Structure of 7-Methyl-8-azaadenine. A Crystallographic and Molecular Orbital Study

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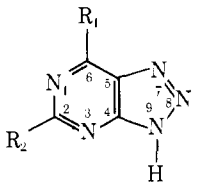
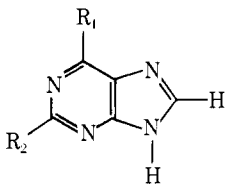
Abstract: The crystal and molecular structure of 7-methyl-8-azaadenine (6-amino-7-methyl-8-azapurine), $C_5H_6N_6$, has been determined from three-dimensional x-ray counter data obtained using Mo Kα radiation. The material crystallizes in the orthorhombic space group *Pbcn* with eight formula units in a cell of dimensions a = 7.578 (2), b = 13.328 (3), and c = 12.566 (4) Å. The observed and calculated densities are 1.57 (3) and 1.572 g cm^{-3}, respectively. The structure has been refined to a final value of the conventional R factor (on F) of 0.041 using 1125 independent intensities. The azapurine ring is approximately planar, with no atom deviating from the least-squares plane by more than 0.03 Å. There is considerable intermolecular hydrogen bonding in the crystals, involving N(1) and N(3) as acceptors and the amino group as the donor. It is noteworthy that neither N(8) nor N(9) participate in hydrogen bonding. A CNDO/2 molecular orbital calculation provides an explanation for this observation by showing that the residual negative charges on N(1) and N(3) (−0.27 and −0.23 electron, respectively) are much larger than those on N(8) and N(9) (−0.01 and −0.16 electron, respectively).

The 8-azapurines (I), which are purines (II) in which the imidazole ring has been changed to a 1,2,3-triazole, are of



I



II

considerable importance because of their use in the treatment of cancer,[1-4] asthma, and allergenic diseases.[5,6] Consequently, these molecules have received much attention during the past few years. It has been suggested, for example, that the nucleosides of these azapurines adopt a glycosyl conformation which is different from that in the natural nucleosides and that this feature may be significant in determining their clinical activity.[7] A number of crystal structure determinations, performed both in our laboratories[8-12] and elsewhere,[13-18] have lent support to this hypothesis.

The electronic effects of the replacement of CH by N in the 8 position of the purines are not yet well understood. In the analogous 6-azapyrimidines,[8,10,11,19-21] atom N(6) apparently has virtually zero net residual charge, but the charges on other atoms in the ring are different from those in the parent pyrimidines. In some 8-azapurines, there is apparently a small negative charge on N(8).[11,12] Molecular orbital calculations[22] have demonstrated that the energetically favored tautomer in most 8-azapurines is N(9)-H, but while this tautomer is observed in the structure of 8-azaguanine,[23,24] it is the less favorable N(8)-H tautomer which is found in the solid state for 8-azaxanthine[25,26] and 8-azahypoxanthine.[27] Moreover, the cationic forms of 8-azaguanine[28,29] and 2,6-diamino-8-azapurine[27,30] have the N(3)-H, N(8)-H tautomer in the solid state. Recently we have observed[31] metal coordination to N(3) of an 8-azapurine cation, while similar coordination has not been observed for the purines. All of these observations suggest that atom N(3) in the 8-azapurines may be much more electron rich than in the natural purines.

In order to investigate the electronic and structural effects of replacement of CH by N in the 8 position of purines, we have undertaken a comprehensive crystallographic and molecular orbital study of the 8-azapurines. We here report the results of such an investigation on 7-methyl-8-azaadenine (or 6-amino-7-methyl-8-azapurine), in which R_1 = NH_2 and R_2 = H in I. The potential medicinal value of this compound has not yet been studied.

Experimental Section

Molecular Orbital Calculations. The MO calculations were made using the CNDO/2 approximation;[32] the program used was the Q.C.P.E. Program No. 141. The atomic coordinates were those obtained from the refinement of the crystal structure (vide infra).

