6-Azapurines. Part 2.[1] Crystal and Molecular Structure of 8,9-Dimethyl-6-azapurin-2-one†

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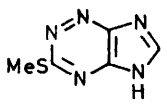
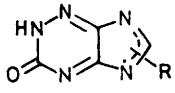
The crystal and molecular structure of 8,9-dimethyl-6-azapurin-2(1*H*)-one has been determined by single-crystal *X*-ray diffraction methods and represents the first such study on this novel heterocyclic system. The compound crystallizes in the monoclinic space group $P2_1/c$ in a cell of dimensions a = 6.601(2), b = 10.598(3), c = 10.384(3) Å, β = 99.37(2)°, Z = 4. The structure was solved by direct methods and refined using blocked-cascade full-matrix least-squares calculations, which converged to a final R_w index of 0.044 for 813 (of 941 unique) observed data. The C(11) methyl group exhibited rotational disorder which was accounted for in the refined model. Molecules form an intermolecular hydrogen-bonded chain, connecting H(N1) to N(7) along the c crystallographic axis. The N(1)H tautomer of this 6-azapurine is preferred in the solid state.

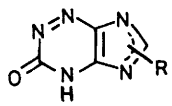
We are involved in the synthesis of 6-azapurines (imidazo-[4,5-*e*]-*as*-triazines) and examining their physical and chemical behaviour. Recent work from our laboratories [1] reported the preparation of 2-methylthio-6-azapurine (**1**) and the determination of the predominant tautomer as depicted in (**1**) occurring in the imidazole portion of this heterocycle by ^{13}C and ^{15}N n.m.r. spectroscopy. In an effort to expand these studies, *i.e.*, to inspect a heterocycle in which tautomerism was possible throughout the entire molecule, an oxo group was introduced into the 2-position of the 6-azapurine ring. Of concern to us was the possible lactam–lactim tautomerism in the *as*-triazine moiety and especially the contribution of the N(1)H and N(3)H lactam forms, (**2**) and (**3**), respectively. Certain 6-azapurin-2-ones prepared for this investigation were found to undergo a



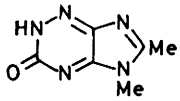
(**1**)



(**2**) R = H or Me



(**3**) R = H or Me



(**4**)

regiospecific addition of solvent across the azomethine bond located in the imidazole portion of these heterocycles.[2a] For example, 7-methyl-6-azapurin-2-one, in the presence of water, underwent covalent hydration and concomitant ring opening to furnish 5-(*N*-methylformamido)-6-azacytidine.[2b] Thus, the susceptibility of these heterocycles to solvent addition and subsequent ring opening prevented a thorough n.m.r. spectroscopic evaluation of the tautomeric processes that may occur in solution. Therefore, to establish which of the two lactam forms, N(1)H or N(3)H, is favoured, an *X*-ray crystallographic study was conducted. A suitable candidate for this study was 8,9-dimethyl-6-azapurin-2-one (**4**) which could be crystallized readily from absolute ethanol. Although the results of our *X*-ray analysis cannot describe exact solution behaviour of this heterocycle, it does ascertain that (**4**) is the most stable tautomer in the crystalline state.

Experimental

Synthesis.—^1H and ^{13}C n.m.r. spectra were obtained on Varian EM-390 and CFT-20 spectrometers, respectively, using [$^2H_6$]dimethyl sulphoxide as solvent. Chemical shifts are expressed in p.p.m. with respect to Me_4Si. For the ^{13}C n.m.r. spectra a flip angle of 45° was employed. Elemental analyses were performed by M–H–W Laboratories, Phoenix, Arizona U.S.A.

