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References

BERGMANN, L. (1954). *Der Ultraschall*, 6th ed. Stuttgart: Hirzel.

BORN, M. & HUANG, K. (1954). *Dynamical Theory of Crystal Lattices*. Oxford: Clarendon Press.

FUES, E. & LUDLOFF, H. (1935). *S. B. Berliner Akad. Wiss. Phys. Math.* **14**, 225.

HAUSSÜHL, S. (1957). *Fortschr. Min.* **35**, 4.

HUGHES, W. & TAYLOR, C. A. (1953). *J. Sci. Instrum.* **30**, 105.

JOEL, N. & WOOSTER, W. A. (1957). *Nature, Lond.* **180**, 430.

JOEL, N. & WOOSTER, W. A. (1958*a*). *Nature, Lond.* **182**, 1078.

JOEL, N. & WOOSTER, W. A. (1958*b*). *Acta Cryst.* **11**, 575.

JONA, F. (1950). *Helv. Phys. Acta*, **23**, 795.

LAVAL, J. (1951). *C. R. Acad. Sci., Paris*, **232**, 1947.

LAVAL, J. (1952). *L'état Solide*. Rapports et Discussions, Congrès Solvay 1951. Bruxelles: Stoops.

LAVAL, J. (1957). *J. Phys. Radium*, **18**, 247, 289, 369.

LECORRE, Y. (1954). *Bull. Soc. franç. Minér. Crist.* **77**, 1363.

NOMOTO, O. (1943). *Proc. Phys. Math. Soc., Jap.* **25**, 240.

SPANGENBERG, K. & HAUSSÜHL, S. (1957). *Z. Kristallogr.* **109**, 422.

TOPPING, J. (1955). *Errors of Observation and their Treatment*. London: The Institute of Physics.

ZUBOV, V. G. & FIRSOVA, M. M. (1956). *Kristallographia*, **1**, 546.

ZWICKER, B. (1946). *Helv. Phys. Acta*, **19**, 523.

Acta Cryst. (1960). **13**, 525

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

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The structure of the hydrochloride of *dl*-alphaprodine (*dl*-α-1:3-dimethyl-4-phenyl-4-propionoxy piperidine) has been determined by the isomorphous-replacement method with the aid of data for the hydrobromide. Zero-level normal, and first-level generalized, projections along the three axes have been employed. The structure has been refined by three-dimensional Fourier and differential syntheses. The stereochemical configuration found for the alphaprodine molecule agrees with that of one of four possible isomers and confirms that proposed by Beckett and co-workers on conformational and other grounds. The piperidine ring has the chair form with the phenyl ring equatorial and the propionoxy chain axial; the methyl group on C(3) is *trans* to the phenyl ring on C(4).

Introduction

Ziering & Lee (1947) were the first to prepare *dl*-1:3-dimethyl-4-phenyl-4-propionoxy piperidine, $C_{16}H_{23}NO_2$, and to show that it can be obtained in two diastereoisomeric (α and β) forms which have since received the common names, alphaprodine (Nisentil^{R}) and betaprodine. Alphaprodine hydrochloride has a higher melting point and lower analgesic potency than the corresponding salt of the beta isomer.

Four *cis–trans* configurations of the molecule of 1:3-dimethyl-4-phenyl-4-propionoxy piperidine are possible according to the relative positions of H and CH_3 attached to C(3) and of $OCOC_2H_5$ and C_6H_5 attached to C(4) of the piperidine ring. Assuming that this ring has the chair form, the several possible isomers are illustrated in Fig. 1, where Ph = phenyl (C_6H_5), Pr = propionoxy ($OCOC_2H_5$), Me = methyl (CH_3), *a* = axial to the piperidine ring, *e* = equatorial to the piperidine ring.

Some important relationships are summarized in Table 1, from which it is apparent that the *cis* or *trans* designation of the members of a single pair of prodine

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isomers requires specific mention of the substituents concerned; thus configuration I (Fig. 1) is *cis* from a consideration of Me/Ph or H/Pr (Table 1) but *trans* if the designation is based on Me/Pr or H/Ph.