Crystallographic. A sample of the title compound was synthesized[33] by Professor A. Albert and generously donated to us by him. Colorless, needle-shaped crystals were obtained by slow evaporation of a hot aqueous solution. On the basis of Weissenberg and precession photographs, the crystals were assigned to the orthorhombic system. The observed systematic absences are $h0l$ for l odd, $0kl$ for k odd, and $hk0$ for $h + k$ odd, which suggests that the space group is *Pbcn* (D_{2h}^{14}). The cell constants, obtained by least-squares methods, are a = 7.578 (2), b = 13.328 (3), and c = 12.566 (4) Å. The observations were made at 20.5° with the wavelength assumed as λ(Mo Kα_1) = 0.7093 Å. A density of 1.572 g cm^{-3} calculated for eight formula units in the cell compares well with a value of 1.57 (3) g cm^{-3} observed by flotation. Hence, in space group *Pbcn*, no crystallographic symmetry is imposed on the molecules.

Diffraction data were collected from an hexagonal prismatic crystal with faces (100), ($\bar{1}$00), (001), (00$\bar{1}$), (011), (0$\bar{1}\bar{1}$), (01$\bar{1}$), and (0$\bar{1}$1). The separations between opposite pairs of faces were as follows: (100) and ($\bar{1}$00), 0.068 cm; (001) and (00$\bar{1}$), 0.053 cm; (011) and (0$\bar{1}\bar{1}$), 0.48 cm; (01$\bar{1}$) and (0$\bar{1}$1), 0.045 cm. The crystal was mounted in a glass capillary normal to the (100) planes, and in this orientation intensity data were collected on a Picker four-circle automatic diffractometer equipped with a graphite monochromator and using Mo Kα radiation. The mosaicity of the crystal was examined by means of the narrow-source, open-counter ω-scan technique and was judged to be acceptable.

Twelve reflections, accurately centered through a narrow vertical slit at a takeoff angle of 1.0°, formed the basis for the least-squares refinement of cell parameters and orientation using the logic documented by Busing and Levy[34] for the PDP-8/L computer.

Intensity data were collected at a takeoff angle of 1.3°; at this angle the intensity of a typical reflection was approximately 85% of the maximum as a function of the takeoff angle. The receiving aperture was 5.0 mm high by 5.0 mm wide and was positioned 32.0 cm from the crystal. The data were collected by the θ–2θ scan technique at a scan rate of 1.0°/min. Allowance was made for the presence of both Kα_1 and Kα_2 radiations, the peaks being scanned from 0.90° in 2θ below the calculated Kα_1 peak position to 0.90° in 2θ above the calculated Kα_2 position. Stationary-counter, stationary-crystal background counts of 10 s were taken at each end of the scan. The pulse height analyzer was set for approximately a 90% window, centered on the Mo Kα peak.

A unique data set having $2° \leq 2\theta \leq 58°$ was gathered; a total of 1932 intensities was recorded. The intensities of three standard re-

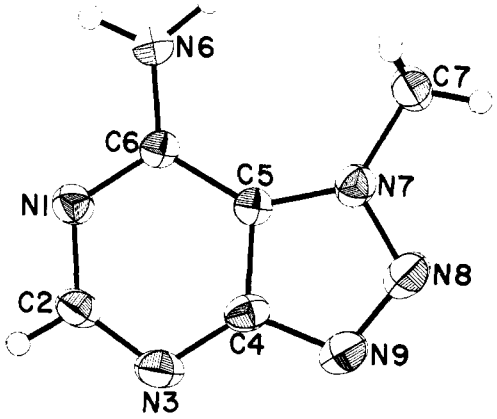


Figure 1. View of a single molecule of 7-methyl-8-azaadenine. Hydrogen atoms are shown as open circles of arbitrary size; other thermal ellipsoids are drawn at the 50% probability level.

flections, measured after every 100 reflections, showed no decline throughout the run.

Data processing was carried out as described by Corfield et al.[35] After correction for background, the intensities were assigned standard deviations according to the formula[36]

$$\sigma(I) = [C + 0.25(\mathrm{ts/tb})^2(\mathrm{BH} + \mathrm{BL}) + (pI)^2]^{1/2}$$

and the value of p was selected as 0.040. The values of I and $\sigma(I)$ were corrected for Lorentz-polarization effects but not for absorption factors. The absorption coefficient of this compound for Mo Kα radiation is 1.05 cm^{-1}, and for the crystal chosen the effects of absorption are negligible. Of the 1932 data collected, 1125 were greater than three times their estimated standard deviations; only these data were used in the subsequent structure analysis and refinement.

