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Structure of 6-Methylisocytosine*

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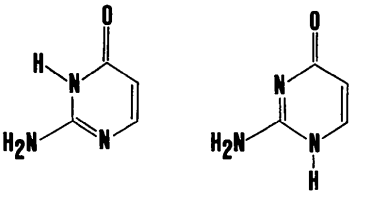
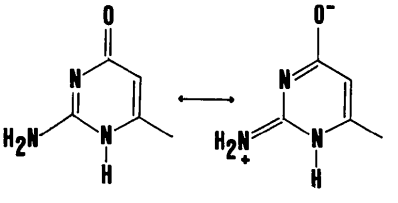
Abstract. 2-Amino-6-methylpyrimidin-4(1*H*)-one, $C_5H_7N_3O$, $M_r = 125{\cdot}14$, monoclinic, $P2_1/n$, $a = 7{\cdot}653$ (1), $b = 6{\cdot}567$ (1), $c = 11{\cdot}815$ (3) Å, $\beta = 98{\cdot}12$ (2)°, $U = 587{\cdot}8$ Å^3, $Z = 4$, $D_x = 1{\cdot}414$ Mg m^{-3}, Cu $K\alpha$ radiation, $\lambda = 1{\cdot}54178$ Å, $\mu = 0{\cdot}881$ mm^{-1}, $F(000) = 264$, $T = 291$ (2) K, final $R = 0{\cdot}060$ for 1094 unique reflections with $F_o > 3\sigma(F_o)$. Only the tautomer protonated at N(1) is present in the crystal. Bond distances are generally similar to those reported for the corresponding tautomer of isocytosine. The 6-methylisocytosine molecules are stacked and hydrogen-bonded in a pattern based on N—H···N interactions around a center of symmetry and N—H···O hydrogen bonds from ring NH and amino NH of one molecule both to the same oxygen atom of an adjacent molecule.

Introduction. Dihydrofolate reductase (DHFR) is one of the most important target enzymes for the chemotherapy of infectious diseases and cancer. Its natural substrates contain a pteridine ring with 2-amino and 4-oxo substituents. Simply changing the 4-oxo group of folic acid to a 4-amino group improves binding to DHFR by several orders of magnitude. Although there exist crystallographic studies of both protonated and unprotonated 2,4-diaminopteridines and a wealth of such studies on 2,4-diaminopyrimidines (Schwalbe & Cody, 1983), results on the 4-oxo systems are relatively rare. The pterins and folates seem to crystallize best as cations from strongly acidic media; however, great skill is often required to get these compounds to crystallize in any form. Among single-ring model compounds the crystal structure of neutral isocytosine (1*a*,*b*) is of particular interest in that two distinct tautomers co-crystallize, one bearing a hydrogen atom at N(1) and the other at N(3) (Sharma & McConnell, 1965). The two molecules form a triply hydrogen-bonded duplex in the manner of a Watson–Crick G:C base pair involving the 2-, 3-, and 4-positions of each ring. Addition of a 6-methyl substituent should not, in principle, preclude similar tautomerism and hydrogen bonding. If another example of the N(1)-protonated tautomer were found, it would strengthen the suggestion that the N(1)-protonated tautomer of folates could be significant under some conditions. Therefore the crystal-structure study of 6-methylisocytosine (2) was undertaken.



(1*a*) (1*b*)



(2*a*) (2*b*)

Experimental. Specimen crystal selected from a sample of 6-methylisocytosine purchased from the Sigma Chemical Company; a trapezoidal prism bounded by faces at the following distances in mm from an arbitrary origin within the crystal: (001), 0·001; (011), 0·001; (00$\bar{1}$), 0·14; (0$\bar{1}$1), 0·12; ($\bar{1}$01), 0·001; (10$\bar{1}$), 0·13. Unit-cell dimensions from least-squares analysis of setting angles of 25 reflections with $6{\cdot}50 \le \theta \le 39{\cdot}49°$ for graphite-monochromated Cu $K\alpha$ radiation on an Enraf–Nonius CAD-4 diffractometer. Intensity data

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obtained by ω–2θ scans with ω scan rates 0·75–3·3° min^{-1} depending on intensity and ω scan interval $(1{\cdot}50 + 0{\cdot}35\tan\theta)°$ with background counts taken from extensions of the scans. Intensity and orientation standards re-measured every 1 h and every 100 reflections respectively; no significant decomposition or movement of the crystal. 3038 reflections collected with θ between 1 and 78° and $-9 \le h \le 9$, $-8 \le k \le 0$, $-14 \le l \le 14$. Estimated standard deviations σ based on counting statistics and an allowance of $0{\cdot}02F_o$ for the minimum expected experimental instability, and merged ($R_{int} = 0{\cdot}036$) to give 1094 unique observed reflections with $F_o > 3\sigma(F_o)$. The magnitude of $F(103)$ was noteworthy, being about three times as large as the next highest structure amplitude. Data corrected for Lorentz–polarization effects assuming an ideally imperfect monochromator, but not for absorption in view of the small size and prismatic shape of the crystal (maximum and minimum expected corrections to F_o 1·09 and 1·04).

