 3 in the same schematic form as for alphaprodine (Kartha, Ahmed & Barnes, 1960, Fig. 6). The e.s.d.'s of the angles, calculated according to the equation recommended in the *International Tables for X-ray Crystallography* (1959, p. 331), vary from 0·4° to 0·8°. Although no attempt was made to refine the coordinates of the hydrogen atoms obtained from the single difference synthesis, the C–H bonds have an average length of 1·09 Å with a standard deviation of 0·02 Å. The forty-one N–C–H, C–C–H, and H–C–H angles, which might be expected to be close to the tetrahedral value of 109° 28′, have a mean value of 109·2° (standard deviation, 5°), and the ten C–C–H and H–C–H angles of the phenyl ring have a mean value of 119·6° (standard deviation, 3°) which is very close to the 120° to be expected. It is of interest that all hydrogen atoms (with the exception of that associated directly with Br) should have appeared clearly in the difference synthesis despite the presence of bromine in the structure. The electron-density distribution in the planes through each of the triplets of hydrogen atoms in CH_3', CH_3'', and CH_3''' is reproduced in Fig. 4; all atoms are clearly resolved and there is no indication of free rotation of any of the groups.

The mean plane through N(1), C(3), C(4), and C(6)

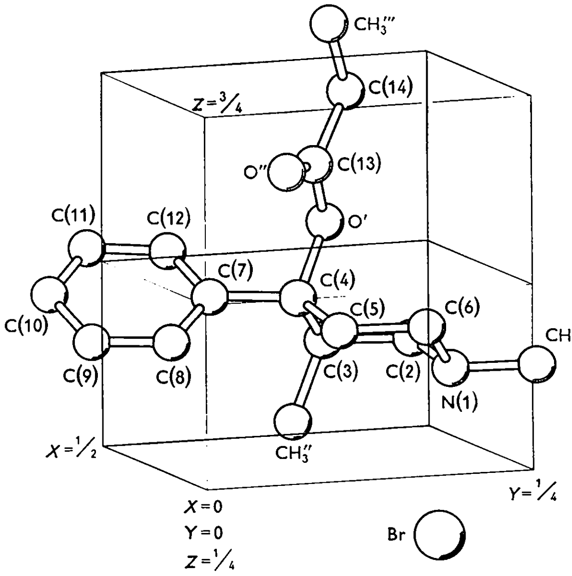

Fig. 2. Perspective view of the molecule of betaprodine.