8,9-*Dimethyl*-6-*azapurin*-2(1H)-*one* (**4**).—To a well stirred suspension of 6-amino-5-methylamino-*as*-triazin-3-one[3] (424 mg, 3 mmol) in triethyl orthoacetate (25 ml) was added concentrated hydrochloric acid (2 ml). The reaction mixture was heated at reflux (oil-bath 130 °C) for 18 h. The mixture was allowed to cool to room temperature and the solid was filtered off washed with cold, absolute ethanol, and air-dried. This material was crystallized from absolute ethanol to provide (**4**) (383 mg, 77.2%), m.p. 268 °C (slow decomp.) (Found: C, 43.48; H, 4.24; N, 41.99. $C_6H_7N_5O$ requires C, 43.64; H, 4.27; N, 42.40%); δ_H 2.50 (3 H, s, 8-Me), 3.40 (3 H, s, 9-Me), and 12.79 (1 H, br s, NH); δ_C 14.9_3 (8-Me), 27.7_9 (9-Me), 144.5_1 (C-5), 153.5_0 (C-4), 154.9_6 (C-2), and 166.3_2 (C-8).

Crystal Data.—$C_6H_7N_5O$, M = 165.2. Monoclinic, a = 6.601(2), b = 10.598(3), c = 10.384(3) Å, β = 99.37(2)°, V = 716.8(5) Å^3 (by least-squares refinement of diffractometer angles for 25 automatically centred reflections between 24—26° 2θ, λ = 0.710 69 Å), space group from systematic absences ($0k0$ for $k = 2n + 1$, $h0l$ for $l = 2n + 1$) $P2_1/c$, Z = 4, D_m (by flotation in hexane–CCl_4) 1.55(2) g cm^{-3}, D_x = 1.53 g cm^{-3}. The data crystal was a colourless, stout needle with crystal dimensions 0.25 × 0.25 × 0.40 mm, μ(Mo–K_α) 1.2 cm^{-1}.

Data Collection and Processing.—Nicolet R3M/E autodiffractometer, θ/2θ data collection mode with variable scan speed

† 5,6-Dimethylimidazo[4,5-*e*]-*as*-triazin-3(2*H*)-one.

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(4.88—29.30 deg min^{-1}), using graphite-monochromated Mo-K_α radiation; 941 unique reflections measured at ambient temperature [294(1) *K*] between 3.5° < 2θ < 45.0° for *h*, *k*, ±*l* of which 813 had $F_o > 2.5\ \sigma(F_o)$ and were considered observed. Intensities were corrected for minor deviations in standards (minimum 0.9929; maximum 1.0103), as well as Lorentz and polarization effects. No absorption corrections were applied.

Structure Analysis and Refinement.—The structure was solved and refined using the program package SHELXTL[4] which uses complex scattering factors from International Tables for *X*-ray Crystallography.[5] Positional and anisotropic thermal parameters for all non-hydrogen atoms were refined, based on *F*, by blocked-cascade least-squares. All hydrogen atoms were located from a difference Fourier map. Isotropic thermal parameters for hydrogens were fixed at 1.2 times the corresponding equivalent isotropic thermal parameters of the atoms to which they were attached. Difference maps revealed rotational disorder of the hydrogen atoms attached to C(11). Occupancy factors for two partial methyl groups refined to 0.49(2), and 1.00—0.49(2) (only one set of H atoms is shown on ORTEP[6] plots for clarity). For several strong reflections, F_o was significantly smaller than F_c, and in the final stages of refinement an extinction correction was applied. Final discrepancy indices, $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(F_o)^2]^{\frac{1}{2}}$ respectively, for 141 parameters refined. Reflections were weighted in the final stages of refinement according to the weighting scheme $w = 1/[\sigma^2(F_o) + g(F_o)^2]$ (where $g = 0.0008$). The goodness-of-fit (GOF) was 1.167 and GOF/slope of the normal probability plot = 1.14. The mean shift/e.s.d. was 0.02 with a maximum shift at 0.028 for *X*/*a* for H11A. The final difference electron density map showed maxima and minima of 0.150 and −0.152e A^{-3}.

Positional and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Results and Discussion

An ORTEP[6] diagram showing the numbering scheme of (**4**) is presented in Figure 1. Atomic co-ordinates are listed in Table 1 and bond lengths and bond angles are given in Table 2. The molecule is essentially planar, with the C(10) and C(11) methyl groups displaced −0.031 and +0.052Å respectively from the least-squares plane. [The C(10) and C(11) methyl groups were not included in the least-squares plane calculation.] The angle between the six- and five-membered rings is 0.6°. Since the standard deviation of torsion angles is 0.3° this angle (0.6°) is 2σ and therefore not significant.

