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The Crystal Structure of the Hydrochloride and Hydrobromide of the Dihydrotriazine Metabolite of Proguanil

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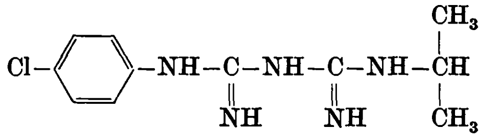
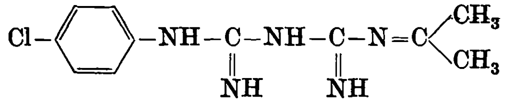
The crystal structure has been determined of the isomorphous hydrochloride and hydrobromide of 4:6-diamino-1-*p*-chlorophenyl-1:2-dihydro-2:2-dimethyl-1:3:5-triazine. The configuration of the molecule has been confirmed, and the relative orientations and packing of the molecules in the unit cell have been found. The coordinates have been refined by Fourier projections in two directions.

Introduction

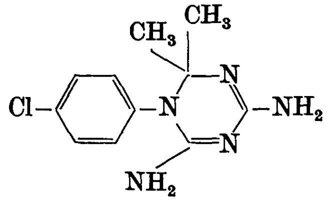
The antimalarially active metabolite of 'Paludrine', isolated by Carrington, Crowther, Davey, Levi & Rose (1951), has the empirical formula $C_{11}H_{14}N_5Cl$, which is consistent with the linear molecule I, or with either of the closed ring molecules II or III.



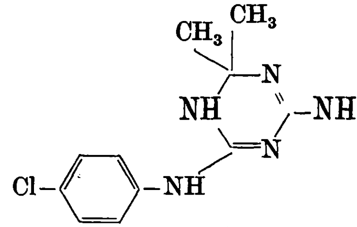
Paludrine



I



II



III

The crystal structure determination was undertaken to decide which isomer corresponds to the active metabolite. A preliminary survey of several halogen derivatives of the metabolite was made by single-crystal oscillation and rotation photographs, and of these the isomorphous hydrochloride and hydrobromide compounds were selected for detailed analysis.

Crystal data

Both the hydrochloride and hydrobromide compounds form compact, colourless, monoclinic crystals, space group $P2_1/n$, with four molecules in the unit cell.

Hydrochloride	Hydrobromide
$a = 15{\cdot}46$ Å	$a = 15{\cdot}82$ Å
$b = 10{\cdot}37$ Å	$b = 10{\cdot}56$ Å
$c = 8{\cdot}82$ Å	$c = 8{\cdot}82$ Å
$\beta = 95°$	$\beta = 97°$

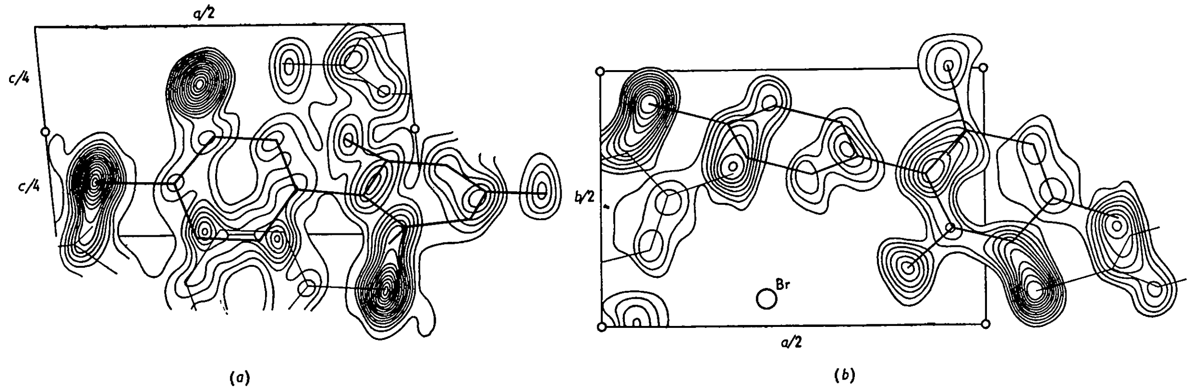
The hydrochloride of the unsubstituted phenyl compound also gave colourless monoclinic crystals with space group $P2_1/n$. There are four molecules in one unit cell of dimensions $a = 14{\cdot}1$ Å, $b = 10{\cdot}8$ Å, $c = 9{\cdot}0$ Å, $\beta = 103°$. The similarity of unit-cell dimensions and space group of this compound and the hydrochloride and hydrobromide of the *p*-chlorophenyl compound, suggests that they are iso-structural.

Other derivatives examined included the hydrochlorides of the *p*-chlorophenyl, *p*-bromophenyl, and *p*-iodophenyl compounds. No isomorphism was found, and the crystals of the bromo and iodo compounds deteriorated on exposure to the atmosphere.

