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2,4-Diaminopteridine Monohydrate

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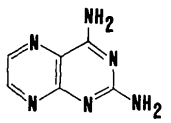
Abstract. $C_6H_6N_6.H_2O$, $M_r = 180{\cdot}17$, triclinic, $P\bar{1}$, $a = 6{\cdot}761\ (2)$, $b = 7{\cdot}316\ (1)$, $c = 8{\cdot}542\ (2)$ Å, $\alpha = 98{\cdot}80\ (1)$, $\beta = 98{\cdot}78\ (2)$, $\gamma = 109{\cdot}76\ (2)°$, $U = 383{\cdot}4$ Å^3, $Z = 2$, $D_x = 1{\cdot}561$ Mg m^{-3}, Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}1268$ mm^{-1}, $F(000) = 188$, $T = 291\ (2)$ K, final $R = 0{\cdot}059$ for 1299 independent observed reflections. All ring and exocyclic C–N bond distances lie within a 0·05 Å range indicating extensive π-system delocalization. The hydrogen-bonded water molecule donates protons to N(3) and N(8), and accepts a proton from the 4-amino group. Diaminopteridine molecules also join in hydrogen-bonded dimers around centers of symmetry.

Introduction. The title compound (I) possesses good diuretic activity (Weinstock, Wilson, Wiebelhaus, Maass, Brennan & Sosnowski, 1968) and also serves as a relatively simple model for the therapeutically valuable diaminopteridine antifolate drugs. Comparison of its structure with that of unsubstituted pteridine (Hamor & Robertson, 1956; Shirrell & Williams, 1975) affords insight into the effect of adding exocyclic amino groups.



(I)

Experimental. Specimen crystal an elongated prism 0·60 × 0·19 × 0·16 mm from slightly acidified aqueous solution. Triclinic symmetry indicated photographically and by the diffractometer system. Space group $P\bar{1}$ suggested by intensity statistics, later confirmed by a successful refinement. Unit-cell dimensions by least-squares analysis of setting angles of 22 reflections, $4{\cdot}4 \le \theta \le 21{\cdot}0°$. 3073 reflections collected by ω–2θ scans, ω scan range $(1{\cdot}50 + 0{\cdot}35\tan\theta)°$, ω scan rate 1·4–2·0° min^{-1}, on an Enraf–Nonius CAD-4 four-circle diffractometer for $-4 \le h \le 9$, $-9 \le k \le 9$, $-11 \le l \le 11$ to $2\theta \le 58°$ with graphite-monochromated Mo $K\alpha$ radiation. Three intensity and two orientation monitor reflections collected every 1 h and 100 reflections, respectively; no significant alteration. 1767 unique reflections ($R_{int} = \{\sum_{hkl}[N \times \sum_{eq} w(\bar{F} - F)^2]/\sum_{hkl}[(N-1)\sum_{eq} wF^2]\}^{1/2} = 0{\cdot}009$, 1299 deemed observed ($F > 3\sigma$) with σ based on counting statistics and an allowance of 0·02 F for the minimum expected experimental instability. Data subjected to Lorentz and polarization corrections as well as absorption correction calculated by integration over a Gaussian grid (Busing & Levy, 1957), the calculated transmission factors ranging from 0·972 to 0·984.

Direct phasing with *SHELX*76 (Sheldrick, 1976) revealed the orientation of the molecule. The pteridine ring position was corrected by analysis of prominent intermolecular vectors in the Patterson map. The amino groups and the water molecule then appeared in an electron density map. After least-squares refinement of non-H-atom coordinates with isotropic temperature factors all H atoms were located in a difference Fourier synthesis. Final refinement, which was with *SHELX*76 and based on stored scattering factors (Cromer & Mann, 1968; Stewart, Davidson & Simpson, 1965), minimized $\sum w(|F_o| - |F_c|)^2$, and adjusted the coordinates and anisotropic thermal parameters of non-H atoms, the scale factor, an empirical extinction parameter and common isotropic temperature factors for ring, amino and water H atoms, but not H-atom positions. In the weighting scheme $w = k/[\sigma^2(F_o) + gF_o^2]$, the parameters converged to $k = 2{\cdot}4526$ and $g = 0{\cdot}000278$ at discrepancy indices $R = 0{\cdot}059$, $wR = 0{\cdot}055$ for the observed reflections. The final maximum shift/e.s.d. ratio was 0·02, and no feature on a difference electron density map exceeded ±0·37 e Å^{-3}.