Table 1

(*e*, equatorial; *a*, axial)

		I	II	III	IV
C(3)	Me	*e*	*a*	*e*	*a*
	H	*a*	*e*	*a*	*e*
C(4)	Ph	*a*	*e*	*e*	*a*
	Pr	*e*	*a*	*a*	*e*
Me/Ph		*cis*	*cis*	*trans*	*trans*
H/Pr		*cis*	*cis*	*trans*	*trans*
Me/Pr		*trans*	*trans*	*cis*	*cis*
H/Ph		*trans*	*trans*	*cis*	*cis*

From a comparison of the structural formula of prodine with that of dihydrodesoxymorphine-D, which, at the time, was assumed to have a *cis* relationship between the piperidine ring and the carbocyclic ring III (to which the O of the five-membered oxide ring is attached, see, for example, Lindsey & Barnes, 1955, Fig. 1) and because of the relatively high analgesic effect of betaprodine, Ziering & Lee (1947) tentatively assigned configuration I (Fig. 1) to alphaprodine and III to betaprodine. Although it was established later that ring III in dihydrodesoxymorphine-D actually is *trans* to the piperidine ring (substantiated by the results of X-ray crystal structure studies of morphine hydriodide dihydrate, Mackay & Hodgkin, 1955, and of codeine hydrobromide dihydrate, Lindsey & Barnes, 1955), Ziering, Motchane & Lee (1957), largely on the basis of infrared spectral data, concluded that configuration I should be retained for alphaprodine but that III should be inverted to IV for betaprodine. In the meantime, Beckett & Casy (1954) and Beckett & Walker (1955), from conformational analysis and a study of rates of hydrolysis, had reversed the designations of Ziering & Lee (1947) with the assignment of configuration III (Fig. 1) to alphaprodine and I to betaprodine. Since the start of the present X-ray structure investigation, Beckett, Casy & Walker (1959) have adduced additional experimental data in support of these conclusions, and Archer (1958) has presented further arguments in favour of III for alphaprodine but has suggested II (the inverted form of I) for betaprodine.

As the result of an inquiry from Dr John Lee regarding the possible existence of X-ray crystallographic data which might resolve the problem of the stereochemical configurations of alpha- and betaprodine the present investigation of the structure of alphaprodine hydrochloride was undertaken. The alpha isomer was selected for a start in preference to the beta on the basis of unit cell and space-group data already available for the hydrochlorides of *dl*-alphaprodine and *dl*-betaprodine (Barnes & Forsyth, 1954). In order to take advantage of the isomorphous replacement method it was desirable to obtain the corresponding hydrobromides and these salts were kindly prepared by Dr John Lee.

Crystal data

dl-Alphaprodine hydrochloride is monoclinic with space group $P2_1/c$, $Z=4$, and

$$a=15{\cdot}77,\ b=8{\cdot}15,\ c=13{\cdot}95\ \text{Å};\ \beta=107^\circ\ 00';$$
$$D_o=1{\cdot}167\ \text{g.ml.}^{-1},\ D_c=1{\cdot}154\ \text{g.ml.}^{-1}$$

(Barnes & Forsyth, 1954). Long lath-shaped crystals, suitable for the collection of X-ray data, were obtained by crystallization from acetone.

dl-Alphaprodine hydrobromide also was crystallized from acetone but came out as thin plates which fractured easily along *b* and *c* and usually showed plastic deformation. Selected fragments, however, gave reasonably satisfactory diffraction patterns. The unit-cell constants were determined from precession photographs. The space group is $P2_1/c$, $Z=4$, and

$$a=15{\cdot}93,\ b=8{\cdot}00,\ c=14{\cdot}47\ \text{Å};\ \beta=106^\circ\ 06'.$$

These data, together with the similarity of the diffraction effects with those of the corresponding hydrochloride, strongly supported the expected isomorphous relationship with *dl*-alphaprodine hydrochloride.

Intensity data

Zero- and first-level photographs along each of the three crystallographic axes of both the hydrochloride and the hydrobromide of *dl*-alphaprodine were recorded with an integrating precession instrument and Mo $K\alpha$ radiation ($\lambda=0{\cdot}7107$ Å). For three-dimensional

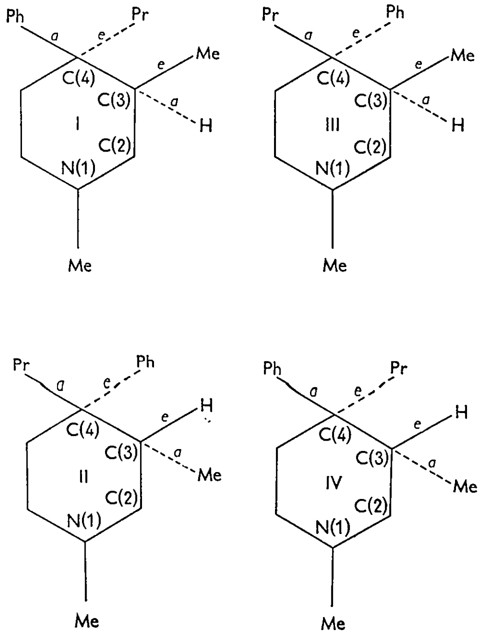

Fig. 1. Possible stereoisomers of 1:3-dimethyl-4-phenyl-4-propionoxy piperidine (prodine).

refinement of the structure of the hydrochloride, integrated and non-integrated Weissenberg photographs were taken of the levels $h0l$ to $h6l$, inclusive, and $hk0$ to $hk8$, inclusive, using Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å) and the multiple-film technique.