Experimental

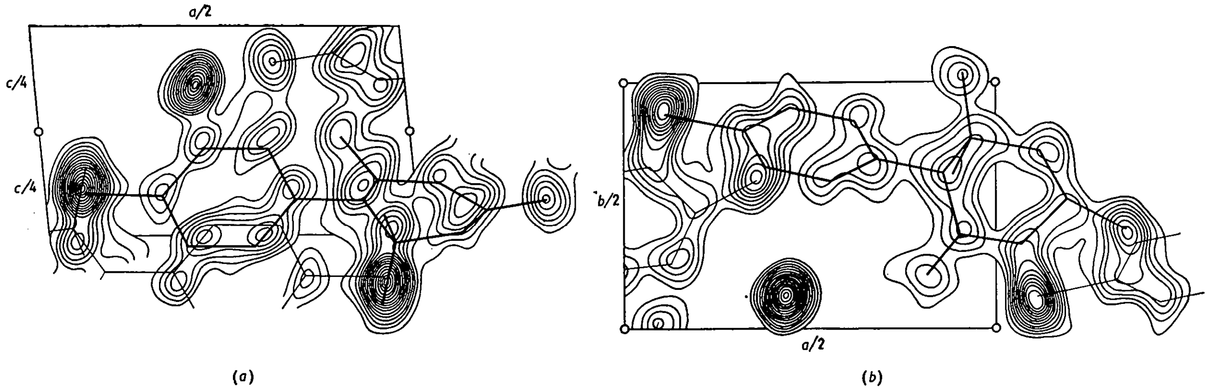
The preparation of the antimalarially active metabolite of 'Paludrine' is described by Carrington, Crowther & Stacey (1954), who also made available the various halogen derivatives for the X-ray investigation.

Filtered copper $K\alpha$ radiation was used throughout. The cell dimensions were measured from rotation and Weissenberg photographs, and the intensity data were recorded on [*b*] and [*c*] zero-layer Weissenberg photographs of both compounds. Three superposed films were used for a long and short exposure of each zone, and the intensities were estimated visually by comparison with a calibrated scale of time exposures from



(a) (b)

Fig. 1. (a) Electron-density map of the hydrobromide projected on (010). Intermediate bromine contours omitted. (b) Electron-density map of the hydrobromide projected on (001). All bromine contributions subtracted from the F_o's.



(a) (b)

Fig. 2. (a) Electron-density map of the hydrochloride projected on (010). (b) Electron-density map of the hydrochloride projected on (001).

the same crystal. The (*h*0*l*) and (*hk*0) structure amplitudes were deduced, after application of the appropriate geometrical correction factors, and were converted to the absolute scale by comparison with the calculated structure amplitudes.

A temperature factor $\exp(-4{\cdot}0 \sin^2 \theta/\lambda^2)$ was obtained graphically, and was applied to the Hartree scattering curves for carbon, nitrogen, chlorine and bromine, no allowance being made for the hydrogen contributions.

Structure determination

Since the configuration of the molecule was unknown, the positions of the heavy halogen atoms were first deduced by correlation between the [*b*] and [*c*] Patterson projections of the hydrochloride and the hydrobromide. The peaks due to the four Cl–Cl vectors in the hydrochloride derivative were not sufficiently pronounced to be identified directly. When referred to the Patterson projections of the hydrobromide derivative however, they correspond to one Cl–Cl peak of the same height, two Cl–Br peaks of twice the height, and one Br–Br peak of four times the height.

The halogen coordinates determined in this way were:

Cl_{17}	0·054*a*, 0·433*b*, 0·833*c*.
Cl_{18}^- and Br_{18}^-	0·217*a*, 0·067*b*, 0·113*c*.

These coordinates were used to calculate the values of the (*hk*0) and (*h*0*l*) structure amplitudes for the halogen atoms only. From a comparison of the observed structure amplitudes of the two compounds with each other and with the calculated halogen contributions, it was possible to deduce the signs of a large proportion of the (*hk*0) and (*h*0*l*) reflexions, and these were incorporated into projections along the *b* and *c* axes.

Coordinates were assigned to all the atoms in the initial projections, and were refined as far as possible by successive Fourier syntheses, and by subtractive syntheses in which the contributions of either one or both of the halogen atoms were subtracted from the experimental structure amplitudes.

The refinement of the hydrobromide was complete after four projections on (010) (Fig. 1(*a*)), and three projections on (001) (Fig. 1(*b*)).

The refinement of the hydrochloride, which was carried out concurrently, was obtained more slowly, and required six projections on (010) (Fig. 2(*a*)), and six projections on (001) (Fig. 2(*b*)).

