

3.56 Å, is very close to the value of 3.55 Å for DSP molecules. The former is identical to that of pure P2VB but the latter is rather longer than that of pure DSP (3.49 Å). Between P2VB and DSP the corresponding interatomic distance is 3.752 (6) Å from C(4) of P2VB to C(3) of DSP, and 4.033 (6) Å from C(3) of P2VB to C(4) of DSP. Thus, the double bonds are no longer parallel.

The relationship between these geometric factors and photochemical and spectroscopic behaviour will be described elsewhere.

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Structure of 1-[(3,4-Dichlorophenyl)methoxy]-1,6-dihydro-6,6-dimethyl-1,3,5-triazine-2,4-diamine Hydrochloride 0.29-Hydrate

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Abstract. $C_{12}H_{16}Cl_2N_5O^+ \cdot Cl^- \cdot 0.29H_2O$, $M_r = 357.7$, monoclinic, $P2_1/c$, $a = 5.989$ (1), $b = 8.000$ (1), $c = 34.143$ (3) Å, $\beta = 91.32$ (2)°, D_{obs} (aqueous KI) = 1.452, $D_{calc} = 1.453$ Mg m⁻³ for $Z = 4$; Mo $K\alpha$ diffractometer data; final $R = 0.046$. The dihydrotriazine nucleus is protonated at N(5), a position which maximizes positive-charge delocalization. All of the H atoms on N are involved in either H...N or H...Cl contacts, with the exception of one H on N(4). This H atom forms a 1.9 Å contact with a *ca* 2 e Å⁻³ atom, which we have arbitrarily treated as an O atom, believing it to be due to a disordered water molecule.

Introduction. The most widespread of all human parasitic diseases is malaria, afflicting substantial numbers of people over a large geographical area. The disease is one of the most common causes of death today. Malaria is transmitted by the Anopheles mosquito, and control and eradication of the disease

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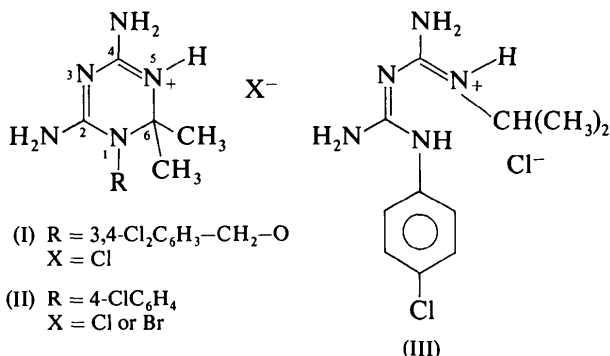
have been achieved in many regions through extensive insecticide spraying programs, destruction of breeding areas, etc. Chemotherapy has been very successful in the control and treatment of the disease, although in recent years drug-refractory strains of malaria have emerged.

The mechanisms of action of the majority of anti-malarial drugs fall into two general categories: (1) antifolates; (2) interactions with DNA. The title compound was first reported to have antimalarial activity in 1969, and it was found to be active against both sensitive and several drug-resistant strains of *Plasmodium berghei* in mice. Its mechanism of action is that of an antifolate (Lee, Heiffer & Kinter, 1976; Genter & Smith, 1977). We have been interested in antimalarial structures for some time, and the present study gave us the opportunity of obtaining accurate structural data for a cyclic biguanidinium compound for comparison with an acyclic form (III; Ammon & Plastas, 1973). We were particularly interested in the position of protonation of the dihydrotriazine nucleus. Although earlier work (Bailey, 1954) on the HCl and

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HBr salts of cycloguanil (presumably structure II) was not of sufficient accuracy for these comparisons, a redetermination of the structure of cycloguanil hydrochloride was reported (Schwalbe & Hunt, 1978) just as this work was completed.