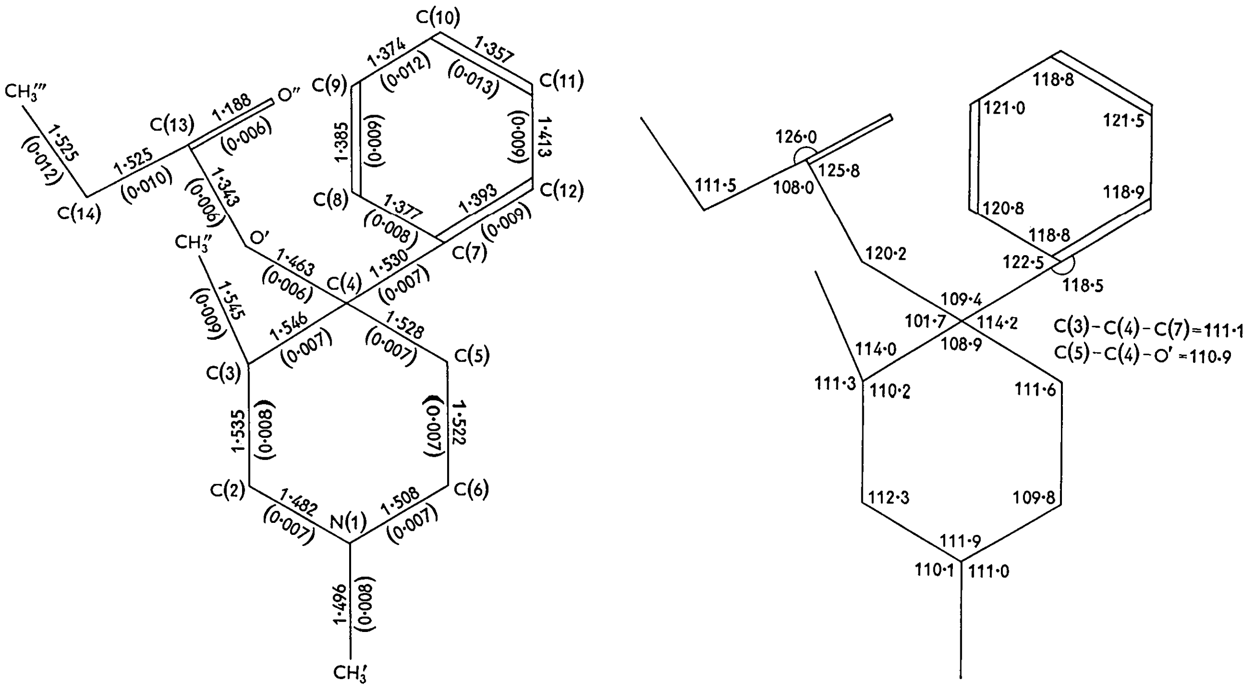

Fig. 3. Bond lengths (Å; e.s.d.'s in parentheses) and bond angles (°).

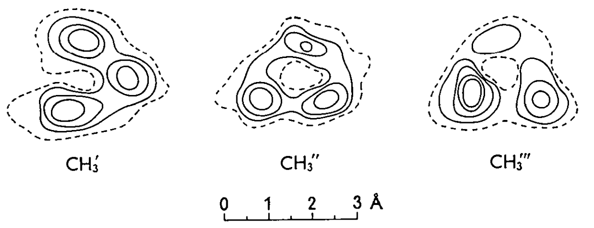

Fig. 4. Electron-density distribution in the planes of the hydrogen atoms of the methyl groups. Contours at intervals of 0·1 e.Å^{-3} with the 0·2 e.Å^{-3} contour indicated by broken lines.

of the piperidine ring is represented by the equation

$$0{\cdot}3455x-0{\cdot}2719y-0{\cdot}8982z+5{\cdot}6933=0 \qquad (1)$$

referred to the crystallographic axes. A projection of the piperidine ring and its substituents along [100] is shown in Fig. 5 together with the distance (in Å) of each atom from this plane, a + sign indicating that the atom is on the same side of the plane as the origin and a − sign indicating that it is on the opposite side. Among the equatorial substituents it may be noted that H(4) on C(5) is on the same side of the plane as C(7) of the phenyl ring on C(4), and as H(7) on C(6); this appears to arise from the close proximity of O″ at 2·47 Å from H(4). The most important features of Fig. 5, however, may be summarized as follows. Atoms N(1), C(3), C(4), and C(6) lie within ±0·002 Å of their mean plane. Atoms C(2) and C(5) are on opposite sides of this plane at distances of −0·647 Å and +0·687 Å, respectively, thus demonstrating that the piperidine ring has the chair form. The methyl group (CH$_3'$) on N(1) at −0·674 Å, H(3) on C(3) at −0·694 Å, and C(7) of the phenyl ring on C(4) at +0·597 Å, respectively, from the mean plane are all in *equatorial* positions, while the methyl group CH$_3''$ on C(3) at +1·397 Å, and O′ of the propionoxy chain on C(4) at −1·435 Å, respectively, from the mean plane are in *axial* positions. The salient *cis–trans* relationships are CH$_3''$/phenyl, H(3)/propionoxy, CH$_3'$/H(3), and CH$_3'$/propionoxy, all *cis*, with CH$_3''$/propionoxy, H(3)/phenyl, CH$_3'$/CH$_3''$, and CH$_3'$/phenyl, all *trans*. In conformation and configuration, therefore, the molecule of betaprodine in the crystal structure of *dl*-betaprodine hydrobromide corresponds exactly with model II of Fig. 1, and thus is in complete agreement with the deductions of Archer (1958) regarding the betaprodine molecule in solution.

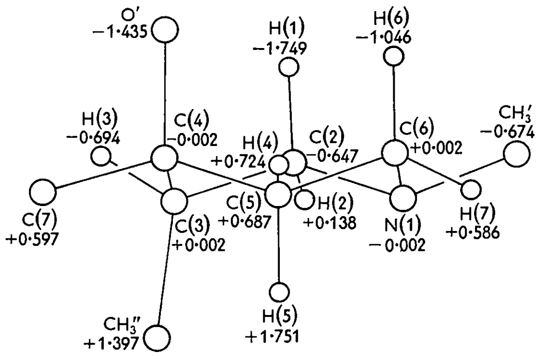

Fig. 5. Projection of the piperidine ring and its substituents down [100], with distances (Å) of the atoms from the mean plane through N(1), C(3), C(4), C(6).