All intensities were estimated by visual comparison with a standard set of spots, the stronger intensities from integrated films and the weaker ones from non-integrated films. No corrections for varying spot shapes are necessary in the case of integrated photographs but some qualitative allowance for this factor was made in the estimation of intensities from the non-integrated films. So many of the same reflections were observed in both the b and c axis sets of Weissenberg photographs that there was no difficulty in placing the reflection intensities from both sets on the same scale. An approximate absolute scale was established by the application of Wilson's method (Wilson, 1942) to the intensities of the $h0l$ reflections and this was adjusted during refinement by comparison of F_o and F_c, ϱ_o and ϱ_c. In those cases in which the value of the Lp correction factor for the intensity of a particular reflection was more uncertain in one set of films than in the other, or the diffraction spot had a more irregular shape in one set than in the other, or was too weak to be observed in one, the more reliable value for the corrected intensity was employed; in most cases, however, the values obtained for the same reflection from both sets of films were in good agreement and the mean was adopted. No absorption corrections were applied because the linear absorption coefficient of the hydrochloride for Cu $K\alpha$ radiation is only about 20 cm.$^{-1}$ and the largest dimension of any of the crystals employed was less than 0·4 mm. Approximately 2400 (more than 85%) of some 2750 possible non-equivalent reflections within the Cu $K\alpha$ sphere were observed.

Structure determination

Normal projections

The structure determination was commenced with a study of the b axis projection of the hydrobromide. Approximate unitary structure factors for the $h0l$ reflections were derived by means of the expression, $U_{h0l} = (I_{h0l}/I_{\text{av.}})^{\frac{1}{2}}$, in which I_{h0l} is the observed intensity of a given reflection (after application of the Lp correction) and $I_{\text{av.}}$ is the mean of all the values of I_{h0l} within the same $\sin\theta$ region. The signs of two strong, low-angle, reflections were assigned arbitrarily, and the relationship $s(\mathbf{h}, \mathbf{l}) = s(\mathbf{h}', \mathbf{l}')s(\mathbf{h}+\mathbf{h}', \mathbf{l}+\mathbf{l}')$ (Cochran, 1952, expression 18) was employed to establish the signs of most of the other strong reflections. The distribution of positive and negative signs was suggestive of a fringe system of the two bromine atoms in the projection of the unit cell on (010).

On the basis of these signs a Fourier synthesis was calculated and the resulting map clearly showed the bromine atom and the six carbon atoms of the phenyl ring, together with two bands of high electron density tentatively identified as representing the unresolved atoms of the piperidine ring viewed edgewise and the unresolved atoms of the propionoxy chain. Because each of these groups has approximately the same number of atoms it was not possible to distinguish between them at this stage. Assuming true isomorphism between the hydrochloride and the hydrobromide the signs of almost 70% of the $h0l$ reflections from the hydrochloride were determined and a Fourier synthesis was calculated. The corresponding electron-density map showed the same general features as that of the hydrobromide. The x and z co-ordinates of all the resolved atoms were obtained from the maps, structure factors were calculated, and the Fourier syntheses were repeated. Although the resulting electron-density maps of both the hydrochloride and the hydrobromide were improved no details emerged in the unresolved bands.

In an attempt to determine the y co-ordinate of the bromine atom a Patterson synthesis was calculated with the data for the $hk0$ reflections. The Patterson map, however, showed only a band of high vector density with a value of x corresponding to that found for Br in the projections on (010), and a few higher peaks in other regions. Application of a sharpening factor improved the appearance of the map and brought up a peak with approximately the appropriate x co-ordinate for the Br–Br vector but the y co-ordinate could not be fixed unambiguously. Calculation of difference-Patterson syntheses (Kartha & Ramachandran, 1955) with $(F^2_{\text{Br}} - F^2_{\text{Cl}})$ as coefficients to remove the effects of interactions among the light atoms, and with $(|F_{\text{Br}}| - |F_{\text{Cl}}|)^2$ as coefficients to remove the effects of all interactions except those among the heavy atoms, however, gave maps from which consistent values of y for the bromine atom were obtained. They also showed that the z co-ordinates established from the projections on (010) should be increased by $\frac{1}{4}$ in order to refer all co-ordinates to a true inversion centre rather than to the pseudo-centre which was chosen inadvertently in the initial stages of the first Fourier synthesis by the necessity of assigning two signs arbitrarily and by the pseudo-halving of the c axis in the projection on (010).

