Cycloguanil Hydrochloride: *X*-Ray Crystal Structure of the Antifolate Drug

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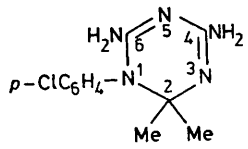
Summary The important antimalarial drug cycloguanil shares the following features with other antifolate agents studied crystallographically: (i) protonation at N(3), and (ii) a phenyl ring nearly perpendicular to the heterocycle.

THE antimalarial drug 4,6-diamino-1-*p*-chlorophenyl-1,2-dihydro-2,2-dimethyl-*s*-triazine (I) (cycloguanil) has been extensively used in Guatemala[1] and is the active metabolite of proguanil B.P.[2] It is believed to act by blocking the

interconversion of dihydrofolate and tetrahydrofolate.[2] New insight into the binding of inhibitors to the dihydrofolate reductase enzyme has recently been obtained from structural studies[3] of the dihydrofolate reductase methotrexate complex (DHFR·MTX). The importance was



(I)

emphasized of protonation at a ring nitrogen, N(1) in MTX, for an attractive interaction with an aspartate residue lining the binding cleft. If this feature is generally required, it is an important design criterion for antifolate drugs. We have examined by *X*-ray crystallography the structure of cycloguanil hydrochloride (Figure 1) for similarities to bound MTX. Since the pK_a of protonated cycloguanil[4] is 11·2, it will remain almost entirely in protonated form at physiological pH.

The unit cell dimensions obtained: monoclinic, $a = 8{\cdot}87(2)$, $b = 10{\cdot}39(2)$, $c = 17{\cdot}14(3)$ Å, $\beta = 115{\cdot}2(1)°$, $U = 1430(10)$ Å^3, $Z = 4$, and space group, $P2_1/c$, are in reasonable agreement with earlier data[5] ($U = 1410$ Å^3, space group $P2_1/n$). Data collection on a two-circle diffractometer yielded 3042 observed reflections [$F > 2\sigma(F)$]. After initial phasing based on chlorine and triazine ring positions from a Patterson synthesis the structure was refined to $R = R_w = 0{\cdot}06$ on the SHELX system.[6]†

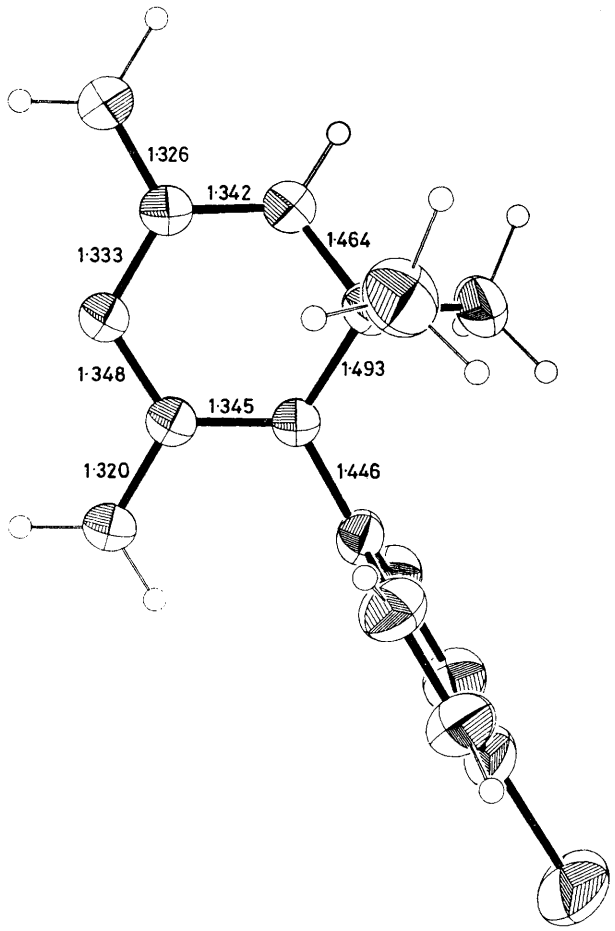


FIGURE 1. ORTEP drawing of protonated cycloguanil with some important bond distances (Å) involving the heterocycle.

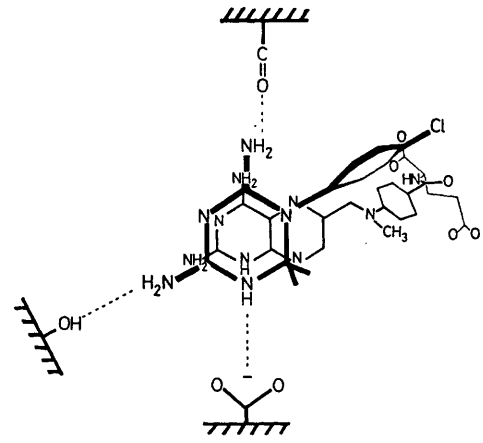


FIGURE 2. Superposition of protonated cycloguanil over protonated MTX (ref. 3) showing likely hydrogen bonds to dihydrofolate reductase.

There are obvious similarities to MTX (Figure 2). The site of protonation is N(3) in cycloguanil, which means that the same $+HN \cdots C(NH_2) \cdots N \cdots C(NH_2)$ unit is present as in the protonated drugs MTX,[3] pyrimethamine,[7] triazinate,[8a] and 2,4-diamino-5-methyl-6-benzylpyrido-[2,3-*d*]pyrimidine[9] (DMBPP). The acidic hydrogen of protonated cycloguanil participates in N–H · · · · Cl^- hydrogen bonding. The C–N bonds to the amino-groups are short (Figure 1), suggesting immonium character and good proton donor capability. These donor groups appear to match acceptor groups in DHFR.[3] Bond distances indicate extensive delocalization within the heterocyclic ring which could be advantageous for π–π interaction[3] with DHFR.

The triazine ring atoms N(1), N(3), C(4), N(5), and C(6) are coplanar within ±0·05 Å, but their least-squares plane intersects the phenyl plane with an angle of 80°, thus avoiding steric hindrance. Nearly perpendicular heterocyclic systems and phenyl rings are also found in MTX,[3] with two intervening atoms, in DMBPP[9] and trimethoprim[10] with one, and triazinate[8] with none; in pyrimethamine[7] with no intervening atoms the angle is 67°.

We hope to obtain more accurate hydrogen co-ordinates from neutron diffraction data and have so far measured

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

approximately 300 of the largest neutron structure factors. Results of this analysis and further details of the structure will be reported elsewhere.

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