Solution and Refinement of the Structure. The structure was solved by direct methods[37] using the highest 116 normalized structure amplitudes (E's) in the program MULTAN.[38] The chosen solution, which had an R_{Karle} of 15.85 and an absolute figure of merit of 1.0813, gave an E map which clearly revealed the locations of the 11 nonhydrogen atoms; these 11 positions were contained in the 13 highest peaks in the map. Isotropic least-squares refinement[39] of these 11 positions led to values of the conventional agreement factors $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_2 = [\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2]^{1/2}$ of 0.099 and 0.105, respectively. Anisotropic refinement reduced R_1 and R_2 to 0.072 and 0.104, respectively. All least-squares refinements in this analysis were carried out on F, the function minimized being $\Sigma w(|F_o| - |F_c|)^2$ where the weights w were taken as $4F_o^2/\sigma^2(F_o^2)$. In all calculations of F_c, the atomic scattering factors for nonhydrogen atoms were from International Tables[40] while those for hydrogen were from Stewart et al.[41] The hydrogen atoms were readily located in a difference Fourier map. Least-squares refinement in which the nonhydrogen atoms were refined anisotropically while the hydrogen atoms were refined isotropically gave values of R_1 and R_2 of 0.042 and 0.051, respectively. Examination of the data suggested that they were suffering from secondary extinction, and a correction of the form described by Zachariasen[42] was applied; the final value of the extinction coefficient was $1.2(3) \times 10^{-8}$, and the final values of R_1 and R_2 were 0.041 and 0.050, respectively. In the final cycle of least-squares refinement, no parameter experienced a shift of more than 0.6σ, which is taken as evidence of convergence. The value of R_2 showed no unexpected dependence on $|F_c|$ or sin θ. A final difference Fourier was featureless. The positional and thermal parameters, along with their standard deviations as estimated from the inverse matrix, are listed in Tables I and II. A compilation of observed and calculated structure amplitudes is available.[43]

Results and Discussion

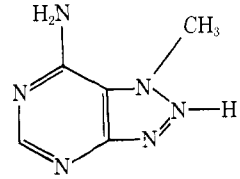
The structure consists of 7-methyl-8-azaadenine molecules which are hydrogen bonded to each other in the crystals. A view of a single molecule is given in Figure 1.

The intramolecular bond lengths are listed in Table III. The bond distances in the six-membered ring are consistent with those tabulated by Ringertz[44] for a variety of substituted adenines and with those in 8-azaadenosine.[9,45] The bond lengths in the five-membered triazole ring are more difficult to assess, since this is the first structural report of a 7-substituted 8-azapurine. As a result of the 7 substitution, the principal resonance contributor in this case must be III, rather than

Table I. Positional Parameters for 7-Methyl-8-azaadenine

Atom	X	Y	Z
N(1)	0.0870 (2)	0.3938 (1)	0.0782 (1)
C(2)	0.1112 (3)	0.2953 (1)	0.0979 (1)
N(3)	0.1915 (2)	0.2520 (1)	0.1789 (1)
C(4)	0.2525 (2)	0.3203 (1)	0.2496 (1)
C(5)	0.2385 (2)	0.4232 (1)	0.2380 (1)
C(6)	0.1528 (2)	0.4619 (1)	0.1460 (1)
N(7)	0.3173 (2)	0.4610 (1)	0.3273 (1)
N(8)	0.3736 (2)	0.3848 (1)	0.3888 (1)
N(9)	0.3362 (2)	0.2994 (1)	0.3433 (1)
N(6)	0.1314 (2)	0.5583 (1)	0.1235 (1)
C(7)	0.3426 (3)	0.5635 (1)	0.3638 (2)
H(2)[a]	0.068 (3)	0.252 (1)	0.050 (2)
H(61)[b]	0.180 (2)	0.610 (1)	0.163 (1)
H(62)[b]	0.085 (3)	0.574 (1)	0.061 (2)
H(71)[c]	0.393 (4)	0.563 (2)	0.430 (3)
H(72)[c]	0.236 (5)	0.595 (3)	0.366 (3)
H(73)[c]	0.386 (4)	0.605 (2)	0.313 (2)

[a] Attached to C(2). [b] Attached to N(6). [c] Attached to C(7).