A sample of the title compound (structure I, WR-38839), obtained from the Walter Reed Army Institute of Research, crystallized from ethanol as colorless prisms. The space group and approximate cell parameters were obtained from precession photographs taken with Zr-filtered Mo radiation. More accurate lattice-parameter and all intensity measurements were made with a Picker FACS-I diffractometer with Mo radiation [graphite monochromator, $\lambda(K\alpha) = 0.71069 \text{ \AA}$]. The diffractometer crystal was a $0.29 \times 0.34 \times 0.34 \text{ mm}$ rectangular parallelepiped which was aligned to place $[\bar{1}, 0, 28]$ parallel to the instrument's ϕ axis. The final unit-cell parameters were obtained by least squares from the Bragg angles of 18 general reflections manually centered at $\pm 2\theta$ (average of $|2\theta_o - 2\theta_c| = 0.005^\circ$).

Intensities were measured with the θ - 2θ scan method with a 2θ rate of $2.0^\circ \text{ min}^{-1}$, and 20 s backgrounds. Three standard reflections were measured at 100 reflection intervals. 4704 data were measured to a 2θ maximum of 55° giving 3771 unique reflections (excluding systematically absent data); 2667 were 3σ above background. The structure was solved by the routine application of direct methods with the XRAY system (Stewart, Kruger, Ammon, Dickinson & Hall, 1972), subprogram PHASE. Structure refinement was by full-matrix least squares, minimizing the function $\sum w(F_o - F_c)^2$, where $w = 1$ for $F_o \leq 30$ and $w = (30/F_o)^2$ for $F_o > 30$ (Hughes, 1941); only those F_o 's for which $I_c > 3\sigma(I_o)$ were included in the summation. The calculations used anisotropic temperature factors for C, N, O and Cl, isotropic terms for H, and included corrections for Cl dispersion and isotropic secondary extinction. The H-atom positions were initially located in a difference map.

A routine examination of a difference map to check the progress of the structure refinement revealed a peak close to $\frac{1}{2}, 0, 0$, with a maximum electron density of 1.7 e

\AA^{-3} . The peak was 1.48 \AA from its centrosymmetrically related image at $1 - x, -y, -z$, and there was another peak, 0.9 e \AA^{-3} maximum, $ca 0.9 \text{ \AA}$ from the chloride ion at $x, -1 + y, z$; these two unidentified maxima were $ca 2.1 \text{ \AA}$ apart. A careful check of the data revealed no outstanding errors, and several experiments with different weighting functions for structure refinement had no appreciable effect on the maxima. The possibility that the two peaks were due to a partial occupancy of the region by ethanol ($\text{CH}_3\text{-CH}_2\text{-OH}$) seemed unlikely, since a third peak corresponding to the methylene C in ethanol was not evident, and because of the proximity of the 0.9 e \AA^{-3} peak to Cl^- . We opted to assign the 1.7 e \AA^{-3} peak to the O atom [called O(W)] of a disordered molecule of water. O(W) was assigned an isotropic temperature factor slightly larger than that of the main-frame oxygen (O), and an occupancy factor of 0.3 for preliminary structure refinement; an anisotropic temperature factor was used in the later calculations. Additionally, the O(W) occupancy and temperature factors were not allowed to vary simultaneously in any of the subsequent cycles of refinement. The R ($\sum |F_o| - |F_c| / \sum |F_o|$) and weighted R $\{[\sum w(F_o - F_c)^2 / \sum wF_o^2]^{1/2}\}$ factors prior to introduction of the new atom were 0.063 and 0.084 respectively, and 0.046 and 0.055 after introduction and additional refinement. On the basis of Hamilton's (1965) R -factor test, the weighted R -factor ratio of $0.084/0.055 = 1.5$ suggests that the structure without O(W) can be rejected at the 0.5% significance level. Evidence for the reality of the atom is available from the 1.9 \AA O(W) \cdots H(3) contact. This distance is appropriate for a strong intermolecular O \cdots H bond and, furthermore, it utilizes H(3) in a hydrogen-bonding interaction where previously none had existed [in the absence of O(W)]. Furthermore, the inclusion of 0.29 molecules of H_2O in the formula weight of a 'molecule' in the crystal provides excellent agreement between the calculated and measured crystal densities ($1.453 \text{ vs } 1.452 \text{ Mg m}^{-3}$); 1.431 Mg m^{-3} was calculated without the extra water. The aforementioned 0.9 e \AA^{-3} peak was still present in a final difference map.