By application of the isomorphous-replacement method, and with the use of the x, y, z co-ordinates of Br and Cl, about 70% of the signs of the $hk0$ and $0kl$ reflections were determined although this was not possible in the case of several strong, low angle, reflections to which Br (or Cl) made only a small contribution. Electron-density maps based on these data gave more accurate values for the y co-ordinates of the bromine and chlorine atoms but otherwise they were difficult to interpret because of extensive overlap. Knowing the x co-ordinates of each of the carbon atoms of the phenyl ring it was possible to assign approximate values for y (or $\frac{1}{2}-y$, owing to the reflection plane at $y=\frac{1}{4}$ in the c axis projection) and to include the contributions of these atoms in the structure factor calculations for the $\{hk0\}$ and $\{0kl\}$ zones. Although this increased the number of reflections to which signs could be given, no very marked improvement in the electron-density projections down [001] or [100] was achieved.

Generalized projections

In order to improve resolution in the electron-density maps, generalized projections (Cochran & Dyer, 1952) along each of the three crystallographic axes of the hydrobromide were prepared from the data for the first levels.

Starting with the b axis, and utilizing the intensity data for the hydrobromide and the hydrochloride, the signs of as many as possible of the $h1l$ reflections from the hydrobromide were found by the isomorphous-replacement method. The signs of most of the reflections for which l is even were fixed unequivocally because of the large contributions of the bromine atom, the y co-ordinate of which is nearly $\frac{1}{4}$. Furthermore, the number of reflections for the first level is twice that for the zero level because of the space-group symmetry. Consequently, the sine Fourier synthesis, which involves only terms with l even, was very successful. The bromine contributions to those reflections for which l is odd, however, are in general not as large so that many terms for the corresponding cosine Fourier synthesis were of uncertain sign and could not be used.

The electron-density map plotted from the results of the sine Fourier synthesis showed very sharp, well resolved, peaks corresponding to those previously found for bromine and the six carbon atoms of the phenyl group in the normal projection on (010). In addition, eight well resolved peaks (+ or −) appeared in the regions of the two unresolved bands of electron density present in the zero-level normal projection. Thus the x and z co-ordinates of the bromine atom, the six carbon atoms of the phenyl group, and eight other atoms were established, leaving five light atoms (excluding H) still to be located. Furthermore, from the heights and the signs of the peaks in the sine Fourier map, approximate y co-ordinates were determined for the 15 atoms mentioned, although there was some ambiguity between y and $\frac{1}{2}-y$ in some cases. The cosine Fourier synthesis, however, was of assistance in resolving this difficulty for most of the atoms concerned, in spite of the lack of detail in the cosine electron-density map.

Structure-factor calculations based on the co-ordinates of the 15 atoms whose positions were now known enabled the signs of many of the $1kl$ and $hk1$ reflections to be fixed, and first-level generalized projections were made along the a and c axes. Detailed examination of the positive and negative peaks in the corresponding sine and cosine electron-density maps enabled the sites of all 20 atoms (excluding hydrogens) in the asymmetric unit to be identified and gave more accurate values for the y co-ordinates employed in the structure-factor calculations. At this stage the overall discrepancy factor, R, for the hydrobromide, calculated for the three zero and three first levels, was 0·21.

One more set of the three normal zero-level Fourier syntheses, and two more sets of the three generalized first-level syntheses, were calculated and all positive and negative peaks in the final electron-density maps were accounted for in terms of a consistent set of x, y, z co-ordinates for the 20 atoms (excluding hydrogens) in the asymmetric unit.

A trial structure for the hydrochloride based on that of the hydrobromide was assumed and then refined by a cycle of structure-factor calculations followed by zero-level normal, and first-level generalized, projections along each of the three crystallographic axes. The results fully confirmed the assumption of isomorphism and gave reasonably accurate x, y, z co-ordinates for all 20 atoms (excluding hydrogens) in the asymmetric unit of *dl*-alphaprodine hydrochloride.

