function – the water molecule. However, N(1) does participate as proton acceptor in a dimeric hydrogen-bonding interaction [2·995 (3) Å] with amino N(2) of a centrosymmetrically related molecule, as is found in many 2,4-diaminopyrimidines (Koetzle & Williams, 1976). The other amino group finds a proton acceptor in the pyrazine moiety of another centrosymmetrically related molecule, forming an unusual cyclic dimer with N(4)···N(5) distance 3·066 (3) Å. Each diamino-pteridine stacks with a centrosymmetrically related partner, giving good overlap and contacts as close as 3·234 (3) Å for N(2)···C(5). The **a** unit-cell translation develops the stacks into infinite columns.

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Structure of 2,4-Diamino-6,7-dimethylpteridine Hydrochloride Monohydrate

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Abstract. $C_8H_{11}N_6^+Cl^-.H_2O$, $M_r = 244{\cdot}70$, triclinic, $P\bar{1}$, $a = 9{\cdot}472$ (1), $b = 10{\cdot}856$ (2), $c = 11{\cdot}846$ (1) Å, $\alpha = 71{\cdot}43$ (1), $\beta = 76{\cdot}51$ (1), $\gamma = 76{\cdot}10$ (1)°, $U = 1104{\cdot}5$ Å^3, $Z = 4$, $D_x = 1{\cdot}47$ Mg m^{-3}, Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}287$ mm^{-1}, $F(000) = 512$, $T = 291$ (2) K, final $R = 0{\cdot}059$ for 3330 independent reflections with $F > 3\sigma$. The two independent cations are almost identical in geometry. The shortest C—N distances in the structure [1·306 (3), 1·316 (4) Å] are to the exocyclic amino groups indicating extensive donation of electrons to the π-deficient ring system. Cations are linked by paired N—H···N hydrogen bonds around a pseudocenter of symmetry, and stacked around true centers of symmetry. The cations also donate protons from ring N(1), the site of protonation, to water, and from amino groups to Cl^-.

Introduction. 2,4-Diamino-6,7-dimethylpteridine (I) exhibits powerful diuretic activity in a variety of animal models and promotes Na^+ excretion while sparing K^+ (Weinstock, Wilson, Wiebelhaus, Maass, Brennan & Sosnowski, 1968). It is also a reasonably effective inhibitor of dihydrofolate reductase (DHFR) from certain pathogenic organisms; for instance, $ID_{50} = 8 \times 10^{-6}$ M for DHFR from *Trypanosoma equiperdum* (McCormick & Jaffe, 1969).

We have chosen to study the structure of this drug in its protonated form since the cation is believed to be responsible for strong binding of antifolates to DHFR (Matthews *et al.*, 1977) and since basicity of the pteridine nucleus appears essential for good diuretic activity (Weinstock *et al.*, 1968).

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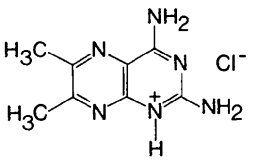

(I)

Experimental. Rose-colored crystals of the title compound from aqueous HCl. A truncated triangular pyramid chosen for analysis, bounded by (101), $(\bar{1}0\bar{1})$, $(0\bar{1}\bar{1})$, $(01\bar{1})$ and $(\bar{1}01)$ at distances from an arbitrary origin within the crystal of 0·01, 0·34, 0·01, 0·01 and 0·34 mm, respectively. No systematic absences in precession photographs. Lattice parameters obtained by least-squares analysis of peak positions for 25 reflections with θ values between 6·9 and 19·8°, Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Mo $K\alpha$ radiation. Space group $P\bar{1}$ suggested by intensity statistics and confirmed by successful refinement. 4895 reflections with $-12 \le h \le 0$, $-13 \le k \le 12$, $-14 \le l \le 14$, and $2 \le \theta \le 54°$ measured by the ω–2θ scan technique, ω scan width $(1{\cdot}50 + 0{\cdot}35 \tan\theta)°$, ω scan speed 1·2–2·0° min^{-1}. 3330 reflections deemed observed ($F > 3\sigma$), with σ based on counting statistics and an allowance of $0{\cdot}02F_o$ for experimental instability. Intensities of two monitor reflections, remeasured every hour, showed no significant variation during data collection. Data corrected for Lorentz and polarization effects, and absorption correction (Busing & Levy, 1957) calculated by integration over a Gaussian grid (range of transmittances 0·888–0·961). Structure determination by the centrosymmetric direct methods procedure in *SHELX*76 (Sheldrick, 1976), which revealed all non-H atoms in an *E* map. After refinement by least squares with isotropic temperature factors, all H atoms appeared in a difference electron density map. For the final least-squares refinement with anisotropic thermal parameters it was necessary to refine pyrimidine and pyrazine atoms in separate blocks. H-atom positions were not refined, except that methyl groups were treated as rigid bodies, but common isotropic temperature factors were refined for ring, amino, methyl and water H atoms. An empirical extinction parameter was refined as well. Scattering factors were taken from Stewart, Davidson & Simpson (1965) for H atoms and from Cromer & Mann (1968) for non-H atoms. The function $\sum w(|F_o| - |F_c|)^2$ was minimized, in which weights were assigned as $w = k/[\sigma^2(F_o) + gF_o^2]$, where k converged to 1·4398 and g was kept fixed at 0·0012. In the last two cycles the maximum shift in any parameter was 0·10 e.s.d., and no feature on a difference electron density map exceeded $\pm 0{\cdot}44$ e Å^{-3}. Final discrepancy indices were $R = 0{\cdot}059$ and $wR = 0{\cdot}070$ for the observed reflections.