Atomic scattering factors for C, N, O and Cl were calculated from the analytical expressions of Cromer & Mann (1968); the scattering factors for H were interpolated from the tabulated values of Stewart, Davidson & Simpson (1965). The atomic coordinates are listed in Table 1.* All calculations were carried out on a Univac 1108 computer at the University's Computer Science Center with the 1972 and 1976 versions of the XRAY

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34741 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Fractional coordinates with e.s.d.'s in parentheses

	x	y	z
C(2)	0.3079 (5)	0.5025 (4)	0.05246 (8)
C(4)	0.0720 (6)	0.3015 (4)	0.02810 (9)
C(6)	0.0625 (5)	0.3617 (4)	0.09763 (8)
C(7)	0.2254 (7)	0.2370 (5)	0.1159 (1)
C(8)	-0.1224 (6)	0.4062 (5)	0.1253 (1)
C(9)	0.1875 (6)	0.7598 (4)	0.12338 (9)
C(10)	0.2518 (6)	0.8104 (4)	0.16441 (8)
C(11)	0.1118 (5)	0.7713 (4)	0.19491 (9)
C(12)	0.1707 (5)	0.8155 (4)	0.23308 (9)
C(13)	0.3688 (5)	0.8989 (4)	0.24086 (9)
C(14)	0.5085 (6)	0.9388 (4)	0.2106 (1)
C(15)	0.4500 (6)	0.8939 (4)	0.17247 (9)
N(1)	0.1773 (4)	0.5155 (3)	0.08484 (7)
N(2)	0.4810 (5)	0.6002 (4)	0.04891 (7)
N(3)	0.2525 (5)	0.3977 (3)	0.02312 (7)
N(4)	-0.0015 (6)	0.2088 (4)	-0.00198 (9)
N(5)	-0.0394 (5)	0.2973 (3)	0.06143 (8)
O	0.2856 (4)	0.5951 (3)	0.11708 (6)
O(W)*	0.408 (2)	-0.048 (1)	0.0044 (3)
Cl(1)	-0.0078 (2)	0.7632 (1)	0.27032 (3)
Cl(2)	0.4433 (2)	0.9580 (1)	0.28818 (2)
Cl ⁻	0.7112 (2)	0.9488 (1)	0.07538 (3)
H(2A)	0.520 (5)	0.673 (4)	0.0652 (9)
H(2B)	0.554 (6)	0.598 (5)	0.026 (1)
H(4A)	0.077 (8)	0.196 (6)	-0.024 (1)
H(4B)	-0.119 (7)	0.144 (5)	0.001 (1)
H(5)	-0.134 (6)	0.217 (4)	0.065 (1)
H(7A)	0.343 (6)	0.205 (5)	0.097 (1)
H(7B)	0.140 (6)	0.141 (5)	0.123 (1)
H(7C)	0.286 (6)	0.288 (5)	0.140 (1)
H(8A)	-0.218 (6)	0.494 (5)	0.114 (1)
H(8B)	-0.196 (6)	0.312 (5)	0.131 (1)
H(8C)	-0.059 (7)	0.456 (5)	0.149 (1)
H(9A)	0.249 (6)	0.835 (5)	0.104 (1)
H(9B)	0.022 (5)	0.751 (4)	0.1187 (9)
H(11)	-0.022 (6)	0.713 (4)	0.190 (1)
H(14)	0.639 (6)	1.000 (4)	0.216 (1)
H(15)	0.553 (6)	0.925 (4)	0.152 (1)

* The refined occupancy factor is 0.291 (6).

system (Stewart *et al.*, 1972; Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976).

Discussion. An ORTEP II (Johnson, 1971) drawing with bond lengths and angles is given in Fig. 1. The benzene ring is planar, with a maximum deviation of the six C atoms from their least-squares plane of 0.003 Å. The seven atoms forming the cyclic biguanidinium cation [N(1)–N(5), C(2), C(5)] are surprisingly planar, with maximum and average deviations from their least-squares plane of 0.100 and 0.054 Å. The sixth dihydrotriazine atom [C(6)] is 0.541 Å out of this plane. The two four-atom guanidinium units [N(1)–N(3), C(2) and N(3)–N(5), C(4)] are highly planar, and there is a 7.9° angle between these planes. The geminal methyl groups, C(7) and C(8), are, respectively, 2.056 and -0.003 Å out of the biguanidinium