Three-dimensional refinement

Assuming an overall temperature-factor constant, B, of 3·5 Å^2, the structure factors of all observed reflections from the hydrochloride were calculated and the R-factor was found to be 0·32. Omitting 200 weak reflections, the signs of which were uncertain, a three-dimensional Fourier synthesis was evaluated and, by algebraic interpolation, atomic co-ordinates were deduced which differed on the average by about 0·05 Å from those derived from the two-dimensional data alone. Adoption of the new co-ordinates, and $B=$ 4·5 Å^2, reduced the R-factor to 0·23, and the number of reflections with uncertain signs to 93. A differential synthesis, evaluated with all the observed data with the exception of these 93 reflections, gave mean atomic shifts of 0·022, 0·020, and 0·018 Å along x, y, and z, respectively, and brought the R-factor down to 0·21.

Refinement was continued with the introduction of different isotropic temperature factors for the individual light atoms and an anisotropic temperature factor for the chlorine atom. The need for the latter was indicated by the non-spherical distribution of electron density and the unequal curvatures for this atom. For the calculation of structure factors, therefore, the anisotropic chlorine atom was represented by four isotropic atoms in the (001) plane equally spaced around the atomic centre, and each of $\frac{1}{4}$ weight, to simulate the ellipsoid of thermal vibration with its shortest axis along z (Kartha & Ahmed, 1960). Two cycles of refinement by differential syntheses, including correction for finite-summation errors, reduced the R-factor to 0·16$_7$.

Almost from the first structure-factor calculations each of the three methyl groups was assigned a scattering factor appropriate to a freely rotating CH_3 group (Cruickshank, 1955). Now on the assumption that the remaining hydrogen atoms occupy their theoretical positions at 1·08 Å from their respective carbon atoms, their contributions were added to the calculated structure factors and the R-factor became $0{\cdot}15_6$ for all the observed three-dimensional data, and 0·16, 0·13, 0·16 for the *hk*0, 0*kl*, and *h*0*l* reflections, respectively.

Table 2. *Fractional atomic co-ordinates*

Atom	x	y	z	r.m.s. $\{\sigma(x), \sigma(y), \sigma(z)\}$ (Å)
N(1)	0·0530	0·2287	0·1297	0·005
C(2)	0·1148	0·3507	0·1946	0·006
C(3)	0·2069	0·3392	0·1806	0·006
C(4)	0·2456	0·1623	0·1989	0·006
C(5)	0·1766	0·0430	0·1339	0·006
C(6)	0·0876	0·0575	0·1537	0·007
C(7)	0·3354	0·1538	0·1780	0·007
C(8)	0·4138	0·1905	0·2504	0·010
C(9)	0·4939	0·1954	0·2303	0·013
C(10)	0·4984	0·1638	0·1341	0·012
C(11)	0·4208	0·1266	0·0604	0·009
C(12)	0·3411	0·1229	0·0825	0·008
C(13)	0·2817	−0·0156	0·3458	0·007
C(14)	0·2828	−0·0207	0·4531	0·009
CH_3'	−0·0400	0·2469	0·1408	0·008
CH_3''	0·2651	0·4720	0·2466	0·008
CH_3'''	0·2984	−0·1908	0·4971	0·013
O′	0·2548	0·1325	0·3046	0·004
O″	0·3011	−0·1310	0·3003	0·006
Cl	0·0499	0·1986	0·4160	0·002

Final differential syntheses, evaluated for all the observed and calculated data with the exception of 58 reflections of doubtful signs, gave the atomic co-ordinates shown in Table 2, where the r.m.s. of the estimated standard deviations, assuming $\sigma(F) = |\Delta F|$ and omitting the unobserved reflections, are given in the last column. Because the average change in the co-ordinates during the final cycle of refinement was only 0·002 Å, and the average series-termination error was 0·007 Å, the structure factors were not recalculated after the last synthesis. The values and the mean curvatures of the observed and calculated electron densities together with the final values of the temperature-factor constant are listed in Table 3.

Table 3. *Observed and calculated electron densities* (e.Å^{-3}), *mean curvatures* (e.Å^{-5}) *and isotropic B values* (Å^2)

Atom	ϱ_o	ϱ_c	ϱ_o''	ϱ_c''	B
N(1)	9·64	9·87	74·4	76·0	3·3
C(2)	7·90	8·04	62·8	64·7	3·2
C(3)	8·04	8·17	63·0	64·6	3·2
C(4)	8·10	8·01	62·1	62·7	3·2
C(5)	7·19	7·63	57·5	59·8	3·5
C(6)	6·97	7·06	52·0	53·2	4·2
C(7)	7·33	7·64	55·0	58·8	3·5
C(8)	5·65	5·67	37·3	38·0	6·5
C(9)	5·04	5·35	31·0	35·1	5·8
C(10)	5·16	5·45	32·8	34·7	5·8
C(11)	5·68	5·88	39·8	40·9	5·4
C(12)	6·70	6·93	49·1	51·1	4·2
C(13)	7·01	7·14	53·2	53·3	4·2
C(14)	6·03	6·16	40·7	41·7	5·2
CH_3'	6·59	6·64	46·8	49·3	4·7
CH_3''	6·45	6·58	45·7	47·9	4·7
CH_3'''	4·71	5·06	28·9	31·2	6·5
O′	11·23	11·42	84·1	84·7	3·5
O″	8·84	9·20	61·4	63·0	5·2
Cl	26·34	25·42	216·1	211·1	3·4*