The bond lengths of (**4**) are compatible with those reported for 1-methylisoguanine dihydrate[7] and 9-methylisoguanine hydrochloride dihydrate,[8] two purines selected as model compounds. It is also worth noting that the bond lengths of the *as*-triazine moiety of (**4**) compare favourably with those observed for 6-azauracil,[9] 6-azathymine,[10] and 6-azacytidine,[11] with the exception of the N(3)–C(4) bond (Table 2) which exhibits greater double-bond character.[12] Hodgson and Singh[9–11] compared the bond lengths of the aforementioned 6-azapyrimidines with those of their respective pyrimidine counterparts and found that the C(4)–C(5) bond of the 6-azapyrimidine ring was longer and the C(5)–N(6) bond much shorter. They attributed these differences in bond length and character solely to the replacement of the C(6) atom on the pyrimidine ring with a nitrogen atom.

* For details see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1987, Issue 1, Sect. 5.6.3.

Table 1. Atomic co-ordinates (× 10^4) for compound (**4**)

Atom	*x*	*y*	*z*
C(2)	2 557(3)	10 362(2)	−1 239(2)
C(4)	2 511(3)	9 813(2)	857(2)
C(5)	2 594(3)	11 098(2)	1 263(2)
C(8)	2 480(3)	10 002(2)	2 964(2)
C(10)	2 395(4)	9 583(3)	4 306(2)
C(11)	2 422(4)	7 755(2)	2 068(3)
O	2 568(2)	10 165(1)	−2 399(1)
N(1)	2 638(3)	11 603(1)	−788(1)
N(3)	2 487(2)	9 406(1)	−327(2)
N(6)	2 655(2)	12 016(2)	443(2)
N(7)	2 580(3)	11 179(2)	2 593(2)
N(9)	2 434(2)	9 138(2)	1 957(1)

Table 2. Bond lengths (Å) and bond angles (°) for compound (**4**)

C(2)–O	1.224(4)	C(2)–N(1)	1.394(5)
C(2)–N(3)	1.393(5)	C(4)–C(5)	1.424(5)
C(4)–N(3)	1.301(5)	C(4)–N(9)	1.356(5)
C(5)–N(6)	1.298(5)	C(5)–N(7)	1.395(5)
C(8)–C(10)	1.474(5)	C(8)–N(7)	1.310(5)
C(8)–N(9)	1.386(5)	C(11)–N(9)	1.470(5)
N(1)–N(6)	1.349(5)		
O–C(2)–N(1)	119.1(2)	O–C(2)–N(3)	123.4(2)
N(1)–C(2)–N(3)	117.5(2)	C(5)–C(4)–N(3)	126.2(2)
C(5)–C(4)–N(9)	105.1(2)	N(3)–C(4)–N(9)	128.7(2)
C(4)–C(5)–N(6)	121.8(2)	C(4)–C(5)–N(7)	110.4(2)
N(6)–C(5)–N(7)	127.9(2)	C(10)–C(8)–N(7)	125.2(3)
C(10)–C(8)–N(9)	120.9(3)	N(7)–C(8)–N(9)	113.8(2)
C(2)–N(1)–N(6)	128.2(2)	C(2)–N(3)–C(4)	113.9(2)
C(5)–N(6)–N(1)	112.5(2)	C(5)–N(7)–C(8)	104.1(2)
C(4)–N(9)–C(8)	106.7(2)	C(4)–N(9)–C(11)	126.4(2)
C(8)–N(9)–C(11)	126.8(2)		