Table 1. *Atomic coordinates and equivalent isotropic vibration terms for the nonhydrogen atoms* (×10^4)

$U_{iso} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{iso}
Cl(1)	2495 (1)	4473 (1)	515 (1)	443 (3)
O(1)	829 (3)	13878 (2)	−1209 (3)	515 (11)
N(1)	1717 (3)	11127 (2)	−714 (2)	290 (10)
C(2)	2661 (3)	10596 (3)	90 (3)	253 (11)
N(2)	3027 (3)	11376 (2)	585 (2)	335 (10)
N(3)	3238 (3)	9296 (2)	417 (2)	275 (9)
C(4)	2865 (3)	8495 (3)	−69 (3)	267 (11)
N(4)	3397 (3)	7229 (2)	236 (3)	373 (11)
C(4*a*)	1860 (3)	8999 (3)	932 (3)	262 (11)
N(5)	1505 (3)	8170 (3)	−1405 (2)	307 (10)
C(6)	580 (4)	8696 (3)	−2189 (3)	311 (12)
C(61)	184 (4)	7780 (4)	−2728 (4)	444 (16)
C(7)	8 (4)	10072 (3)	−2497 (3)	315 (12)
C(71)	−1058 (4)	10646 (4)	−3371 (4)	470 (16)
N(8)	358 (3)	10888 (3)	−2021 (2)	314 (10)
C(8*a*)	1305 (3)	10332 (3)	−1243 (3)	265 (11)
Cl(1′)	4861 (1)	10593 (1)	2853 (1)	393 (3)
O(1′)	6610 (3)	1174 (2)	4538 (2)	481 (11)
N(1′)	6206 (3)	3924 (2)	3667 (2)	298 (10)
C(2′)	5426 (3)	4489 (3)	2744 (3)	263 (11)
N(2′)	4965 (3)	3712 (3)	2307 (3)	355 (11)
N(3′)	5067 (3)	5801 (2)	2279 (2)	285 (9)
C(4′)	5511 (3)	6598 (3)	2723 (3)	260 (11)
N(4′)	5149 (3)	7877 (2)	2310 (3)	363 (11)
C(4*a*′)	6386 (3)	6067 (3)	3682 (3)	269 (11)
N(5′)	6851 (3)	6891 (3)	4093 (2)	324 (10)
C(6′)	7601 (4)	6342 (3)	4998 (3)	328 (13)
C(61′)	8148 (5)	7255 (4)	5454 (4)	481 (17)
C(7′)	7875 (3)	4951 (3)	5501 (3)	320 (12)
C(71′)	8651 (4)	4346 (4)	6575 (3)	458 (16)
N(8′)	7437 (3)	4137 (3)	5074 (2)	322 (10)
C(8*a*′)	6704 (3)	4714 (3)	4144 (3)	270 (11)

Discussion. Atomic coordinates are given in Table 1, atomic nomenclature in Fig. 1, and bond lengths and angles in Table 2.*

The geometry of the two independent cations is very similar. No corresponding bond distances or angles differ by more than 1·5 times the individual standard deviations. On the assumption that errors in the data and the refinement model dominate any genuine differences between structural units, only average values with pooled standard deviations will be discussed. Extensive donation of electrons from the exocyclic amino groups to the ring π system is manifested in the short bond distances: 1·306 (3) Å for C(4)—N(4) and 1·316 (4) Å for C(2)—N(2). With four electron-attracting ring N atoms in this protonated pteridine the average exocyclic C—N distance of 1·311 (5) Å is shorter than the corresponding values in protonated diaminotriazines with only three ring N atoms: 1·319 (4) Å in 4,6-diamino-1-[4-(4′-fluorosulfonyl-3′-methylanilinocarbonylethyl)phenyl]-1,2-dihydro-2,2-dimethyl-*s*-triazine ethanesulfonate (IBAF) and 1·321 (4) Å in 4,6-diamino-1-[3-chloro-4-(*m*-dimethylcarbamoylbenzyloxy)]phenyl-1,2-dihy-