* Isotropic temperature factor of the ¼ chlorine atoms placed at (±0·157, ±0·114, 0) Å from the centre of the chlorine atom.

Table 4. *Agreement summary*

	Category and limits	Reflections
1.	$\lvert\Delta F\rvert \le 2$ or $\lvert\Delta F\rvert \le 0{\cdot}2\lvert F_o\rvert$	1960
2.	$\lvert\Delta F\rvert \le 4$ or $\lvert\Delta F\rvert \le 0{\cdot}4\lvert F_o\rvert$	367
3.	$\lvert\Delta F\rvert \le 6$ or $\lvert\Delta F\rvert \le 0{\cdot}6\lvert F_o\rvert$	34
4.	$\lvert\Delta F\rvert \le 8$	10
5.	$\lvert\Delta F\rvert \le 11$	1

$|\Delta F| = |F_o - F_c|$

On the basis of 2372 observed reflections, and $|F_o|_{\text{min.}} = 2$, a summary of the agreement between $|F_o|$ and $|F_c|$ arranged in categories similar to those of Hanson & Ahmed (1958, p. 726) is presented in Table 4. Only 45 reflections (~2%) of relatively high discrepancy occur (categories 3, 4, and 5), none of these is very strong, and $|F_o| \le 10$ for 32 of them, while $|F_o|_{\text{max.}} = 160$. Only 318 possible reflections within the Cu sphere were *not* observed and of these $|F_c| < 2$ for 171. Of the remainder, $|F_c| = 10{\cdot}1$ for one, lies between 8·4 and 5·0 for 20, between 4·9 and 4·0 for 23, between 3·9 and 3·0 for 42, and between 2·9 and 2·0 for 61.

Results and discussion

Electron-density projections of the structure of *dl*-alphaprodine hydrochloride along each of the three crystallographic axes, calculated with the structure-factor data immediately prior to the last three-dimensional differential synthesis, are reproduced in Figs. 2, 3, 4. A perspective drawing of the alphaprodine molecule is shown in Fig. 5, and the intramolecular bond lengths (with their e.s.d.'s) and the bond angles are indicated in Fig. 6. The r.m.s. of the estimated standard deviations of these angles (Ahmed & Cruickshank, 1953) are 41′ for those of the phenyl

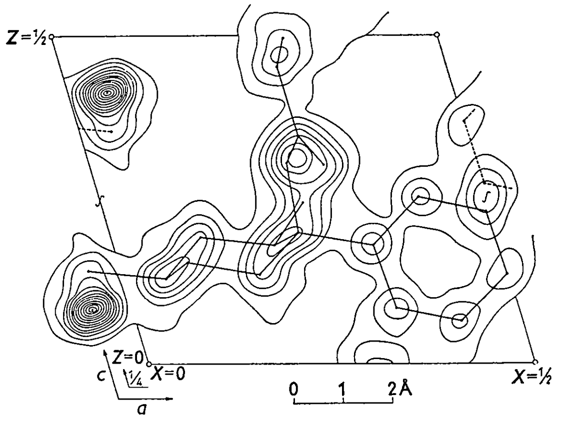

Fig. 2. Final electron-density projection of *dl*-alphaprodine HCl down [010]; contours at intervals of 2 e.Å^{-2} with the first at 2 e.Å^{-2}.

ring, 25′ for those of the piperidine ring, and 33′ for those of the propionoxy chain.

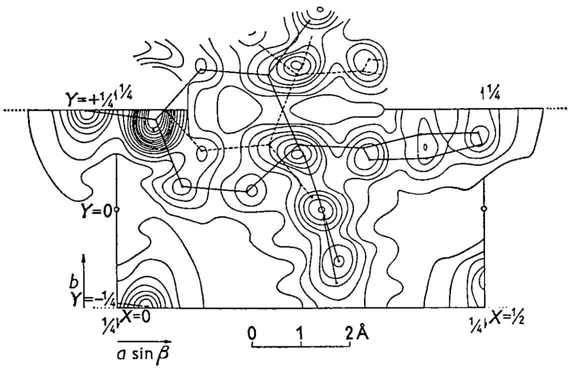

Fig. 3. Final electron-density projection of *dl*-alphaprodine HCl down [001]; contours at intervals of 2 e.Å^{-2} with the first at 2 e.Å^{-2}.