III

I. Hence, we anticipate that, in the present compound, the N(7)-N(8) bond is largely a single bond while the N(8)-N(9) bond contains much double-bond character; in the unsubstituted and 9-substituted 8-azapurines, the reverse is true. The results are in complete accord with this hypothesis. Thus, the N(8)-N(9) bond of length 1.306 (2) Å is considerably shorter than the N(7)-N(8) bond and is in the range of 1.293-1.313 Å reported[23,24,45] for the N(7)-N(8) bond in compounds of type I. Similarly, the N(7)-N(8) bond length of 1.346 (2) Å found here is comparable with the N(8)-N(9) distance in these other structures and also with the average value[44] of 1.373 Å for the C(8)-N(9) bond in substituted adenine structures if allowance is made for the difference in size between C and N. The C(4)-N(9) and C(5)-N(7) distances are approximately equal, suggesting equal bond orders for these two bonds.

The bond angles in the six-membered ring agree well with the suggestions of Ringertz[44] and Singh[46] who have noted that the internal angles in the purine ring are dependent on the nature of the substituent atoms. The angles in the triazole portion are in the ranges tabulated by Purnell and Hodgson[47] for substituted 8-azapurines, provided again that allowance is made for the N(7) rather than N(9) substitution here. Thus, for example, in 8-azaadenosine[45] the substituent is at N(9) and the angle at N(9) is larger [109.8 (2)°] than that at N(7) [108.6 (2)°]; in the present case, therefore, it is to be expected that the angle at N(7) [109.4 (1)°] is larger than that at N(9) [107.5 (1)°]. Similarly, in 9-substituted adenines[44] the C(4)-C(5)-N(7) angle is approximately 5° larger than the C(5)-C(4)-N(9) angle; in the present case, the angle at C(4) [109.2 (2)°] is 5.0° larger than that at C(5) [104.2 (1)°]. The angle of 109.8 (1)° at N(8) is roughly 1° larger than the average of those in other 8-unprotonated systems[47] but is within

Table II. Thermal Parameters for 7-Methyl-8-azaadenine

Atom	β_{11}[a] or B (Å^2)	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	0.0141 (3)	0.0031 (1)	0.0034 (1)	−0.0007 (1)	0.0004 (1)	−0.0001 (1)
C(2)	0.0160 (4)	0.0028 (1)	0.0036 (1)	−0.0009 (2)	0.0012 (2)	−0.0005 (1)
N(3)	0.0177 (4)	0.0028 (1)	0.0047 (1)	0.0005 (1)	0.0012 (1)	0.0000 (1)
C(4)	0.0117 (3)	0.0031 (1)	0.0037 (1)	0.0008 (1)	0.0014 (2)	0.0005 (1)
C(5)	0.0090 (3)	0.0028 (1)	0.0029 (1)	0.0000 (1)	0.0009 (1)	0.0000 (1)
C(6)	0.0089 (3)	0.0028 (1)	0.0029 (1)	−0.0003 (1)	0.0011 (1)	0.0002 (1)
N(7)	0.0112 (3)	0.0037 (1)	0.0036 (1)	−0.0003 (1)	0.0000 (1)	0.0003 (1)
N(8)	0.0146 (3)	0.0047 (1)	0.0047 (1)	0.0004 (1)	−0.0010 (2)	0.0010 (1)
N(9)	0.0170 (4)	0.0040 (1)	0.0051 (1)	0.0010 (1)	−0.0007 (2)	0.0010 (1)
N(6)	0.0176 (4)	0.0029 (1)	0.0044 (1)	−0.0005 (1)	−0.0022 (2)	0.0004 (1)
C(7)	0.0153 (4)	0.0038 (1)	0.0039 (1)	−0.0013 (2)	−0.0002 (2)	−0.0005 (1)
H(2)	3.3 (4)					
H(61)	2.5 (4)					
H(62)	3.4 (5)					
H(71)	6.6 (8)					
H(72)	8.1 (10)					
H(73)	6.0 (8)					

[a] The form is $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

Table III. Intramolecular Distances (Å) in 7-Methyl-8-azaadenine

Atoms	Distance	Atoms	Distance
N(1)-C(2)	1.349 (2)	N(7)-N(8)	1.346 (2)
C(2)-N(3)	1.319 (2)	N(7)-C(7)	1.454 (2)
N(3)-C(4)	1.354 (2)	N(8)-N(9)	1.306 (2)
C(4)-C(5)	1.384 (2)	C(2)-H(2)	0.90 (2)
C(4)-N(9)	1.366 (2)	N(6)-H(61)	0.93 (2)
C(5)-C(6)	1.423 (2)	N(6)-H(62)	0.89 (2)
C(5)-N(7)	1.367 (2)	C(7)-H(71)	0.91 (3)
C(6)-N(1)	1.341 (2)	C(7)-H(72)	0.91 (4)
C(6)-N(6)	1.325 (2)	C(7)-H(73)	0.91 (3)

the observed range. All bond angles are tabulated in Table IV.