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and least-squares planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42926 (25 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond distances* (Å) *and angles* (°) *for the two independent molecules with e.s.d.'s in parentheses*

	Unprimed	Primed
N(1)–C(2)	1·356 (4)	1·360 (4)
C(2)–N(2)	1·316 (5)	1·316 (5)
C(2)–N(3)	1·349 (4)	1·343 (4)
N(3)–C(4)	1·332 (5)	1·330 (5)
C(4)–N(4)	1·307 (4)	1·304 (4)
C(4)–C(4*a*)	1·449 (5)	1·450 (5)
C(4*a*)–N(5)	1·338 (5)	1·341 (5)
N(5)–C(6)	1·326 (4)	1·324 (5)
C(6)–C(61)	1·494 (7)	1·504 (7)
C(6)–C(7)	1·419 (4)	1·419 (5)
C(7)–C(71)	1·501 (6)	1·504 (5)
C(7)–N(8)	1·326 (5)	1·330 (5)
N(8)–C(8*a*)	1·338 (4)	1·340 (4)
C(4*a*)–C(8*a*)	1·375 (4)	1·378 (4)
N(1)–C(8*a*)	1·382 (5)	1·380 (5)
C(2)–N(1)–C(8*a*)	120·2 (3)	119·7 (3)
N(3)–C(2)–N(1)	123·0 (3)	123·3 (3)
N(2)–C(2)–N(1)	118·9 (3)	118·4 (3)
N(2)–C(2)–N(3)	118·1 (3)	118·3 (3)
C(4)–N(3)–C(2)	118·7 (3)	118·9 (3)
C(4*a*)–C(4)–N(3)	121·1 (3)	120·9 (3)
N(4)–C(4)–N(3)	120·2 (3)	120·3 (3)
N(4)–C(4)–C(4*a*)	118·7 (3)	118·7 (3)
N(5)–C(4*a*)–C(4)	119·8 (3)	119·7 (3)
C(8*a*)–C(4*a*)–C(4)	118·2 (3)	118·0 (3)
C(8*a*)–C(4*a*)–N(5)	122·1 (3)	122·3 (3)
C(6)–N(5)–C(4*a*)	116·7 (3)	116·6 (3)
C(7)–C(6)–N(5)	120·7 (4)	120·8 (4)
C(61)–C(6)–N(5)	117·1 (3)	117·1 (3)
C(61)–C(6)–N(7)	122·2 (3)	122·1 (3)
N(8)–C(7)–C(6)	122·4 (3)	122·3 (3)
C(71)–C(7)–C(6)	120·0 (4)	120·3 (4)
C(71)–C(7)–C(8)	117·7 (3)	117·4 (3)
C(8*a*)–N(8)–C(7)	115·6 (3)	115·8 (3)
N(1)–C(8*a*)–N(8)	118·6 (3)	118·6 (3)
N(1)–C(8*a*)–C(4*a*)	118·8 (3)	119·2 (3)
N(8)–C(8*a*)–C(4*a*)	122·6 (4)	122·2 (4)

dro-2,2-dimethyl-*s*-triazine ethanesulfonate (BAF) (Camerman, Smith & Camerman, 1979), 1·320 (14) Å in 1-[(3,4-dichlorophenyl)methoxy]-1,6-dihydro-6,6-dimethyl-1,3,5-triazine-2,4-diamine hydrochloride 0·29-hydrate (WR-38839) (Ammon & Plastas, 1979), and 1·323 (3) Å in cycloguanil hydrochloride (Schwalbe & Hunt, 1978). As expected, the average in a protonated diaminopyrimidine is even longer: 1·34 (1) Å in trimethoprim acetate (Haltiwanger, 1971).

Compared with 2,4-diaminopteridine (Schwalbe & Williams, 1986) the effect of protonation at N(1) is to reduce its π-bond order, lengthening N(1)–C(2) by 0·017 (6) Å and N(1)–C(8*a*) by 0·043 (7) Å. As expected from valence-shell electron-pair repulsion effects, the intra-annular bond angle at protonated N(1) is 4·5 (4)° larger than in the unprotonated species. In compensation the adjacent angles N(1)–C(2)–N(3) and N(1)–C(8*a*)–C(4*a*) decrease by 3·2 (4) and 4·5 (4)°, respctively, and lesser changes occur throughout the pyrimidine ring. The pyrazine ring shows the influence of methylation, in that contacts between the adjacent methyl groups are partially relieved by stretching C(6)–C(7) by 0·031 (6) Å. In addition, the methyl groups are bent away from each other in the plane of the ring, and in the primed molecule they are twisted slightly ($\leq$ 0·12 Å) out of plane. However, the pteridine ring skeletons stay coplanar with a maximum deviation of 0·03 Å from the least-squares plane.