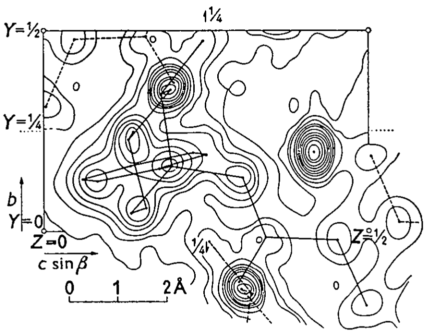

Fig. 4. Final electron-density projection of *dl*-alphaprodine HCl down [100]; contours at intervals of 2 e.Å^{-2} with the first at 2 e.Å^{-2}.

The aromatic bonds of the phenyl ring are all very nearly of the same length with a mean of 1·381 Å, and all the C atoms of this ring lie within ±0·003 Å of the best mean plane referred to the orthogonal axes $x' = x + z\cos\beta$, y, $z' = z\sin\beta$ and expressed by the equation

$$0{\cdot}0751x' - 0{\cdot}9718y + 0{\cdot}2243z' + 0{\cdot}3450 = 0\,. \quad (1)$$

The phenyl ring is definitely planar because $\chi^2 = 0{\cdot}34$, $\nu = 3$, and $P = 0{\cdot}95$ (Weatherburn, 1947, p. 171).

In the piperidine ring the C–C single bonds vary in length from 1·512 Å to 1·557 Å, with a mean value of 1·535 Å. The two C–N bonds within the ring have virtually the same length, 1·497 Å and 1·500 Å, which represents a just possibly significant difference from the CH_3'–N bond length of 1·526 Å. The mean of all three bonds is $1{\cdot}50_7$ Å.

The best mean plane through N(1), C(3), C(4), and C(6), referred to the same set of orthogonal axes as the phenyl ring, is represented by the equation

$$0{\cdot}3008x' - 0{\cdot}0844y - 0{\cdot}9500z' + 1{\cdot}7358 = 0 \quad (2)$$

and C(2) is 0·67 Å away from this plane on one side and C(5) is 0·68 Å away from it on the opposite side. Thus, as expected, the piperidine ring has the Sachse *trans* (chair) form. It is of interest to note that the angle between the normals to the planes represented by equations (1) and (2) is almost 84°.

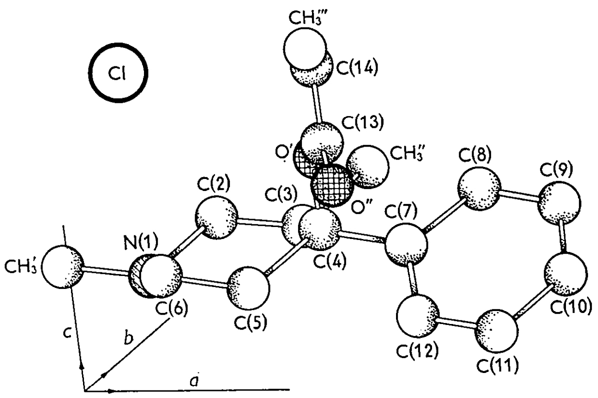

Fig. 5. Perspective view of the molecule of alphaprodine.

The most important features of the piperidine ring and its substituents, however, are as follows: (*a*) The methyl group (CH_3'') attached to C(3), and the oxygen atom (O′) of the propionoxy chain joined to C(4), are located on the same side of the plane containing N(1), C(3), C(4), C(6) while C(7) of the phenyl ring attached to C(4) is situated on the opposite side of this plane, so that the configuration is *trans* from the point of view of Me/Ph; (*b*) the methyl group on C(3), and C(7) of the phenyl ring on C(4), are only 0·76 Å and 0·75 Å perpendicularly from this plane while the oxygen atom (O′) of the propionoxy chain on C(4) is 1·38 Å from it, thus demonstrating that the methyl group and the phenyl ring are equatorial and the propionoxy chain is axial to the piperidine ring. The stereochemical configuration of the alphaprodine molecule in the crystal structure of *dl*-alphaprodine hydrochloride, therefore, corresponds with III of Fig. 1 and Table 1 and the deductions of Beckett & co-workers (1954, 1955, 1959) from conformational analysis, hydrolysis studies, and other indirect methods regarding the configuration of the alphaprodine molecule are thus fully confirmed (Ahmed, Barnes & Kartha, 1959).