As is shown in Table V, the molecule is approximately planar, with no ring atom deviating from the best least-squares plane through the nine atoms by more than 0.03 Å; the extracyclic atoms N(6) and C(7) are 0.034 Å above and 0.026 Å below this plane, respectively. Alternatively, the purine analogue can be viewed as being composed of a planar six-membered ring (maximum deviation, 0.015 Å) and a planar five-membered ring (maximum deviation, 0.003 Å) which are inclined at an angle of 1.58°.

The intermolecular hydrogen bonding, which is shown in Figure 2, is unusual in that neither N(8) nor N(9) appear to participate. This is the first example, to our knowledge, of an 8-azapurine in which there is no hydrogen bonding interaction involving the triazole moiety of the molecule.[27-31,48] The hydrogen bonding is restricted to N(1), N(3), and the amino group, there being only two kinds of hydrogen bonds in the structure. The first kind is an N(6)-H···N(1) hydrogen bond of length 3.094 (2) Å and an N-H···N angle of 167 (2)°. Pairs of these hydrogen bonds, related by the inversion center, link adjacent pairs of azapurines; these N(6) donor and N(1) acceptor hydrogen bonds are similar to those found in the A-T

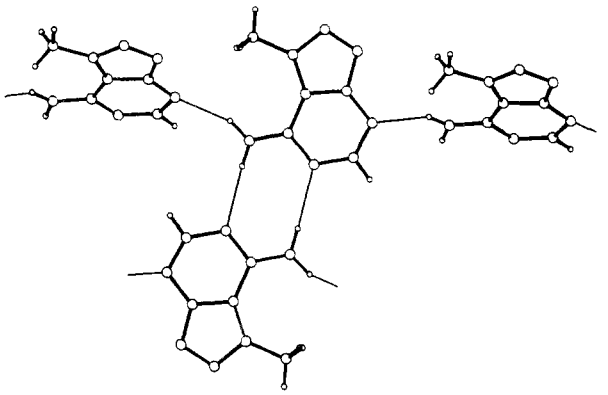


Figure 2. The hydrogen bonding (thin lines) in the crystals of 7-methyl-8-azaadenine. The lower molecule is related to the central (reference) molecule by inversion; the upper left and right molecules are related to the reference molecule by the *b* glide. The *b* axis is horizontal in the figure.

Table IV. Selected Bond Angles (Degrees) in 7-Methyl-8-azaadenine

Atoms	Angle	Atoms	Angle
C(2)-N(1)-C(6)	119.4 (2)	C(7)-N(7)-N(8)	119.1 (2)
N(1)-C(2)-N(3)	129.1 (2)	N(7)-N(8)-N(9)	109.8 (2)
C(2)-N(3)-C(4)	111.7 (1)	C(4)-N(9)-N(8)	107.5 (1)
N(3)-C(4)-C(5)	124.9 (2)	N(1)-C(2)-H(2)	117 (1)
N(3)-C(4)-N(9)	125.9 (2)	N(3)-C(2)-H(2)	114 (1)
C(5)-C(4)-N(9)	109.2 (2)	C(6)-N(6)-H(61)	124 (1)
C(4)-C(5)-C(6)	118.7 (2)	C(6)-N(6)-H(62)	118 (1)
C(4)-C(5)-N(7)	104.2 (1)	H(61)-N(6)-H(62)	117 (2)
C(6)-C(5)-N(7)	137.1 (1)	N(7)-C(7)-H(71)	109 (2)
N(1)-C(6)-C(5)	116.2 (1)	N(7)-C(7)-H(72)	109 (2)
N(1)-C(6)-N(6)	118.4 (2)	N(7)-C(7)-H(73)	113 (2)
C(5)-C(6)-N(6)	125.5 (2)	H(71)-C(7)-H(72)	110 (3)
C(5)-N(7)-N(8)	109.4 (1)	H(71)-C(7)-H(73)	120 (2)
C(5)-N(7)-C(7)	131.5 (2)	H(72)-C(7)-H(73)	94 (3)