The equation representing the mean plane of the phenyl ring is

$$0{\cdot}7448x+0{\cdot}3238y+0{\cdot}5833z-6{\cdot}0750=0\,, \qquad (2)$$

referred to the crystallographic axes, and the six C atoms lie within ±0·02 Å of this plane. The ring appears not to be as regular as the corresponding one in the alphaprodine molecule (Kartha, Ahmed & Barnes, 1960). Thus, although the mean C–C distances are virtually the same (1·383 Å in betaprodine, 1·381 Å in alphaprodine), individual bond lengths vary by about ±0·03 Å in betaprodine compared with < ±0·01 Å in alphaprodine. On the other hand, individual C–C–C angles (mean = 120·0° in each isomer) show greater deviations from the mean in alphaprodine. Because of the primary interest in the configuration and conformation of the molecules of alpha- and betaprodine, no attempt has been made to reconcile these differences in the results for the phenyl rings by further structure refinement. The observed differences are not considered to be significant.

The angle between the normals to planes (1) and (2) in the molecule of betaprodine is about 64°, compared with almost 84° in alphaprodine. Molecular models indicate that such a reduction in this angle is to be expected in going from the *cis* CH$_3''$/propionoxy configuration in alphaprodine to the corresponding *trans* configuration in betaprodine.

The only intermolecular distances (excluding H atoms) in the structure of *dl*-betaprodine hydrobromide which are <3·5 Å are O″ to CH$_3'$ = 3·153 Å, O″ to C(10) = 3·211 Å, O″ to C(9) = 3·287 Å, C(8) to C(10) = 3·413 Å, and C(9) to C(9) = 3·473 Å.

Each bromine atom is only 3·209 Å from the nearest atom of nitrogen whereas a separation of at least about 3·43 Å might be expected if the bromine ion were present as such. It is probable, therefore, that Br is H-bonded to N in betaprodine hydrobromide as Cl is to N in alphaprodine hydrochloride (Kartha, Ahmed & Barnes, 1961). Because of the close proximity of the heavy Br, however, the hydrogen atom that would be involved in such bonding was the only one in the structure which was not located with any certainty, so that the bond shortening may be due, in part, to dipole–dipole interactions. Comparable Br to N distances (3·17 to 3·38 Å), indicative of hydrogen bonding, have been reported in certain other organic hydrobromides (Robertson & Beevers, 1951; Trommel & Bijvoet, 1954; Sim, 1955; Hanson & Ahmed, 1958). The three Br–N–C angles

(Br–N(1)–C(6) = 98°, Br–N(1)–CH_3' = 98°, Br–N(1)–C(2) = 126°) in the present structure differ more widely from the tetrahedral value than do the corresponding Cl–N–C angles (106·6 to 110·0°) in the crystal structure of alphaprodine hydrochloride (Kartha, Ahmed & Barnes, 1961) but are similar to those in the crystal structure of the monoclinic form of *d*-methadone hydrobromide (Br–N–C_8 = 96°, Br–N–C_9 = 97°, Br–N–C_6 = 120°, calculated from data of Hanson & Ahmed, 1958, where C_8 and C_9 both represent methyl groups). Taking the van der Waals radii of Br and CH_3 as 1·95 and 2·0 Å, respectively (Pauling, 1960, p. 260), a distance of at least 3·95 Å may be expected between Br and the C of CH_3'' in betaprodine hydrobromide (see Fig. 2) and between C_7 of the CH_3 group on C_6 in methadone hydrobromide (see Hanson & Ahmed, 1958, Fig. 1); the observed values are 3·99 and 4·13 Å, respectively. The axial position of CH_3'' on C(3) in betaprodine, therefore, appears to be the principal reason for the increase in the angle Br–N(1)–C(2), and the accompanying decrease in the angles Br–N(1)–C(6) and Br–N(1)–CH_3', from the tetrahedral value, and the position of the CH_3 group (represented by C_7) on C_6 seems to have a similar effect in the methadone hydrobromide structure. With CH_3'' in an equatorial position in the alphaprodine molecule, however, this steric restriction to the approach of the halogen atom towards the nitrogen atom is removed, and the three Cl–N–C angles in the crystal structure of alphaprodine hydrochloride are all very close to the tetrahedral value.

The computations for the present investigation were carried out on IBM 650 computers with programmes written by Ahmed, two of which have been described in detail elsewhere (Ahmed, 1961). Grateful acknowledgment is made to Army Pay Ledger Unit No. 1, Ottawa, and to the University of Ottawa for the use of their computers, and to Mrs M. E. Pippy of this laboratory for much computational assistance.

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