Phases of 400 reflections were determined by *MULTAN* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); all non-hydrogen atoms were located in the resulting E map. Further calculations were performed with the *SHELX* system (Sheldrick, 1976). Full-matrix least-squares refinement of positional parameters and isotropic temperature factors was initiated with all atoms assigned the scattering factor of carbon, reducing the unweighted discrepancy index to 0·19. From the values of the isotropic temperature factors and the bond distances it was possible to assign unambiguously the carbonyl oxygen, amino, and methyl substitutents and to establish the nature of every ring atom. From now on the scattering factor appropriate to each element was used, taken from Stewart, Davidson & Simpson (1965) and Cromer & Mann (1968). After refinement all but one of the hydrogen atoms (one attached to the exocyclic amino group) appeared in a difference electron density map. The missing hydrogen atom was placed in a calculated position. Refinement of coordinates for all atoms (with methyl C—H and amino N—H bond distances restrained) together with anisotropic thermal parameters for non-hydrogen atoms and isotropic temperature factors for hydrogen atoms reduced the final agreement parameters to $R = 0{\cdot}060$ and $wR = 0{\cdot}068$. The function $\sum w(|F_o| - |F_c|)^2$ was minimized, and reflections were weighted according to $w = k/[\sigma^2(F_o) + gF_o^2]$ where k converged at 4·6126 and g refined to 0·0001, indicating no unexpected experimental instability. At termination of refinement no positional parameter shifted by more than 0·011 e.s.d. and a final difference electron density map showed no feature greater than $\pm 0{\cdot}32$ e Å^{-3}.

Discussion. The structure of 6-methylisocytosine as determined crystallographically is shown in Fig. 1 together with the numbering scheme used. Positional parameters and isotropic temperature factors (U_{eq} for non-hydrogen atoms) are given in Table 1, bond distances and angles in Table 2, and important intermolecular contacts in Table 3.* Several pieces of evidence prove that the 1*H* tautomer is present in the crystalline state rather than the 3*H* expected according to conventional arguments (Buckingham, 1982). The hydrogen atom in question, H(1), was located in a difference electron density map and successfully refined. Bonding of N(1) to an H atom would be expected to make the other bonds it forms weaker and hence longer than those to N(3), and this is indeed so: N(1)–C(2) is 1·361 (3) Å *vs* C(2)–N(3) at 1·331 (3) Å, and C(6)–N(1) is 1·373 (3) Å *vs* N(3)–C(4) at 1·360 (3) Å. As observed in numerous pyrimidine structures (Voet & Rich, 1970), the interior bond angle is smaller at the ring N bearing a lone pair of electrons than at the protonated N owing to valence-shell electron pair repulsion; angle C(2)–N(3)–C(4) is 1·9 (3)° less than C(6)–N(1)–C(2).

The rather long C=O bond distance of 1·256 (3) Å is expected for this class of compounds; *cf* the two tautomers of isocytosine [1·246 (3) and 1·248 (3) Å] (Sharma & McConnell, 1965) as well as cytosine and its monohydrate [1·241 (3) and 1·251 (2) Å] (McClure & Craven, 1973). The C(2)–N(7) bond distance of 1·327 (3) Å is also typical; corresponding distances are 1·323 (3) and 1·324 (3) Å in isocytosine, 1·342 (3) Å in cytosine, and 1·326 (2) Å in cytosine monohydrate. Compared with the 1*H* tautomer of isocytosine (1*b*) corresponding ring bond distances are identical within 0·004 (4) Å except for C(5)–C(6) and C(6)–N(1), which are lengthened by 0·015–0·020 (4) Å apparently because of methylation. The methyl group is not placed on the exterior bisector of the C(5)–C(6)–N(1) angle; instead it is bent towards N(1) so that C(5)–C(6)–C(9) exceeds N(1)–C(6)–C(9) by *ca* 10°. The ring and its substituents remain almost coplanar. The largest

* Tables of structure factors, anisotropic thermal parameters, and least-squares-plane data have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43372 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

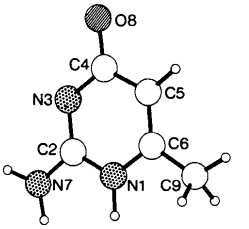

Fig. 1. *PLUTO* (Motherwell & Clegg, 1978) drawing of the molecule projected onto its least-squares plane.