The two independent cations form doubly hydrogen-bonded dimers with N(4) of one cation acting as proton donor and N(3) of the other cation as acceptor. Paired N–H···N hydrogen bonds have been observed in almost every crystalline DHFR inhibitor so far investigated. Here the two molecules are related by a pseudocenter of symmetry at approximately 0·40, 0·75,0·15. The degree of imperfection of this inversion center is suggested by the 11·5 (1)° angle between normals to the two ring planes, yet with N(4)–H(41)···N(3′) and N(4′)–H(41′)···N(3) distances of 2·997 (5) and 3·005 (5) Å the two hydrogen bonds are very similar. Each protonated ring N atom associates with a water molecule at N(1)–H(1)···O(1) and N(1′)–H(1′)···O(1′) distances of 2·807 (5) and 2·792 (5) Å. The water molecules in turn direct their protons towards chloride ions, which also hydrogen bond with the remaining amino protons. Thus each chloride ion participates in five hydrogen bonds, forming H···Cl···H angles between 64 and 164°. The O–H···Cl distances are 3·148 (3) and 3·158 (3) Å, while N–H···Cl distances range from 3·150 (3) to 3·312 (3) Å.

Like cations form stacked pairs (Fig. 2) around a center of inversion with the closest contacts, 3·35–

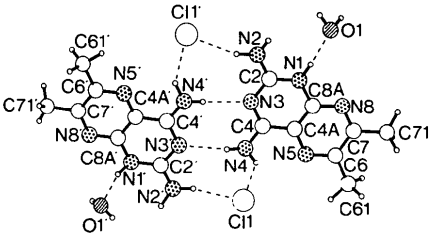

Fig. 1. *PLUTO* (Motherwell & Clegg, 1978) drawing of the two independent molecules projected onto their common least-squares plane. N atoms are stippled, O atoms hatched, and hydrogen bonds shown as dashed lines.

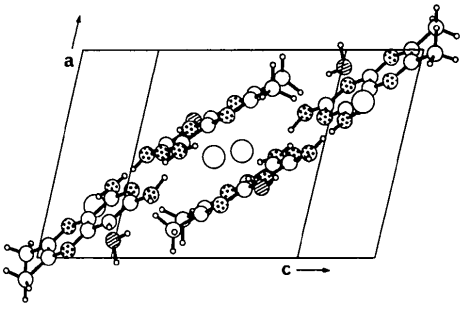

Fig. 2. A projection onto the *ac* plane of four formula units showing the stacking interaction.

3·43 Å, involving C(2)···C(7), C(7)···C(2), and C(8*a*)···C(8*a*) in both types of cation. In one level of the stacks the unlike cations are base-paired; in the other level their hydrophobic C(71) sides are juxtaposed.

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2,4-Diaminoquinazoline Monohydrate: A Redetermination

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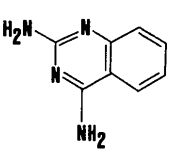
Abstract. $C_8H_8N_4.H_2O$, $M_r = 178{\cdot}20$, tetragonal, $I4_1/a$, $a = b = 21{\cdot}587$ (2), $c = 7{\cdot}622$ (2) Å, $U = 3551{\cdot}8$ Å^3, $Z = 16$, $D_x = 1{\cdot}333$ Mg m^{-3}, Cu $K\alpha$ radiation, $\lambda = 1{\cdot}54178$ Å, $\mu = 0{\cdot}792$ mm^{-1}, $F(000) = 1504$, $T = 291$ (2) K, final $R = 0{\cdot}045$ for 1697 observed reflections. Bond distances within the rings alternate as in naphthalene and exocyclic C—N bonds show considerable double-bond character. Neighboring diaminoquinazoline molecules are hydrogen bonded to water and to each other, stacked, and perpendicularly juxtaposed.

Introduction. 2,4-Diaminoquinazoline (I) is the parent compound of an interesting series of antifolate drugs (Hansch, Fukunaga, Jow & Hynes, 1977). Its structure was determined by Hunt, Schwalbe, Bird & Mallinson (1980), although the data suffered from inaccuracies attributed to the Renninger effect (Hunt, 1979). Two other structures in the 2,4-diaminoquinazoline (DAQ) series have also been determined: 2,4,6-triamino-5-chloroquinazoline (II) shows interesting $NH_2\cdots NH_2$ hydrogen bonding with partially pyramidal amino group geometry (Rogan & Williams, 1980), and diethyl *N*-[*p*-(2,4-diamino-6-quinazolinylmethyl)amino]benzoyl-aspartate is a powerful antifolate drug with similarities to methotrexate (Mastropaolo, Smith, Camerman & Camerman, 1981). To aid the discussion of substituent effects it appeared desirable to undertake a higher-precision structure determination of DAQ monohydrate.



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