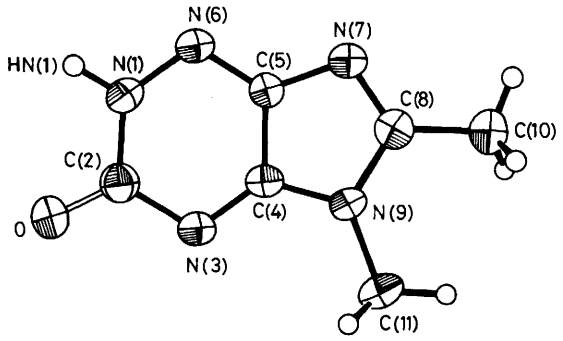

Figure 1. ORTEP[6] drawing of the title compound (**4**) viewed approximately along the *a*-axis. Thermal ellipsoids are drawn at the 50% probability level, while hydrogen atoms are represented by spheres of arbitrary size

The bond lengths located in the imidazole portion of (**4**) are similar to those observed for 9-methylisoguanine and 1-methylisoguanine. However, the N(9)–C(8) and C(8)–N(7) bonds of (**4**) are slightly longer and most probably reflect the effect of methyl substitution at N(9) and C(8).[7]

The average value for the internal C–N–C angles in the imidazole ring is 105.4° (Table 2) comparable with those recorded for the isoguanines.[8,9] The internal ring angles at the three nitrogen atoms N(1), N(3), and N(6) are in complete agreement with Singh's rule[13] for six-membered nitrogen heterocycles. The C(2)–N(1)–N(6) angle is significantly larger

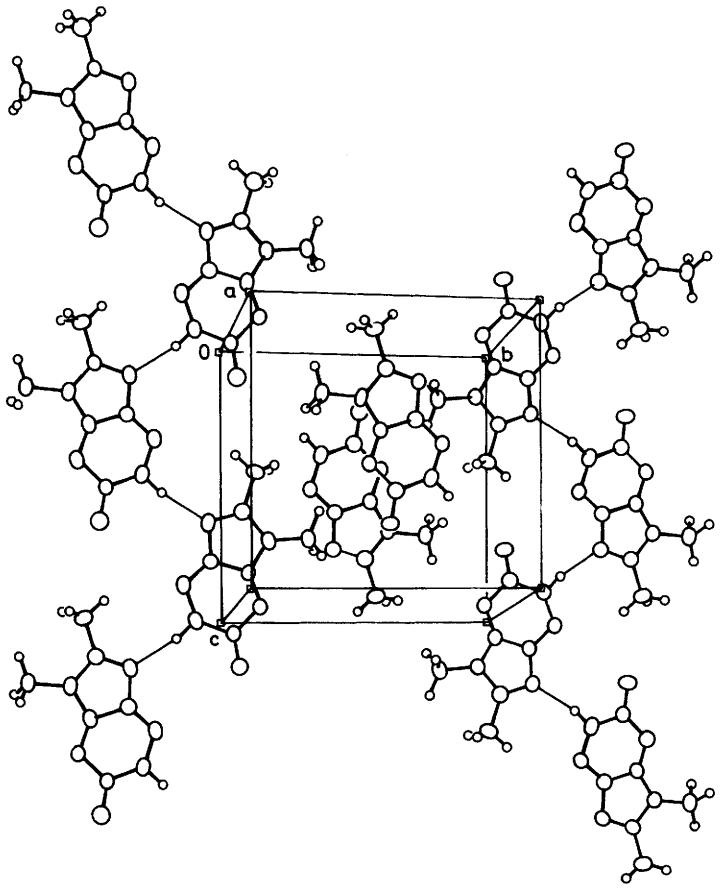

Figure 2. Packing diagram viewed along the $-a$ lattice direction with $+b$ from left to right and $+c$ from top to bottom. The origin is indicated as O

(128.2°) than the C(2)–N(3)–C(4) (113.9°) and the N(1)–N(6)–C(5) (112.5°) angles due to the attachment of the extra-annular hydrogen at N(1).

Molecules of the title compound, related by the glide plane parallel to *c*, form an intermolecular hydrogen-bonded chain, connecting H(N1) of one molecule to N(7) of another. A packing diagram illustrating the hydrogen-bonded network is depicted in Figure 2.

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