

The Crystal and Molecular Structures of Ephedrine Hydrochloride

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The crystal structure of ephedrine hydrochloride has been determined with X-rays by means of electron-density projections on (010) and (001). The phases of reflexions in the centric [010] zone were determined directly by comparison of corresponding reflexions from the isomorphous ephedrine hydrochloride and hydrobromide. The non-centrosymmetric (001) projection was solved by trial-and-error methods based on the known (010) projection. Atomic parameters were refined by the difference-synthesis technique. Bond lengths have been determined with a mean standard deviation of 0.033 Å.

The stereochemical configuration of the molecule, as deduced on purely chemical grounds, has been directly confirmed.

1. Introduction

The alkaloid ephedrine,



is an amino alcohol of considerable physiological importance. Its structure, and the structures of its three optical isomers, have been studied intensively by classical stereochemical methods (Henry, 1949) and the relative configurations of the isomers have long been established. Close (1950) has recently reviewed the state of knowledge of the structures. He has pointed out that the conformation (Wheland, 1949) of ephedrine has not been determined and he has proposed a conformation consistent with all the available chemical evidence. The present structure determination was undertaken to provide as complete a description of the molecule as possible.

L-Ephedrine hydrochloride and L-ephedrine were supplied by B. D. H. Ltd, and the hydrobromide was prepared by Dr F. J. Wright of the Chemistry Department of this College.

2. Experimental

Ephedrine hydrochloride and hydrobromide crystallize readily from ethanol in monoclinic sphenoidal prisms with well formed pinacoids {100} and {001}. There is very ready cleavage parallel to (001). The structures were first investigated by Gossner & Neff (1933), who showed them to be isomorphous, with space group $P2_1$ (only reflexions $0k0$ with k odd absent†) and unit-cell

dimensions $a = 12.64$, $b = 6.15$, $c = 7.34$ kX., $\beta = 102^\circ 6'$ for the hydrochloride and $a = 12.74$, $b = 6.20$, $c = 7.62$ kX., $\beta = 100^\circ 48'$ for the hydrobromide. The cell dimensions of the hydrochloride have now been redetermined by the extrapolation method of Farquhar & Lipson (1946). They are

$$a = 12.65 \pm 0.02, \quad b = 6.09 \pm 0.02, \quad c = 7.32 \pm 0.02 \text{ Å}, \\ \beta = 102^\circ 15' \pm 15'.$$

There are two molecules per unit cell.

The intensities of reflexions in the $h0l$ and $hk0$ zones of ephedrine hydrochloride and the $h0l$ zone of the hydrobromide were determined by visual estimation from Weissenberg photographs taken with Cu radiation. Calculation of representative absorption corrections (Albrecht, 1939) for the hydrochloride crystals showed that the greatest variation in relative intensities caused by absorption is $\pm 5\%$. No correction was applied. After application of the Lorentz and polarization factor corrections, the intensities were put on an approximately absolute scale by the method of Wilson (1942). The extrapolation graphs obtained have been presented by Wilson (1952). Direct comparison of the observed with the final calculated values of the intensities has shown this scale to be in error by less than 5% for each zone. The probability distributions of the intensities have been shown elsewhere to agree closely with the theoretical (Howells, Phillips & Rogers, 1950).

3. Determination of the structure projected on (010)

Only the projection of the structure on (010) is centrosymmetrical. It was determined by the method

exception to the space group is therefore attributed to double Bragg reflexion (Renninger, 1937) by the pairs of planes (002), (01 $\bar{2}$) and (012), (00 $\bar{2}$). The intensity ratio was anomalous because the conditions for these double reflexions were fulfilled more exactly for the $K\beta$ radiation.

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† The presence of a very weak 010 reflexion was observed on an $\{hk0\}$ Weissenberg of the hydrochloride. It was peculiar in that the intensity of Cu $K\beta$ reflexion was greater than that of $K\alpha$. The reflexion did not appear on any photograph taken with the crystal rotated about any other axis. It has been shown that the planes (002) and (012) are in a position to reflect at the same time as (010) when the crystal is rotated about [001] and that these are among the strongest planes. The

of isomorphous replacement so that no assumptions were made about the molecular shape. Patterson projections were used to locate the halogen atoms in the isomorphous structures and the signs of the reflexions in the $h0l$ zones were then calculated directly. The Patterson projection on (010) for the hydrochloride is shown in Fig. 1. There are two outstanding peaks,

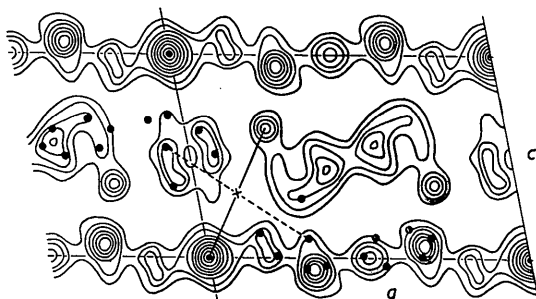


Fig. 1. Patterson projection on (010). A chlorine-chlorine vector and corresponding (chlorine)-(lighter atoms) peaks for two molecules are marked.