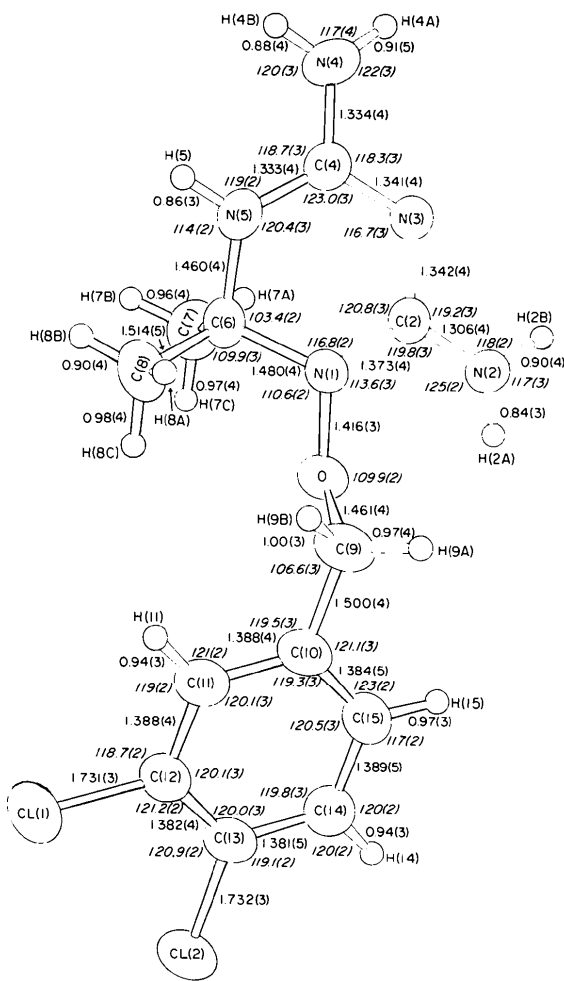


Fig. 1. Bond lengths (Å) and angles (°) with e.s.d.'s in parentheses. The C, N, O and Cl atoms are depicted as 50% probability boundary ellipsoids; H atoms are drawn as 0.1 Å radius circles. The O(W) and Cl⁻ atoms are not shown. Those parameters not recorded in the drawing are:

C(6)–C(7)	1.520 (5) Å	H(8A)–C(8)–C(6)	111 (2)°
C(7)–H(7A)	0.99 (4)	H(8A)–C(8)–H(8B)	114 (3)
C(8)–H(8A)	0.97 (4)	H(8A)–C(8)–H(8C)	104 (3)
N(1)–C(6)–C(7)	111.6 (3)°	H(8B)–C(8)–C(6)	108 (3)
N(5)–C(6)–C(7)	111.6 (3)	H(8B)–C(8)–H(8C)	110 (4)
N(5)–C(6)–C(8)	108.3 (3)	H(8C)–C(8)–C(6)	110 (2)
N(7)–C(6)–C(8)	111.8 (3)	H(9A)–C(9)–C(10)	112 (2)
H(7A)–C(7)–C(6)	112 (2)	H(9A)–C(9)–O	107 (2)
H(7A)–C(7)–H(7B)	111 (3)	H(9A)–C(9)–H(9B)	109 (3)
H(7A)–C(7)–H(7C)	113 (3)	H(9B)–C(9)–C(10)	113 (2)
H(7B)–C(7)–C(6)	107 (2)	H(9B)–C(9)–O	108 (2)
H(7B)–C(7)–H(7C)	109 (3)		
H(7C)–C(7)–C(6)	107 (2)		

plane. The ORTEP diagram (Fig. 1) clearly shows that the methyls are oriented so that the C(7)–C(6) and C(8)–C(6) conformations are staggered.