Table 1. *Fractional coordinates and (equivalent) isotropic temperature factors ($\times 10^4$ for non-hydrogen atoms, $\times 10^3$ for hydrogen atoms) with estimated standard deviations in parentheses*

For non-hydrogen atoms the reported $U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$.

	x	*y*	*z*	*U*(Å²)
N(1)	6480 (3)	−2130 (3)	1208 (2)	311 (10)
C(2)	7873 (3)	−1315 (4)	766 (2)	310 (11)
N(3)	8122 (3)	682 (3)	681 (2)	326 (11)
C(4)	6910 (3)	1965 (3)	1030 (2)	332 (12)
C(5)	5437 (3)	1150 (4)	1518 (2)	350 (13)
C(6)	5252 (3)	−888 (4)	1599 (2)	326 (12)
N(7)	9008 (3)	−2602 (3)	401 (2)	439 (13)
O(8)	7122 (3)	3848 (3)	924 (2)	465 (11)
C(9)	3793 (4)	−1944 (5)	2072 (3)	445 (15)
H(1)	633 (4)	−365 (3)	123 (2)	42 (8)
H(2)	1001 (4)	−214 (5)	3 (2)	57 (9)
H(3)	865 (4)	−398 (4)	44 (3)	67 (11)
H(4)	444 (4)	211 (5)	174 (3)	65 (10)
H(5)	315 (5)	−294 (5)	152 (3)	97 (14)
H(6)	286 (6)	−118 (7)	241 (4)	147 (21)
H(7)	418 (5)	−287 (5)	275 (2)	78 (12)

Table 2. *Bond distances* (Å) *and angles* (°) *with estimated standard deviations in parentheses*

N(1)–C(2)	1·361 (3)	C(6)–N(1)	1·373 (3)
C(2)–N(3)	1·331 (3)	N(1)–H(1)	1·00 (2)*
C(2)–N(7)	1·327 (3)	N(7)–H(2)	0·98 (2)*
N(3)–C(4)	1·360 (3)	N(7)–H(3)	0·95 (2)*
C(4)–O(8)	1·256 (3)	C(5)–H(4)	1·05 (3)
C(4)–C(5)	1·440 (3)	C(9)–H(5)	1·00 (2)†
C(5)–C(6)	1·351 (3)	C(9)–H(6)	1·00 (3)†
C(6)–C(9)	1·489 (3)	C(9)–H(7)	1·02 (3)†
N(1)–C(2)–N(3)	123·0 (2)	C(5)–C(6)–C(9)	125·4 (2)
N(1)–C(2)–N(7)	117·3 (2)	N(1)–C(6)–C(9)	115·8 (2)
N(7)–C(2)–N(3)	119·7 (2)	C(6)–N(1)–C(2)	120·4 (2)
C(2)–N(3)–C(4)	118·5 (2)	C(2)–N(1)–H(1)	120 (2)
N(3)–C(4)–C(5)	119·8 (2)	C(6)–N(1)–H(1)	120 (2)
N(3)–C(4)–O(8)	118·5 (2)	C(2)–N(7)–H(2)	123 (2)
C(5)–C(4)–O(8)	121·7 (2)	C(2)–N(7)–H(3)	113 (2)
C(4)–C(5)–C(6)	119·5 (2)	H(2)–N(7)–H(3)	124 (3)
C(5)–C(6)–N(1)	118·8 (2)		

* H-atom positions refined with a bond distance restrained to 1·01 Å with a standard deviation of 0·03 Å.

† H-atom positions refined with a bond distance restrained to 1·08 Å with a standard deviation of 0·03 Å.

Table 3. *Hydrogen-bond angles and contact distances (e.s.d.'s 3° and 0·003 Å respectively) and important intermolecular contacts involved in stacking (e.s.d.'s 0·003 Å)*

Hydrogen bond	Angle at H (°)	N···O (Å)
N(1)–H(1)···O(8^{i})	150	2·716
N(7)–H(2)···N(3^{ii})	171	2·973
N(7)–H(3)···O(8^{i})	152	2·855

C(4)···N(1^{iii})	3·44 Å	C(2)···C(5^{iii})	3·43 Å
C(5)···N(1^{iii})	3·41	C(6)···C(4^{iii})	3·38

Symmetry codes: (i) x, $1+y$, z; (ii) $2-x$, $-y$, $-z$; (iii) $1-x$, $-y$, $-z$.

deviation by a ring atom from the least-squares plane through the six ring atoms is only 0·012 (3) Å, and the largest deviation by a substituent is 0·033 (3) Å by O(8). As Sharma & McConnell (1965) showed for isocytosine, bonding in this delocalized system is modeled fairly well by invoking contributing structures (2*a*) and (2*b*), with N(1) multiply bonded in some additional structures.