the larger (*A*) at $U = 0.33$, $W = 0.95$ and the smaller (*B*) at $U = 0.25$, $W = 0.65$. The corresponding projection for the hydrobromide is very similar but in it peak (*B*) at $U = 0.26$, $W = 0.63$ is the larger. Peak (*B*) was therefore taken to characterize the inter-halogen atom vector. The correctness of this interpretation was confirmed by calculation of the (001) Patterson projection for the hydrochloride (Fig. 2). There is a marked concentration of peaks along the line $V = 0.50$, establishing the presence of a screw axis, and the only outstanding peak is at $U = 0.25$, $V = 0.50$. The halogen atoms therefore have coordinates in each structure near $X = 0.12_5$, $Z = 0.32_5$, with Y values differing by 0.50.

It is of interest to note that a more detailed interpretation of the (010) Patterson projection is possible

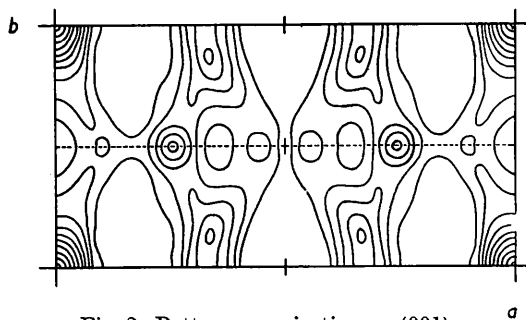


Fig. 2. Patterson projection on (001).

by the method of Sanadze & Zhdanov (1950). All peaks corresponding to vectors of the type (chlorine)-(lighter-atom) are related in pairs by a pseudo centre of symmetry situated at the mid-point of the chlorine-chlorine vector and corresponding to the centre of symmetry in the projected structure. This interpretation is outlined in Fig. 1. It leads immediately to an approximate structure capable of refinement, and

might have been used if the direct method now to be described had not been available.

Since ephedrine hydrochloride and hydrobromide are isomorphous, corresponding atoms occupy nearly the same positions in the two structures. For the centric $h0l$ zones, therefore, corresponding structure factors are related by the equation:

$$F_{\text{Br}}(h0l) - F_{\text{Cl}}(h0l) = 2f_{\text{Br}} \cos 2\pi(hX_{\text{Br}} + lZ_{\text{Br}}) - 2f_{\text{Cl}} \cos 2\pi(hX_{\text{Cl}} + lZ_{\text{Cl}}). \quad (1)$$

If the halogen atoms have the same fractional coordinates (X_H , Z_H), in each structure, this becomes:

$$F_{\text{Br}}(h0l) - F_{\text{Cl}}(h0l) = 2(f_{\text{Br}} - f_{\text{Cl}}) \cos 2\pi(hX_H + lZ_H). \quad (2)$$

The signs of 120 of the 190 observed reflexions from ephedrine hydrochloride were determined from (2) and used in a calculation of the electron density projected on (010). This showed the atomic arrangement clearly, even though subsequent refinement has shown that 20 wrong signs were used in its calculation. The failures of the method were due to several causes. The halogen atoms, at least, occupy slightly different positions in the unit cells so that use of equation (1) might have given better results. Further, because of the differences in unit-cell dimensions, corresponding reflexions occur from the two substances at different angles and are hence not strictly comparable. Such considerations apply principally to the reflexions at high angles; uncertainties in the results for reflexions at small angles arose mainly when the halogen contributions are only small and they were less common for the hydrobromide.

Atomic parameters derived from the first Fourier synthesis of the electron-density projection were used in a calculation of all the structure factors in this zone. At this stage the structure-factor calculating device described by Vand (1948) was used. Carbon, nitrogen and oxygen contributions were included with weights 6:7:8 but with atomic scattering factors of the same form. The chlorine contribution was calculated separately. The reliability index, $R = \sum ||F_o| - |F_c|| / \sum |F_o|$, obtained was 0.30. Three cycles of Fourier refinement

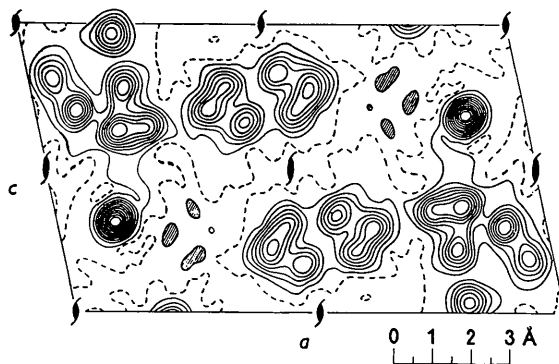


Fig. 3. Electron density projected on (010). Contour lines are drawn at intervals of $1 \text{ e.}\text{\AA}^{-2}$, except for the chlorine atom where the intervals are $2 \text{ e.}\text{\AA}^{-2}$. The one-electron line is broken; negative areas are hatched.