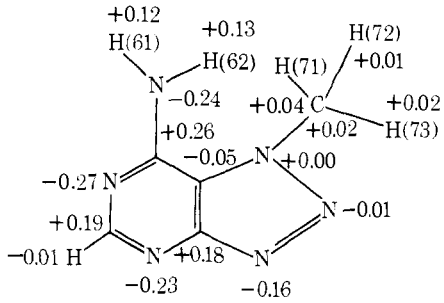
Table V. Deviations (Å) from Least-Squares Planes in 7-Methyl-8-azaadenine

Atoms	Plane I[a]	Plane II[a]	Plane III[a]
N(1)	−0.026	−0.013	
C(2)	−0.010	−0.001	
N(3)	0.020	0.012	
C(4)	0.011	−0.010	0.001
C(5)	0.014	−0.004	
C(6)	0.015	0.015	
N(7)	0.003	−0.032	0.003
N(8)	−0.017	−0.064	−0.002
N(9)	−0.009	−0.048	0.004
N(6)	0.034	0.039	
C(7)	−0.026	−0.066	−0.023

[a] Atoms included in the calculations: plane I, N(1), C(2), N(3), C(4), C(5), C(6), N(7), N(8), N(9); plane II, N(1), C(2), N(3), C(4), C(5), C(6); plane III, C(4), C(5), N(7), N(8), N(9).

pairs in nucleic acids[49] (see Figure 2). The second type of hydrogen bond involves the other amino group proton which forms an N(6)-H···N(3) hydrogen bond of length 2.991 (2) Å with an associated N-H···N angle of 153 (2)°; structural details of these hydrogen bonds are given in Table VI. In the adenine monocation, whose structure has been investigated by a number of workers, atom N(3) does not participate in hydrogen bonding in the crystal.[50-52] Hence, these hydrogen bonds involving N(3) in the present compound provide further evidence for our contention that this atom may be more basic in the 8-azapurines than in the purines;[28] it should be noted, however, that atom N(3) does form N(6)-H···N(3) interpurine hydrogen bonds in the adenine dication[53] and that similar N(2)-H···N(3) hydrogen bonds are found in the guanine monocation.[54] Moreover, base-sugar hydrogen bonding involving N(3) is common in the structures of adenosine nucleosides and nucleotides.[55-57]

The net atomic charge densities, as calculated in the CNDO/2 approximation,[32] are shown in structure IV. The



IV

calculated values suggest that atoms N(1) and N(3) are the most basic[58] ring nitrogen atoms, which is entirely consistent with the observed hydrogen bonding (Figure 2); similarly, as expected, hydrogen atoms H(61) and H(62) are the only appreciably acidic protons in the molecule. In adenine, extended Hückel calculations[60] suggest that N(7) has a higher net charge density than N(3), although more recent CNDO/2 calculations[22] demonstrate that there is little difference between these two sites. It is noteworthy, however, that in 9-methyladenine the residual charges on N(1), N(3), and N(7) are −0.29, −0.24, and −0.21 electron, respectively;[59] these values are comparable with our values of −0.27, −0.23, and −0.16 electron for N(1), N(3), and N(9) in the present molecule. Moreover, the charges calculated for N(1), N(6), H(61), and H(62) are very similar to those reported for the same atoms in 3-deazaadenosine.[61] The virtual absence of any residual charge on atom N(8) suggests that this atom is less basic than in 8-azaadenosine or formycin and is comparable to the N(6) atom in 6-azapyrimidines.[11] We are currently attempting to isolate the cation of 7-methyl-8-azaadenine, and also metal complexes of this ligand, to investigate further the relative basicities of the ring nitrogen atoms.

Table VI. Probable A-H···B Hydrogen Bonds

A	H	B	A···B (Å)	H···B (Å)	A-H···B (deg)
N(6)	H(61)	N(3)	2.991 (2)	2.14 (2)	153 (2)
N(6)	H(62)	N(1)	3.094 (2)	2.22 (2)	167 (2)

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Supplementary Material Available: a listing of observed and calculated structure amplitudes for 7-methyl-8-azaadenine (7 pages). Ordering information is given on any current masthead page.