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

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

	x	y	z	U_{iso}(Å^2)
N(1)	1434 (3)	2768 (3)	5496 (2)	305 (7)
C(2)	917 (4)	2576 (3)	3884 (3)	298 (9)
N(2)	−243 (3)	760 (3)	2972 (2)	395 (8)
N(3)	1431 (3)	4071 (3)	3056 (2)	295 (7)
C(4)	2639 (3)	5889 (3)	3902 (3)	275 (8)
N(4)	3156 (3)	7394 (3)	3141 (2)	358 (8)
C(4*a*)	3399 (3)	6258 (3)	5638 (2)	256 (8)
N(5)	4673 (3)	8096 (3)	6481 (2)	308 (7)
C(6)	5226 (4)	8280 (4)	8067 (3)	357 (9)
C(7)	4466 (4)	6689 (4)	8799 (3)	379 (10)
N(8)	3196 (3)	4876 (3)	7992 (2)	337 (8)
C(8*a*)	2656 (3)	4608 (3)	6351 (3)	262 (8)
O(1)	−26 (3)	2596 (3)	−353 (2)	464 (7)

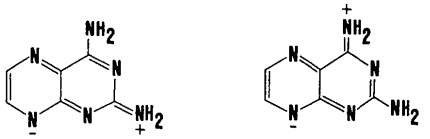
Table 2. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

N(1)–C(2)	1·341 (3)	N(5)–C(6)	1·322 (3)
C(2)–N(2)	1·334 (3)	C(6)–C(7)	1·388 (3)
C(2)–N(3)	1·368 (3)	C(7)–N(8)	1·320 (3)
N(3)–C(4)	1·323 (3)	N(8)–C(8*a*)	1·359 (3)
C(4)–N(4)	1·336 (3)	C(4*a*)–C(8*a*)	1·410 (3)
C(4)–C(4*a*)	1·445 (3)	N(1)–C(8*a*)	1·338 (3)
C(4*a*)–N(5)	1·342 (3)		

C(2)–N(1)–C(8*a*)	115·5 (2)	C(8*a*)–C(4*a*)–C(4)	115·9 (2)
N(3)–C(2)–N(1)	126·6 (2)	C(8*a*)–C(4*a*)–N(5)	123·9 (2)
N(2)–C(2)–N(1)	117·9 (2)	C(6)–N(5)–C(4*a*)	115·3 (2)
N(2)–C(2)–N(3)	115·5 (2)	C(7)–C(6)–N(5)	121·8 (2)
C(4)–N(3)–C(2)	117·7 (2)	N(8)–C(7)–C(6)	123·8 (2)
C(4*a*)–C(4)–N(3)	120·6 (2)	C(8*a*)–N(8)–C(7)	116·2 (2)
N(4)–C(4)–N(3)	119·6 (2)	N(1)–C(8*a*)–N(8)	117·5 (2)
N(4)–C(4)–C(4*a*)	119·9 (2)	N(1)–C(8*a*)–C(4*a*)	123·5 (2)
N(5)–C(4*a*)–C(4)	120·2 (2)	N(8)–C(8*a*)–C(4*a*)	119·0 (2)