Table 1. *Comparison of observed and calculated structure factors*(a) *hOl zone*

<i>hOl</i>	$ F_o $	F_c	<i>hOl</i>	$ F_o $	F_c	<i>hOl</i>	$ F_o $	F_c
100	8.4	+ 2.5	$\overline{10},0,2$	7.0	— 7.7	605	3.5	— 4.1
200	12.5	+12.2	$\overline{11},0,2$	7.5	— 5.7	505	5.5	+ 5.8
300	46.8	—48.9	$\overline{12},0,2$	2.6	+ 2.7	405	8.2	+ 7.7
400	27.0	—25.5	$\overline{13},0,2$	7.7	+ 8.3	305	4.7	+ 3.6
500	9.8	+ 9.7	$\overline{14},0,2$	5.4	+ 5.1	205	6.2	+ 6.9
600	4.4	— 5.6	$\overline{15},0,2$	4.4	+ 3.0	105	2.5	— 1.4
700	2.2	— 0.4	$\overline{16},0,2$	2.6	— 3.1	005	0	— 0.5
800	2.8	+ 2.1	$\overline{13},0,3$	0	0	$\overline{105}$	9.5	— 9.2
900	4.5	+ 3.6	12,0,3	3.1	— 2.4	205	14.7	—12.3
10,0,0	2.4	+ 2.8	11,0,3	0	— 0.2	305	4.1	— 3.2
11,0,0	4.3	— 4.7	10,0,3	0	+ 0.1	405	10.8	+10.3
12,0,0	2.7	— 3.0	903	8.6	+ 8.9	505	26.9	+24.3
13,0,0	5.1	— 5.2	803	8.1	+ 7.4	605	6.3	+ 7.6
14,0,0	0	0	703	5.3	+ 6.3	705	1.2	0
15,0,0	1.8	+ 1.7	603	6.7	— 7.5	805	6.8	— 6.6
14,0,1	3.1	+ 3.4	503	7.0	— 5.5	905	11.9	—13.1
13,0,1	0	+ 1.8	403	24.1	—28.8	$\overline{10},0,5$	2.6	+ 0.5
12,0,1	0	+ 1.3	303	16.2	—18.1	$\overline{11},0,5$	13.9	—10.0
11,0,1	3.9	— 5.3	203	6.3	— 9.2	$\overline{12},0,5$	4.8	+ 4.4
10,0,1	4.6	— 3.5	103	21.7	+18.9	$\overline{13},0,5$	1.8	+ 2.3
901	14.2	—15.6	003	33.9	+34.6	$\overline{14},0,5$	5.1	+ 4.0
801	5.0	— 3.8	$\overline{103}$	14.0	+12.6	906	2.6	+ 2.0
701	2.2	— 3.1	$\overline{203}$	15.4	—15.7	806	8.5	+ 5.1
601	36.3	+37.8	$\overline{303}$	21.3	—17.5	706	1.8	+ 3.1
501	11.2	+11.7	403	10.2	— 8.2	606	0	+ 0.6
401	21.2	+18.2	$\overline{503}$	9.5	— 8.9	506	4.4	— 4.9
301	1.3	— 1.2	603	8.0	+ 8.8	406	10.7	—10.5
201	1.2	— 1.3	703	5.4	+ 5.4	306	7.1	— 6.6
101	17.9	+18.1	803	5.4	+ 6.8	206	6.4	+ 7.8
001	22.3	—22.9	903	10.0	+11.8	106	11.5	+11.3
$\overline{101}$	32.3	—36.5	$\overline{10},0,3$	6.4	— 5.6	006	15.8	+15.1
$\overline{201}$	5.9	+ 9.3	$\overline{11},0,3$	2.6	+ 2.7	$\overline{106}$	4.6	— 3.8
$\overline{301}$	20.2	+18.3	$\overline{12},0,3$	3.1	— 4.5	$\overline{206}$	4.9	— 2.7