The *p*-chlorophenyl group was readily identified in each of the projections. The remaining peaks were not consistent with the ring molecule III; but in projection alone, either molecule I or molecule II was possible. However, on combining the information from the *b* and *c* projections, the distance between the *p*-chlorophenyl substituted nitrogen atom and the dimethyl substituted carbon atom was found to be approximately 1·4 Å—a definite indication of a covalent bond between these atoms. This, therefore, eliminates the linear molecule I, leaving only the triazine ring molecule II as the structural formula of the active metabolite.

Atomic coordinates

The final atomic coordinates, measured from the (*hk*0) and (*h*0*l*) Fourier projections, are listed in Table 1 (see Fig. 3 for atomic subscripts).

Table 1. *Fractional atomic coordinates*

	Hydrochloride			Hydrobromide		
Atom	*x*	*y*	*z*	*x*	*y*	*z*
C_1	0·162	0·402	0·847	0·167	0·398	0·870
C_1	0·222	0·448	0·962	0·228	0·428	0·987
C_3	0·310	0·420	0·958	0·313	0·395	0·977
C_4	0·338	0·345	0·840	0·337	0·328	0·850
C_5	0·278	0·298	0·725	0·275	0·295	0·733
C_6	0·190	0·327	0·728	0·190	0·328	0·743
C_7	0·450	0·190	0·883	0·460	0·190	0·923
C_8	0·597	0·263	0·817	0·588	0·245	0·848
C_9	0·470	0·390	0·733	0·477	0·380	0·768
C_{10}	0·455	0·520	0·800	0·450	0·510	0·725
C_{11}	0·442	0·313	0·583	0·453	0·332	0·608
N_{12}	0·430	0·315	0·837	0·423	0·295	0·840
N_{13}	0·533	0·170	0·880	0·537	0·162	0·917
N_{14}	0·557	0·360	0·758	0·565	0·350	0·783
N_{15}	0·407	0·107	0·983	0·400	0·110	0·980
N_{16}	0·677	0·200	0·833	0·675	0·205	0·845
Cl_{17}	0·055	0·437	0·850	0·063	0·436	0·882
Cl_{18} Br_{18}	0·217	0·068	0·112	0·215	0·065	0·112

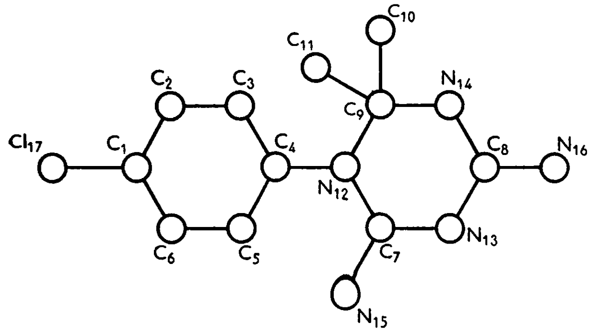


Fig. 3. Nomenclature of the molecule.

Owing to the complex nature of the molecule and of the structure, there was no direction of projection in which all the atoms were clearly and separately resolved; in many cases a composite peak was obtained by the overlap of two, three and sometimes four atoms (see Figs. 1 and 2). When this occurred the atomic coordinates were determined from the peaks in the (*hk*0) and (*h*0*l*) projections to give interatomic distances approximating to generally accepted values. The interatomic distances listed in Table 2 are not accurate determinations of the various bond lengths, but adequately illustrate the configuration of the molecule. Since this, the primary object of the structure determination, has been satisfactorily achieved with the present accuracy, no further refinement by three-dimensional Fourier computations has been undertaken to obtain separate resolution of all the atoms.

Table 2. *Interatomic distances*

	Hydrochloride	Hydrobromide
C_1–C_2	1·40 Å	1·38 Å
C_2–C_3	1·39	1·41
C_3–C_4	1·40	1·41
C_4–C_5	1·40	1·38
C_5–C_6	1·40	1·41
C_6–C_1	1·40	1·41
C_9–C_{10}	1·50	1·47
C_9–C_{11}	1·57	1·50
C_1–Cl_{17}	1·70	1·71
C_4–N_{12}	1·46	1·38
C_7–N_{15}	1·44	1·41
C_8–N_{16}	1·40	1·45
C_7–N_{12}	1·39	1·42
C_8–N_{13}	1·52	1·39
C_9–N_{14}	1·38	1·42
C_9–N_{12}	1·39	1·42
C_7–N_{13}	1·30	1·27
C_8–N_{14}	1·27	1·28

The observed structure amplitudes are compared with those calculated from the final coordinates in Tables 3* and 4* for the (*hk*0) and (*h*0*l*) reflexions respectively of the hydrobromide. The agreement factor $\Sigma(|F_o|-|F_c|)\div\Sigma|F_o|$ has values 0·22 and 0·21 respectively for these planes.