In the structure as a whole the shortest intermolecular distance is 3·60 Å which occurs between C(12) and C(14) of the two molecules related by the *c* glide plane. The chlorine ion is 4·02 Å from the nearest nitrogen atom; this is comparable with the large separation (4·2 Å) between the bromine ion and N in codeine hydrobromide dihydrate (Lindsey & Barnes, 1955). Ignoring hydrogen atoms, no other atom is closer to Cl than 3·71 Å.

Most of the calculations pertinent to this structure investigation were carried out with a basic IBM 650 computer at Army Pay Ledger Unit No. 1, and with the Ferranti computer, TRANSFER, at the National

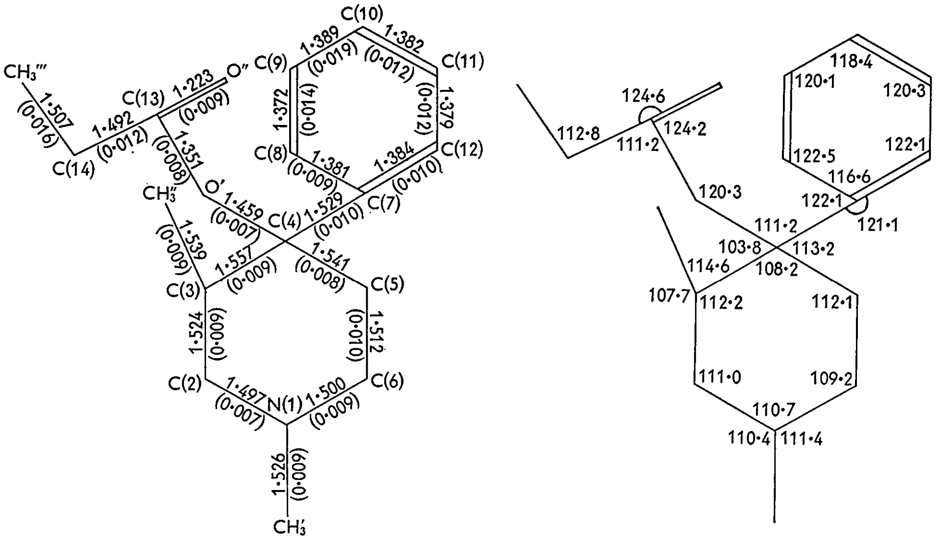

Fig. 6. Intramolecular bond lengths (Å; e.s.d.'s in parentheses) and bond angles (°).

Aeronautical Establishment, both in Ottawa; deep appreciation is expressed for permission to use these machines and for the facilities provided by the staffs in charge. Grateful acknowledgment also is made to Mrs M. E. Pippy of this laboratory for assistance with desk-machine calculations and with the operation of the computers and accessory equipment.

References

Ahmed, F. R., Barnes, W. H. & Kartha, G. (1959). *Chem. & Ind.* p. 485.

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

Archer, S. (1958). *Amer. Chem. Soc. Abstracts*, 4M.

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

Beckett, A. H. & Casy, A. F. (1954). *J. Pharm. Pharmacol.* **6**, 986.

Beckett, A. H., Casy, A. F. & Harper, N. J. (1959). *Chem. & Ind.* p. 19.

Beckett, A. H. & Walker, J. (1955). *J. Pharm. Pharmacol.* **7**, 1039.

Cochran, W. (1952). *Acta Cryst.* **5**, 65.

Cochran, W. & Dyer, H. B. (1952). *Acta Cryst.* **5**, 634.

Cruickshank, D. W. J. (1955). Private communication.

Hanson, A. W. & Ahmed, F. R. (1958). *Acta Cryst.* **11**, 724.

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

Kartha, G. & Ramachandran, G. N. (1955). *Acta Cryst.* **8**, 195.

Lindsey, J. M. & Barnes, W. H. (1955). *Acta Cryst.* **8**, 227.

Mackay, M. & Hodgkin, D. C. (1955). *J. Chem. Soc.* p. 3261.

Weatherburn, C. E. (1947). *Mathematical Statistics.* Cambridge: University Press.

Wilson, A. J. C. (1942). *Nature, Lond.* **150**, 151.

Ziering, A. & Lee, J. (1947). *J. Org. Chem.* **12**, 911.

Ziering, A., Motchane, A. & Lee, J. (1957). *J. Org. Chem.* **22**, 1521.