401	15.0	+13.6	$\overline{13},0,3$	0	— 1.9	$\overline{306}$	6.4	— 7.4
501	0	+ 1.4	$\overline{14},0,3$	0	+ 0.2	406	3.2	+ 1.9
601	39.4	—36.9	$\overline{15},0,3$	0	+ 1.5	506	8.6	— 8.9
701	13.0	—13.4	12,0,4	0	+ 0.4	606	1.2	— 1.4
801	6.9	— 9.5	11,0,4	2.6	— 2.2	706	1.2	+ 0.4
901	8.6	+ 8.4	10,0,4	0	— 1.9	806	4.8	+ 5.7
$\overline{10},0,1$	13.7	+12.9	904	5.4	— 5.5	906	4.4	+ 4.1
$\overline{11},0,1$	7.5	+ 8.0	804	6.3	— 6.6	$\overline{10},0,6$	4.4	— 2.5
$\overline{12},0,1$	2.6	— 1.7	704	0	— 1.7	$\overline{11},0,6$	7.9	— 6.8
$\overline{13},0,1$	3.6	— 3.7	604	6.5	+ 6.2	$\overline{12},0,6$	1.8	— 3.0
$\overline{14},0,1$	4.8	— 4.0	504	8.3	+ 8.5	$\overline{13},0,6$	2.5	— 2.6
$\overline{15},0,1$	1.4	— 0.9	404	3.1	+ 0.9	$\overline{14},0,6$	3.6	+ 2.4
14,0,2	4.8	— 3.7	304	0	— 0.4	707	0	— 0.7
13,0,2	0	— 2.0	204	12.6	—12.1	607	8.9	+ 7.0
12,0,2	0	+ 1.3	104	6.4	— 7.0	507	0	— 0.6
11,0,2	8.7	+ 9.8	004	5.1	— 4.7	407	0	+ 3.3
10,0,2	3.9	+ 5.1	$\overline{104}$	2.9	+ 0.2	307	0	— 0.9
902	2.6	+ 3.1	204	16.6	+18.2	207	2.9	— 4.1
802	2.9	— 3.3	304	16.3	+16.6	107	2.9	— 3.9
702	4.6	— 4.1	404	0	+ 1.5	007	6.2	— 5.9
602	3.5	— 1.8	504	0	— 0.4	$\overline{107}$	2.9	+ 3.7
502	1.7	— 2.7	604	14.6	—14.3	207	8.8	+ 8.4
402	20.9	+21.6	704	9.4	— 8.6	307	6.7	+ 6.5
302	10.9	+14.2	804	1.7	— 1.1	407	2.0	— 1.6
202	3.1	— 1.7	904	7.9	+ 7.8	507	12.0	—11.1
102	2.4	+ 0.4	$\overline{10},0,4$	9.5	+11.4	607	7.7	— 7.5
002	50.7	—64.2	$\overline{11},0,4$	11.5	+10.1	707	7.7	— 6.5
$\overline{102}$	13.3	+11.6	$\overline{12},0,4$	4.8	— 3.2	807	2.0	+ 1.1
$\overline{202}$	43.7	—42.4	$\overline{13},0,4$	5.4	— 4.6	907	5.7	+ 5.8
302	3.9	0	$\overline{14},0,4$	5.7	— 4.4	$\overline{10},0,7$	3.1	+ 3.3
402	8.8	+ 9.0	$\overline{15},0,4$	4.1	— 3.5	$\overline{11},0,7$	8.3	+ 7.4
502	13.3	+12.1	11,0,5	1.8	+ 2.8	$\overline{12},0,7$	3.6	— 1.7
602	22.2	+20.8	10,0,5	2.2	+ 2.2	408	4.4	+ 3.6
702	3.4	+ 2.0	905	2.6	— 2.4	308	2.6	+ 2.7
802	5.6	— 6.2	805	6.0	— 7.3	208	0	+ 0.6
902	11.5	— 9.6	705	2.9	— 2.0	108	0	— 0.5