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

The narrow range of C–N bond distances [1·320 (3)–1·368 (3) Å] indicates that p electrons from every N atom participate in the delocalized π system. Compared with unsubstituted pteridine (Shirrell & Williams, 1975) there are changes exceeding 0·025 Å in the following bond lengths: increases of 0·037 (8), 0·046 (9) and 0·034 (10) Å in N(1)–C(2), C(4)–C(4*a*) and C(7)–N(8), respectively, and decreases of 0·027 (10) and 0·042 (10) Å in N(3)–C(4) and C(4*a*)–N(5). These changes can be rationalized by invoking the resonance structures in which the exo-



cyclic amino groups donate electrons to the ring, and the bond order at N(8) decreases. Both exocyclic C–N bonds are 0·015 (3) Å shorter than those in the diaminopyrimidine derivative trimethoprim (Koetzle & Williams, 1976), presumably owing to the presence of two extra N atoms fused into the ring system. The pteridine ring atoms are coplanar within 0·04 (1) Å, but amino N atoms N(2) and N(4) are displaced by 0·10 (1) and 0·12 (1) Å, respectively, to opposite sides of the ring.

Molecules associate efficiently (Fig. 2) by hydrogen bonding and stacking to form the unusually dense

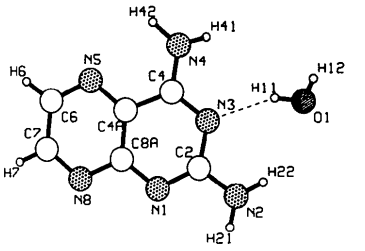


Fig. 1. *PLUTO* (Motherwell & Clegg, 1978) drawing of the molecule projected onto its least-squares plane. N atoms are stippled and the O atom hatched.

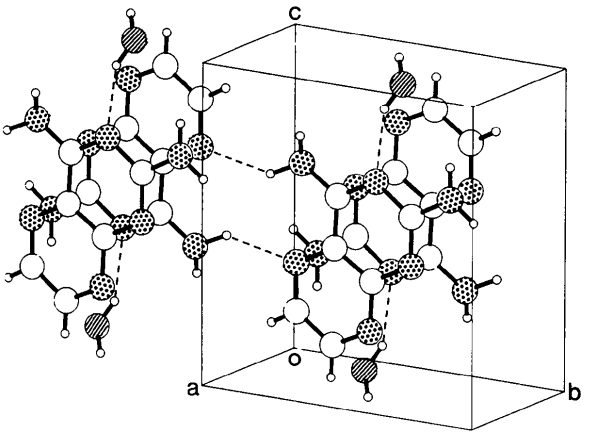


Fig. 2. The contents of two adjacent unit cells viewed down the a^* axis. N atoms are stippled, O atoms hatched, and hydrogen bonds shown as dashed lines.

crystal. Each water molecule links three pteridine units, donating a proton in a strong hydrogen bond [2·839 (3) Å] to N(3) and another to N(8) [2·955 (3) Å], while accepting a proton from N(4) [2·937 (3) Å]. It is interesting to note that the most basic function of this molecule, atom N(1), does not participate in any interaction with the most acidic

* 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 42922 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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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References

BUSING, W. R. & LEVY, H. A. (1957). *Acta Cryst.* **10**, 180–182.
CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* A**24**, 321–324.
HAMOR, T. A. & ROBERTSON, J. M. (1956). *J. Chem. Soc.* pp. 3586–3594.
KOETZLE, T. F. & WILLIAMS, G. J. B. (1976). *J. Am. Chem. Soc.* **98**, 2074–2078.
MOTHERWELL, W. D. S. & CLEGG, W. (1978). *PLUTO*78. A program for plotting molecular and crystal structures. Univ. of Cambridge, England.
SHELDRICK, G. M. (1976). *SHELX*76. Program for crystal structure determination. Univ. of Cambridge, England.
SHIRRELL, C. D. & WILLIAMS, D. E. (1975). *J. Chem. Soc. Perkin Trans.* 2, 40–43.
STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.
WEINSTOCK, J., WILSON, J. W., WIEBELHAUS, V. D., MAASS, A. R., BRENNAN, F. T. & SOSNOWSKI, G. (1968). *J. Med. Chem.* **11**, 573–579.

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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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