References and Notes

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Structure of a New [11]Cytochalasin, Cytochalasin H or Kodo-cytochalasin-1

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Abstract: The crystal structure determination of a new [11]cytochalasin toxin (kodo-cytochalasin-1 or cytochalasin H) has proven the constitution of this compound and provided new information on the conformation of the multiple ring structure in this class of fungal metabolites. The toxin, (7*S*,16*S*,18*S*,21*R*)-21-acetoxy-7,18-dihydroxy-16,18-dimethyl-10-phenyl[11]cytochalasa-6(12),13′,19′-trien-1-one, with the structure I, $C_{30}H_{39}NO_5$, is very similar to cytochalasin D, lacking a keto oxygen at C-17 in the 11-membered ring and having the opposite stereochemistry at C(18). The conformation of the multiple fused ring system is nearly identical with that of a *p*-bromobenzoate derivative of cytochalasin D, indicating that the fused ring system in these [11]cytochalasins is a fairly rigid structural unit. Strong hydrogen bonds involving the NH and C=O functions of the γ-lactam ring, present in all other cytochalasin structures, may be important in binding to the toxin's site of action. The toxin crystallizes from diethyl ether as stocky prisms with the monoclinic space group $P2_1$ and cell constants $a = 7.338\ (2)$ Å, $b = 13.053\ (6)$ Å, $c = 15.330\ (4)$ Å, $\beta = 97.02\ (2)°$, and $Z = 2$. The structure was solved by direct methods and refined by least squares to a final *R* factor of 0.049 for 2707 independent reflections. The ^1H and ^{13}C NMR spectra are also reported.

The toxic effects on a number of crop plants of a fungal metabolite isolated from a fungus (*Phomopsis* sp.) found infecting weevil damaged pecans were recently described. Tests with tobacco, wheat, and bean plants showed significant growth-inhibiting or toxic effects, with single doses as small as 10^{-4} mmol inhibiting floral development in tobacco. The compound was toxic, LD_{50} for day-old cockerels being but 12.5 mg/kg.[2] Preliminary chemical and spectroscopic analyses indicated that the compound was probably a new member of the class of fused polycyclic ring compounds, the cytochalasins. Although the effects of cytochalasin B on tip growth in plants have been described,[3] cytochalasins are best known for their singular and varied effects on animal cells. The most unusual of their properties is their ability to cause cells to extrude their nuclei,[4] leading to the formation of nuclei-free cells. At lower concentrations (ca. 1 μg/mL) cytochalasins interfere with cell division, not by preventing nuclear division but by preventing cytoplasmic division at the final stage by blocking the formation of contractile microfilament structures.[5] The result is binuclear or polynuclear cells.[6] Other effects of these toxins are clot retraction; inhibition of cytoplasmic or protoplasmic streaming, cardiac and smooth muscle contraction; interference with sugar uptake,[7] release of growth hormone,[8] platelet aggregation, nerve outgrowth, and thyroid secretion. Most of these effects are reversible, disappearing when the cells are flushed with toxin-free nutrient. Cytochalasins possess some antibiotic activity[9] and one, cytochalasin D, has been reported to be a selective antitumor agent.[10]

This structural and NMR study was undertaken to unambiguously determine the identity of the new toxin and to examine its relationship with the known cytochalasins.

Experimental Section

Colorless, irregular prismatic crystals of the toxin were grown from diethyl ether solution. Precession photographs indicated a monoclinic crystal system; the systematic absences ($0k0$ absent for $k = 2n + 1$) were consistent with space groups $P2_1$ and $P2_1/m$. $P2_1$ was chosen as the appropriate space group and this choice later confirmed by the intensity distribution statistics. The cell constants were determined by least-squares refinement of the setting angles of 15 well-centered reflections; they appear with other pertinent crystal data in Table I.

Three-dimensional intensity data were collected on an automated four-circle diffractometer using graphite monochromatized Mo Kα radiation. A total of 4531 intensities were measured, using the ω–2θ scan technique, for reflections having 2θ values between 4.0 and 50.0°. Of these, 2707 were independent and remained after averaging of multiply measured and symmetry related reflections. The scan rate for data collection was adjusted on the basis of intensity to give roughly constant relative accuracy for the measurements. Backgrounds were counted for a total of one-half the time spent in each scan, and the scan