Table 1 (cont.)

$h0l$	$ F_o $	F_c	$h0l$	$ F_o $	F_c	$h0l$	$ F_o $	F_c
008	5.1	— 5.5	508	9.7	+ 9.3	10,0,8	1.8	— 2.1
108	5.1	— 3.8	608	3.4	+ 4.1	109	0	+ 3.2
208	6.9	— 7.3	708	2.6	+ 1.4	009	4.1	+ 3.7
308	0	— 0.8	808	3.1	— 4.0	109	0	— 0.4
408	4.1	+ 3.1	908	4.8	— 3.9	209	0	— 1.8

(b) $hk0$ zone

$hk0$	$ F_o $	$ F_c $	$\alpha_c (^\circ)$	$hk0$	$ F_o $	$ F_c $	$\alpha_c (^\circ)$	$hk0$	$ F_o $	$ F_c $	$\alpha_c (^\circ)$
110	18.5	17.2	331	12,2,0	7.8	7.2	207	940	4.7	4.6	348
210	25.2	28.6	69	13,2,0	3.7	4.1	193	10,4,0	0	1.0	131
310	40.0	38.8	84	14,2,0	0	0.5	53	11,4,0	2.9	3.9	159
410	16.8	14.6	88	15,2,0	0	1.3	90	12,4,0	2.5	3.4	162
510	14.4	13.4	23	130	15.8	18.8	79	13,4,0	5.1	3.6	133
610	27.5	27.4	281	230	17.2	17.3	105	150	7.6	7.4	34
710	7.4	5.5	274	330	14.8	13.6	100	250	12.1	14.5	89
810	8.0	7.1	168	430	12.5	12.6	272	350	4.7	4.9	63
910	9.4	9.5	135	530	8.8	10.6	284	450	2.0	4.2	133
10,1,0	8.8	8.9	78	630	6.8	7.8	332	550	2.0	3.4	232
11,1,0	5.5	5.1	85	730	3.5	6.3	230	650	6.6	6.7	257
12,1,0	2.7	1.7	321	830	10.7	12.1	74	750	4.7	3.2	235
13,1,0	3.5	3.3	280	930	3.9	3.3	236	850	0	1.4	256
14,1,0	4.9	4.7	191	10,3,0	9.6	9.5	59	950	0	2.5	49
15,1,0	2.7	2.7	314	11,3,0	3.7	3.9	108	10,5,0	2.1	2.3	66
020	17.8	19.1	354	12,3,0	0	1.0	73	060	8.6	9.1	341
120	20.9	20.2	333	13,3,0	3.1	2.2	130	160	0	3.0	34
220	12.9	12.0	235	14,3,0	6.4	4.2	96	260	5.5	6.3	277
320	4.9	6.3	296	040	12.7	10.8	22	360	2.7	2.3	184
420	19.5	19.0	144	140	9.0	9.0	7	460	6.4	7.6	185
520	7.0	7.3	145	240	5.3	3.8	351	560	1.8	3.0	128
620	0	2.1	188	340	3.3	2.4	280	660	1.8	1.7	287
720	10.1	8.2	343	440	10.1	8.9	179	760	2.9	2.7	338
820	11.5	11.5	352	540	8.6	11.1	202	860	2.5	3.1	16
920	12.3	12.0	40	640	1.9	2.1	149	170	2.0	1.9	52
10,2,0	7.2	6.6	179	740	4.7	6.3	273	270	4.1	3.4	89
11,2,0	6.4	5.7	171	840	9.4	10.4	26				

then gave $R = 0.19$ and the projection of electron density on (010) shown in Fig. 3.

In order to make allowance for termination-of-the-series errors, which are evident in Fig. 3, the refinement was continued by the difference-synthesis method (Booth, 1948; Cochran, 1951). Shifts in atomic parameters up to 0.05 Å were indicated but the main features of the first ($\rho_o - \rho_c$) synthesis were due to inadequacies in the scattering-factor curves used. The neighbourhood of the chlorine atom in this map is

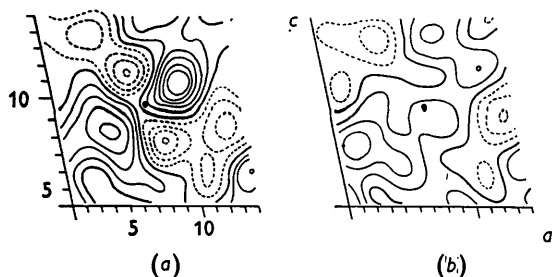


Fig. 4. Neighbourhood of the chlorine atom in (a) the first and (b) the final (010) difference syntheses. Contours are drawn at intervals of 0.2 e.Å⁻³; those for negative values are broken. Lines parallel to a and c are divided into 1/60ths. and 1/30ths. of a and c respectively.

shown in Fig. 4(a). It shows clearly not only that a small adjustment to the position of the atom is necessary but also that it is subject to anisotropic thermal motion with the direction of maximum motion inclined at about 30° to the a axis. Allowance for this motion was made in the final structure-factor calculations by the use of an atomic scattering factor of the form

$$f = f_0 \exp \left[-\{2.8 + 1.4 \sin^2(\varphi - 30^\circ)\} \sin^2 \theta / \lambda^2 \right]$$

(Hughes, 1941). f_0 is the scattering factor for a chlorine atom at rest (*International Tables*, 1935) and φ is the angle which the reciprocal-lattice vector appropriate to the reflexion makes with c^* . The neighbourhood of the chlorine atom in the final difference synthesis is shown in Fig. 4(b). The best mean scattering factor for the lighter atoms was found to be that for nitrogen with an isotropic temperature factor having $B = 4.2 \text{ Å}^2$.

Some slight further improvement could be effected by adjustment of the scattering factors for individual atoms but this has not been undertaken. The final value of R for this projection is 0.15; the structure factors are given in Table 1.