The position of protonation of the dihydrotriazine nucleus is at N(5), providing the maximum opportunity for delocalization of the resulting positive charge

over the entire biguanidinium structure. An analogous site of protonation has been found in (II).HCl (Schwalbe & Hunt, 1978) and in other diamino-triazines. Protonation at N(2), N(3) or N(4) presumably would have resulted in a less stable cation because of limited charge delocalization. C—N bond lengths in the cyclic and acyclic analogs (I–III) are listed in Table 2. With the exception of N(1)—C(2) in (I), the distances are quite similar and typical of C—N bonds with partial double-bond character. [The average C—N distance in biguanide hydrochloride (Ernst, 1977) is 1.335 Å.] The rather long N(1)—C(2) in (I) is probably due to the O substituent on N(1). The greater electronegativity of O compared to C would polarize the N(1) *p* orbitals toward O, thereby reducing the interaction of N(1)'s non-bonding pair of electrons with the remainder of the biguanidinium system. We note that N(2) appears to have somewhat compensated for the decrease in N(1)'s π -electron donation to the biguanidinium system; C(2)—N(2) is 1.306 Å compared to 1.320 Å in (II).HCl. Excluding N(1)—C(2), the major bond-length difference [in C(2)—N(3)] between the cyclic and acyclic systems of (I)–(III) is undoubtedly due to the 59° twist between the N(1)—C(2)—N(2)—N(3) and N(3)—C(4)—N(4)—N(5) regions in the acyclic molecule. The other bond lengths have typical values, and there are no unusual angles.

A packing diagram is shown in Fig. 2. Three of the N—H hydrogen atoms are involved in N—H...Cl⁻ contacts. The N...Cl⁻ distances of 3.23, 3.33 and 3.20 Å for N(2), N(4) and N(5) are typical of —NH₃⁺...Cl⁻ contacts (e.g. 3.21 and 3.24 Å in carminomycin I hydrochloride monohydrate; Von Dreele & Einck, 1977). A 2.07 Å N(2)—H(2)...N(3) contact utilizes the fourth H atom, and the unprotonated N atom, N(3). The fifth H atom, H(3), is in contact only with O(W). The 2.75 Å N(4)...O(W) distance is somewhat shorter than previously reported values for this kind of contact. For example, Pimentel & McClellan (1960) list an average —NH₃⁺...O distance of 2.88 Å, and two N(guanidinium)...O(water) distances in guanidinium 5,5-diethyl-barbiturate dihydrate (McClure & Craven, 1973) average 2.96 Å.

Table 2. Bond lengths (Å) and e.s.d.'s (in parentheses) for the biguanidinium regions of (I), (II).HCl and (III)

	(I)	(II).HCl	(III)
N(1)—C(2)	1.373 (4)	1.345*	1.346 (5)
C(2)—N(2)	1.306 (4)	1.320	1.341 (5)
C(2)—N(3)	1.342 (4)	1.348	1.311 (4)
N(3)—C(4)	1.341 (4)	1.333	1.331 (5)
C(4)—N(4)	1.334 (4)	1.326	1.328 (5)
C(4)—N(5)	1.332 (4)	1.342	1.331 (4)

* E.s.d.'s unknown.

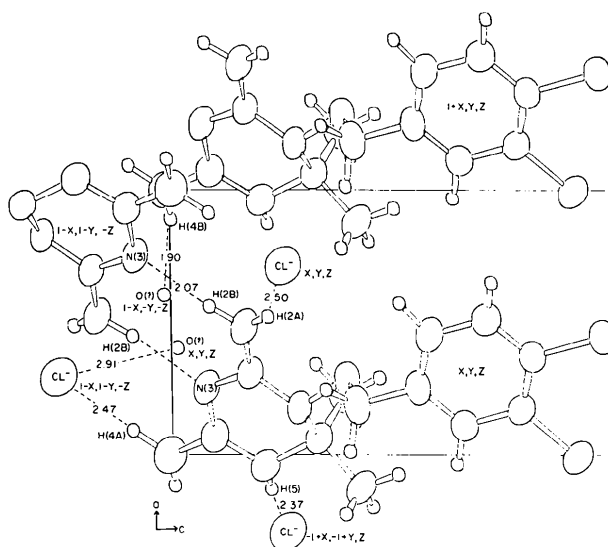


Fig. 2. Intermolecular packing viewed parallel to *b*. Distances are in Å. The H atoms and O(?) are depicted as 0.1 Å circles, and the remaining atoms are drawn as 50% probability ellipsoids.

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