Molecules are arranged within the unit cell almost exactly on (103) planes, thus accounting for the strength of reflection from these planes. Molecules related by a center of symmetry are stacked (Fig. 2 and Table 3) at a distance of 3·26 (1) Å between least-squares planes through adjacent rings. This distance agrees well with the (103) interplanar spacing of 3·28 Å. Equivalent stacking distances in *N*-methylcytosine (Mathews & Rich, 1964), cytosine (Barker & Marsh, 1964), and isocytosine (Sharma & McConnell, 1965) are 3·4, 3·36, and 3·36 Å respectively.

A network of hydrogen bonds (Table 3) connects molecules in the **a** and **b** directions. The paired N–H···N hydrogen bonds about a center of symmetry are a familiar feature in crystals of diamino-substituted antifolate drugs (Schwalbe & Cody, 1983); the N···N contact distance of 2·973 (3) Å found here is rather short for such structures. Bonding in the **b** direction is unusual in that the same atom, O(8), acts as proton acceptor in two hydrogen bonds from the same adjacent molecule, one from the protonated N(1) and the other from the amino group. The result is to produce two opposing chains of molecules in the direction of **b**, linked by the base pair interaction in the direction of **a**. This scheme is entirely different from the pattern of triply-hydrogen-bonded pairs of molecules observed for isocytosine. The scheme found here

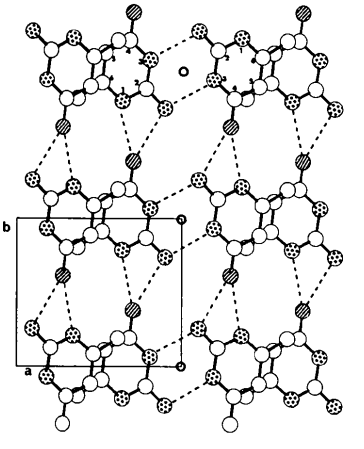

Fig. 2. Packing of molecules viewed down the *c* axis showing hydrogen bonding (dashed lines) and stacking. All hydrogen atoms have been omitted for clarity, as have molecules related by screw axes and glide planes. Nitrogen atoms are stippled; oxygen atoms are hatched.

resembles more closely that in *N*-methylcytosine with its paired N—H···N interactions with one partner molecule and N—H···O with another; however, the striking non-coplanarity of hydrogen-bonded bases in *N*-methylcytosine is not evident here.

This study further strengthens the idea that 2-aminopyrimidin-4-ones are very adaptable both in their tautomeric form and in their intermolecular interactions.

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Structure of (1*S*,6*S*,8*S*,9*S*,1′*S*)-8-(1′-Hydroxyethyl)-9-hydroxymethyl-1,5,5-trimethylbicyclo[4.3.0]nonane

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Abstract. $C_{15}H_{28}O_2$, $M_r = 240{\cdot}39$, orthorhombic, $P2_12_12_1$, $a = 6{\cdot}518\ (2)$, $b = 12{\cdot}849\ (5)$, $c = 17{\cdot}796\ (7)$ Å, $V = 1490{\cdot}4\ (9)$ Å^3, $Z = 4$, $D_x = 1{\cdot}07$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0{\cdot}07$ mm^{-1}, $F(000) = 536$, $R = 0{\cdot}039$ and $wR = 0{\cdot}038$ for 893 observed reflections, $T = 293$ K. The absolute configuration was not determined; stereochemistry at the 8 and 1′ positions is established. The cyclohexane and cyclopentane rings have chair and half-chair conformations, respectively, and are *trans*-fused.

Introduction. Drimenol (1) is a sesquiterpenic alcohol isolated from *Drymis winteri* Forst (Appel, Brooks & Overton, 1959). As part of a systematic study of molecule (1) in order to obtain derivatives of interest in pharmacology (Ley & Mahon, 1981) and perfumery (Brunke, 1980), the tosylated molecule (2) has been synthesized (Planas, Cortés & Bonet, 1985). The reduction of (2) with $LiAlH_4$ gives a product (35%

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