4. Determination of the structure projected on (001)

It is not generally possible to determine the phases of complex structure factors unambiguously, even by the method of isomorphous replacement. A trial structure derived from the fitting of molecular models to the (010) projection was used as the starting point of refinement for this non-centrosymmetric projection. Only one configuration of the molecule was found to fit the (010) projection well; no limitations were placed on the movement of atoms in the refinement process. The complex structure factors were calculated, in the early stages, with the vector plotting device described elsewhere (Phillips, 1952). The refinement proceeded slowly until the difference-synthesis method with double-shift corrections (Cruickshank, 1950a) was adopted. The reliability index was then quickly reduced to 0.12 and the electron-density projection of Fig. 5 was obtained. Refinement was stopped when the

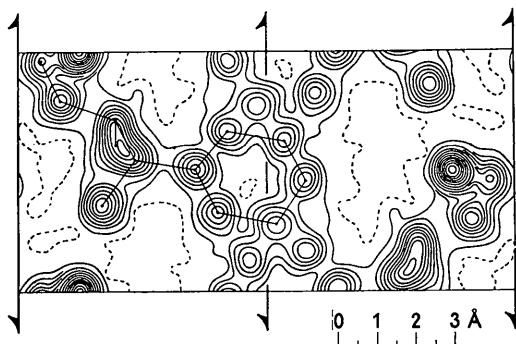


Fig. 5. Electron density projected on (001). Contour lines are drawn at intervals of 1 e.Å⁻², except for the chlorine atom where the intervals are 2 e.Å⁻². The one-electron line is broken.

corrections indicated by the last stage were less than the probable errors in atomic positions.

There was no indication of anisotropic thermal motion of the chlorine atom in this projection. An isotropic temperature factor with $B = 4.2 \text{ Å}^2$ was used with the chlorine and nitrogen scattering factors. The structure factors are given in Table 1. The atomic coordinates derived from the two projections are given in Table 2.

Table 2. Atomic coordinates

Atom	X (010)	X (001)	Y (001)	Z (010)
C ₁	0.4008	0.3960	0.3242	0.7863
C ₂	0.5142	0.5160	0.2856	0.8297
C ₃	0.5790	0.5788	0.4450	0.7830
C ₄	0.5360	0.5368	0.6288	0.6390
C ₅	0.4211	0.4184	0.6688	0.6420
C ₆	0.3578	0.3576	0.5110	0.6970
C ₇	0.2334	0.2350	0.5480	0.6418
C ₈	0.1970	0.1960	0.7040	0.7766
C ₉	0.1963	0.1970	0.6070	0.9672
C ₁₀	0.0478	0.0470	0.9608	0.8060
O	0.1700	0.1700	0.3582	0.6252
N	0.0857	0.0832	0.8006	0.6974
Cl	0.1250	0.1240	0.0000	0.3257

5. Estimation of accuracy

Calculation of the reliability indices provided a useful check on the progress of the refinement but the final values are not easily related to the accuracy of the structure determination. It is, however, of interest to notice the difference between the values obtained for the two zones. This is due not to different degrees of refinement but to the different probability distributions of intensities in the two zones (Phillips, Rogers & Wilson, 1950).

If it is assumed that termination-of-the-series errors have been adequately corrected by the use of the difference-synthesis technique, the standard deviations in atomic positions may be calculated by the method suggested by Cruickshank (1949, 1950b). This is equivalent to a calculation of the mean gradients in the difference syntheses; it is strictly valid only when the refinement is complete and the features remaining in the difference syntheses are completely random. The final difference syntheses in the present example do contain certain systematic features, due to slight variations in the scattering factors appropriate to individual atoms and to the presence of hydrogen atoms. Failure to adjust the atomic scattering factors exactly affects the accuracy of the series-termination corrections but also increases the errors $\Delta F = F_o - F_c$ and is thus, since the effect is small, allowed for in the calculation of the standard deviations. Failure to make allowance for the hydrogen atoms also affects the accuracy since there may be some overlapping of hydrogen and other atoms. The values of ΔF are, however, again increased.

Using Cruickshank's formulae for centric and acentric zones and $\Delta F = F_o - F_c$ we have:

for the (010) projection: $\sigma(x) = 0.016$, $\sigma(z) = 0.017 \text{ Å}$;
for the (001) projection: $\sigma(x) = 0.030$, $\sigma(y) = 0.034 \text{ Å}$.

These figures apply to the carbon atoms, the centres of which may be expressed as $\rho(r) = 7.1 \exp(-3.8r^2)$; the standard deviations for nitrogen and oxygen are slightly smaller and for chlorine they are about half those quoted. Comparison of the two independent estimations of the x coordinates gives a comparable result. Thus $\langle(\Delta x)^2\rangle^{\frac{1}{2}} = 0.024 \text{ Å}$, rather less than the value $(0.016^2 + 0.030^2)^{\frac{1}{2}} = 0.034 \text{ Å}$, calculated from Cruickshank's formulae, which appears to be a safe overestimate. A weighted mean (e.g. Jeffreys, 1948, p. 176) of the two independent estimations of the x coordinates was used in calculating the bond lengths.