Description of the structure

The presence of the triazine ring and the position of the *p*-chlorophenyl group have been established. There are, in addition, two possible stereo-isomers of this molecule, differing in the orientation of the tetrahedrally bonded C_9 relative to the pyramidally bonded N_{12}. In one isomer the bonds C_4–N_{12}–C_9–N_{14} would be coplanar, and the two ring systems represented by directions C_1–C_4–N_{12} and N_{12}–C_8–N_{16} would be approximately collinear. In the other isomer the bonds C_4–N_{12}–C_9–CH_3 would be coplanar, resulting in a bending of the two ring systems at N_{12}, with the directions C_1–C_4–N_{12} and N_{12}–C_8–N_{16} approximately perpendicular. The molecule has been found to have the first of these two configurations, with rotation about the C_4–N_{12} linkage until the planes of the two rings are approximately perpendicular. This is the best position for clearance between C_3 and C_5 in the benzene

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* *Editorial note.*—Tables 3 and 4 have been deposited with the Institute of Physics, 47 Belgrave Square, London S.W. 1, England. Application to inspect these tables should be made to the Secretary of the Institute.

ring on the one hand, and the amine group (N_{15}) and the two methyl groups of the triazine ring on the other hand. The interatomic distances C_3–C_{10}, C_5–C_{11} and C_5–N_{15} are 2·93, 2·93 and 2·71 Å respectively.

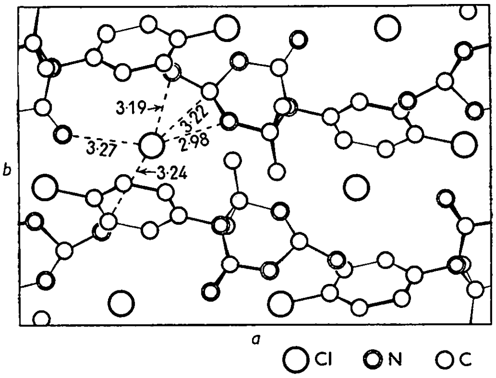

Fig. 4. Projection of the structure of the hydrochloride on (001), showing the environment of the chlorine ion.

The arrangement of the molecules in the unit cell is shown in Fig. 4. In a structure of this type there are two main requirements to be satisfied: the arrangement of the amino groups close to the Cl^- (or Br^-) ions, and the economical packing of the large organic ions. In the present structure each chlorine ion is in contact with three amino groups at 3·24, 3·19 and 3·27 Å respectively, and also with N_{14} and C_8 in the triazine ring at 2·98 and 3·22 Å respectively (Fig. 4). Thus N_{15} is in contact with one chlorine ion at 3·27 Å; N_{16} is in contact with two chlorine ions at 3·19 and 3·24 Å. These distances agree well with those of 3·10, 3·22 and 3·26 Å in *m*-tolidine (Fowweather & Hargreaves, 1950); 3·17 and 3·24 Å in geranylamine hydrochloride (Jeffrey, 1945); and 3·24 Å in glycyl-L-tyrosine hydrochloride (Smits & Wiebenga, 1953). The N_{14}–Cl distance of 2·98 Å may be compared with 3·11 Å for a similar contact in adenine hydrochloride (Broomhead, 1948). The next nearest neighbours of the chlorine ion are the two methyl groups at 3·9 Å and 4·3 Å, and the atoms of the two adjacent benzene rings in the range 4·0–4·5 Å.

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Solution of the Phase Problem for Space Group $P\bar{1}$

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A routine procedure which does not require previous knowledge of any signs has been developed for determining the signs of the structure factors for space group $P\bar{1}$. Only the magnitudes of the structure factors and the chemical composition of the crystal need to be known. The method developed here is readily extended to all the centrosymmetric space groups, and the general treatment may be found in A.C.A. Monograph No. 3.

Introduction

The probability distribution $P_1(A)$ of a structure factor for any centrosymmetric crystal is an even function of A provided that the atoms in the crystal are assumed to occupy all positions with equal probability (Karle & Hauptman, 1953, eq. 20). Thus, the structure factor is just as likely to be positive as negative, even though its magnitude may be known. However, once a set of X-ray intensities is known, the atoms in a crystal no longer occupy all positions with equal probability. If the atoms are assumed to range at random in the unit cell subject to the constraints imposed by the knowledge of a set of intensities, the resulting probability distribution of a structure factor is no longer an even function. The probability that the structure factor has a particular sign is now different from one-half. The purpose of this paper is to derive these probabilities on the basis that certain sets of intensities are specified and to derive therefrom a procedure for phase determination for space group $P\bar{1}$.