The standard deviation for a particular bond depends on its orientation with respect to the crystal axes; it is largest for those bonds directed mainly along b . The mean value is $\sigma = 0.033 \text{ Å}$, corresponding to a probable error of 0.022 Å . The mean standard deviation in bond angle is 2° .

The violent thermal motion of the atoms implied by the high values of the temperature factor is almost certainly not real. The visual estimation of intensities

appears to involve progressively more serious underestimation as $\sin \theta$ increases (Cochran, 1950), an effect which is related to the increasing resolution of the $\text{Cu } K\alpha_1\alpha_2$ doublet, and which leads to artificially large values of the temperature factor. Variations in the temperature factor within a zone may, however, be interpreted in terms of the thermal motion of the atoms. The extreme variation in the temperature-factor constant for the chlorine atom in projection on (010) is $\Delta B = 1.4 \text{ \AA}^2$, so that this atom vibrates in the direction shown in Fig. 6 with an r.m.s. amplitude

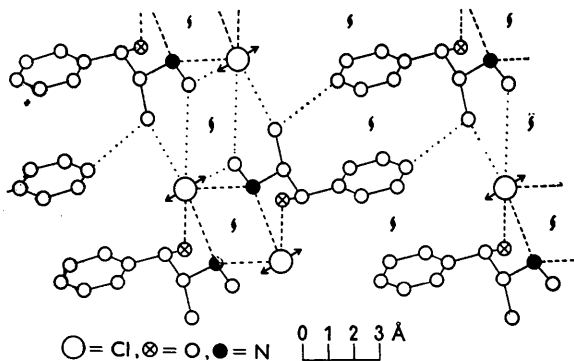


Fig. 6. Structure viewed along the b axis showing ionic and hydrogen bonds (broken lines) and some van der Waals contacts (dotted lines). The direction of maximum thermal motion of the chlorine atom is shown by an arrow.

of at least $(1.4/8\pi^2)^{\frac{1}{2}} = 0.13 \text{ \AA}$. The temperature factor appropriate to the $hk0$ zone agrees well with the maximum value for the $h0l$ zone. This maximum value is nearly that corresponding to the a direction common to the two projections so that, although comparisons between zones are of less significance, the chlorine atom probably vibrates in a plane near that containing [010] and inclined at 30° to (001).

6. Description of the structure

(i) Ephedrine molecule

A drawing of the ephedrine molecule is given in Fig. 7; the bond lengths and bond angles are shown in Tables 3 and 4. The mean lengths of C-C bonds in the benzene ring and in the rest of the molecule are 1.39 and 1.53 \AA respectively. Bond angles in the carbon chain are larger than the tetrahedral angle, in agreement with those observed in L-glutamine and similar

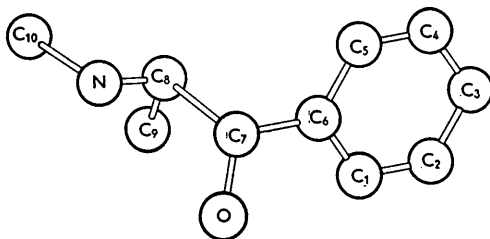


Fig. 7. Drawing of the ephedrine molecule.

Table 3. Bond lengths in the ephedrine molecule

$\text{C}_1\text{--C}_2$	1.43 \AA	$\text{C}_6\text{--C}_7$	1.56 \AA
$\text{C}_2\text{--C}_3$	1.35	$\text{C}_7\text{--C}_8$	1.48
$\text{C}_3\text{--C}_4$	1.36	$\text{C}_8\text{--C}_9$	1.56
$\text{C}_4\text{--C}_5$	1.45		
$\text{C}_5\text{--C}_6$	1.36	$\text{C}_8\text{--N}$	1.50
$\text{C}_6\text{--C}_1$	1.37	$\text{C}_{10}\text{--N}$	1.39
		$\text{C}_7\text{--O}$	1.40

Table 4. Bond angles in the ephedrine molecule

$\text{C}_6\text{--C}_1\text{--C}_2$	121°	$\text{C}_6\text{--C}_7\text{--C}_8$	112°
$\text{C}_1\text{--C}_2\text{--C}_3$	118	$\text{C}_8\text{--C}_7\text{--O}$	115
$\text{C}_2\text{--C}_3\text{--C}_4$	121	$\text{C}_8\text{--C}_7\text{--N}$	109
$\text{C}_3\text{--C}_4\text{--C}_5$	122		
$\text{C}_4\text{--C}_5\text{--C}_6$	116	$\text{C}_7\text{--C}_8\text{--C}_9$	114
$\text{C}_5\text{--C}_6\text{--C}_1$	123	$\text{C}_7\text{--C}_8\text{--N}$	116
		$\text{C}_9\text{--C}_8\text{--N}$	107
$\text{C}_5\text{--C}_6\text{--C}_7$	116		
$\text{C}_1\text{--C}_6\text{--C}_7$	121	$\text{C}_8\text{--N--C}_{10}$	119

compounds (Cochran & Penfold, 1952). The difference between the C-N bond lengths, 1.39 and 1.50 \AA , is possibly significant, particularly since it is associated with a large value of the bond angle $\text{C}_8\text{--N--C}_{10}$.

The configuration of the molecule as now determined is in agreement with that deduced from chemical evidence by a number of workers (Henry, 1949). The X-ray data now presented are, of course, equally consistent with the configuration shown in the diagrams and with its mirror image. The configuration shown is that assigned to (+)-ephedrine from its relation, established by purely chemical methods, to D-glyceraldehyde and hence to D-tartaric acid the absolute configuration of which is now known (Bijvoet, Peerdeman & van Bommel, 1951).

The conformation of the molecule is apparently not that proposed by Close (1950). The chemical evidence all points to the probability that in the ephedrine molecule the hydroxyl and methylamino groups are relatively far apart (while in pseudoephedrine, a stereoisomer, they are relatively close together). This structure determination shows that they are close together in ephedrine hydrochloride. The difference involves a rotation of 120° about the bond C_7C_8 in the way shown in Fig. 8. The conformation proposed from the chemical evidence is that which represents the lowest energy state of the molecule under the condi-

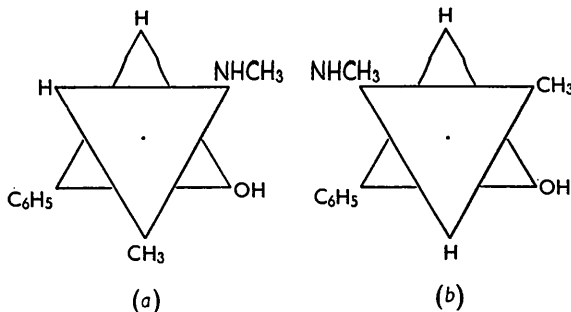


Fig. 8. Arrangement of atoms about the $\text{C}_7\text{--C}_8$ bond (a) in ephedrine hydrochloride, (b) in free ephedrine (Close, 1950).

tions of experiment; the conformation now determined represents the lowest energy state of the molecule in crystals of ephedrine hydrochloride. It is shown below that in these crystals both the hydroxyl and the amino groups are bonded to the chlorine atoms, and it seems likely that they are therefore constrained to adopt relative positions which differ from those suited to other states of aggregation. It is not unlikely, for example, that the conformation in crystalline ephedrine is different from that observed here in ephedrine hydrochloride. The nitrogen-oxygen distance is 3.0 Å. No significant indications of the positions of hydrogen atoms have been obtained and it cannot be suggested from the interatomic distance alone that a bond exists between the two atoms.

(ii) *Molecular packing*

The arrangement of molecules in the unit cell and the coordination of the chlorine and nitrogen atoms are shown in Fig. 6. Each chlorine atom is distant 3.12 and 3.20 Å from two nitrogen atoms so that the nitrogen and chlorine atoms are firmly linked in a helix about a screw axis. These nitrogen-chlorine distances are in good agreement with those (3.11 and 3.24 Å) reported by Binnie & Robertson (1949) in hexamethylenediamine dihydrochloride. They appear to be of two types; the shorter distance is less than the sum of the ionic radii and those authors consider the existence of hydrogen bonding to be a likely explanation. Each chlorine atom appears to be linked, further, with an oxygen atom. The distance between the atoms, 3.06 Å, is similar to the 3.12 Å reported in adenine hydrochloride (Broomhead, 1948; Cochran, 1951) for a well defined OH-Cl bond and the direction of the interatomic vector is consistent with this also being a hydrogen bond. The coordination of the chlorine is increased only by the van der Waals contacts with C₁₀ and C₉. This arrangement of bonds readily permits the anisotropic thermal motion of the chlorine atom, shown in Fig. 6. The direction of maximum vibration is such that bending of the bonds occurs rather than stretching for which the force constants are larger.

The remaining intermolecular bonds are of the van der Waals type. Some of the shorter ones are shown in Fig. 6 but those which link the benzene rings in the usual way have been omitted for clarity. The bonds described are consistent with the usual habit of the crystals, elongated along [010], and with the ready

cleavage in the plane (001), which is now seen to involve only the rupture of weak van der Waals interactions.

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