

References and Notes

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Antiallergenic 8-Azapurines. Structural Characterization of 9-Diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine

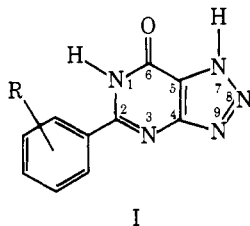
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Abstract: The crystal and molecular structure of 9-diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine, $C_{18}H_{22}N_6O_3$, a derivative of the arylazahypoxanthine series of antiallergenic drugs, has been determined from three-dimensional counter X-ray data obtained using $Cu K\alpha$ radiation. The azapurine crystallizes in the monoclinic space group $P2_1/c$ with four formula units in a cell of dimensions $a = 7.448$ (2) Å, $b = 14.818$ (8) Å, $c = 17.435$ (7) Å, and $\beta = 100.43$ (3)°. The observed and calculated densities are 1.29 (1) and 1.300 $g\ cm^{-3}$, respectively. The structure has been refined by full-matrix least-squares techniques to a final value of the conventional R factor (on F) of 0.046 using 2355 independent intensities. The 8-azapurine ring is planar, with no atom deviating from the least-squares plane by more than 0.005 Å; this plane is inclined at an angle of only 10.1° to the plane of the phenyl ring, so that the entire 2-aryl-8-azahypoxanthine ring system is nearly planar. This near coplanarity of the two ring systems apparently stems in part from the presence of a strong intramolecular hydrogen bond between N(1)-H of the azapurine and the extracyclic oxygen atom of the propoxyphenyl moiety, the N(1)---OP distance and N(1)-H---OP angle being 2.594 (2) Å and 134°, respectively. A CNDO/2 molecular orbital calculation shows that this propoxy oxygen atom is very electron rich, with a residual charge of -0.22 e; this value is exceeded only by those of the carbonyl oxygen atoms and that of N(3), -0.28 e, while the triazole nitrogen atoms N(7), N(8), and N(9) have only small residual charges of -0.06, -0.06, and -0.10 e, respectively. Hence, the present study again suggests that N(3) in 8-azapurines is relatively much more basic than in the natural purines. The molecules stack in the crystal so that the polar propoxy oxygen atom OP sits directly above the phenyl ring of the next molecule.

Introduction

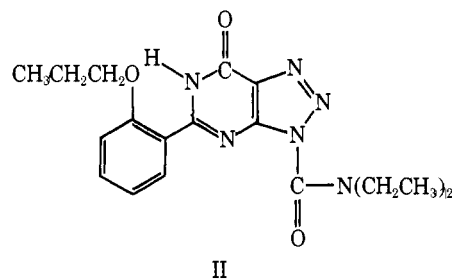
8-Azahypoxanthines have been under recent investigation as antiallergens.¹⁻⁴ In a study of a series of 2-phenyl-8-azahypoxanthines, I, the antiallergenic activity was shown to be



correlated with the size and hydrogen-bonding capacity of the ortho substituent, R, on the phenyl ring.² As a consequence of this observation, it has been suggested that potent antiallergenic activity in this series is associated with coplanarity of the phenyl ring with the azapurin-6-one portion of the molecule;² such planarity would be favored by strong intramolecular hydrogen bonding between the proton on N-1 and the ortho substituent on the phenyl ring. This idea has guided further work seeking increased potency and reduced side effects in the antiallergenic field within the 2-phenyl-8-azahypoxanthine series.

We have recently examined the molecular structures of several of these compounds to test this planarity hypothesis and to determine whether there might be other structural features

that correlate with antiallergenic activity. In this paper we report the crystal and molecular structure of 9-diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine (II), which is



moyl-2-(2-propoxyphenyl)-8-azahypoxanthine (II), which is one of a series of derivatives prepared in order to improve oral absorption in the antiallergenic azahypoxanthine series. Besides the question of the coplanarity of the phenyl group with the azapurin-6-one, we were interested in the site of attachment of the diethylcarbamoyl group. Prior to the present study, this aspect of the structure was uncertain.

As part of our studies on 9-diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine, we have also performed molecular orbital calculations aimed to assess the importance of the electronic environment on the chemical behavior of compounds within this series.

Experimental Section

X-ray Data Collection. A sample of the title compound was gen-

erously provided by Dr. K. R. H. Wooldridge. Colorless, parallelepiped-shaped crystals were obtained by slow evaporation of solvent from a solution of the compound in chloroform and *n*-heptane. On the basis of Weissenberg and precession photographs, the crystals were assigned to the monoclinic system. The observed systematic absences are $0k0$ for k odd and $h0l$ for l odd, which suggests that the space group is $P2_1/c$ ($C2_2h$). The cell constants, obtained by least-squares methods, are $a = 7.448$ (2) Å, $b = 14.818$ (8) Å, $c = 17.435$ (7) Å, and $\beta = 100.43$ (3)°. The observations were made with the wavelength assumed as $\lambda(\text{Cu } K\alpha_1) = 1.5405$ Å. A density of 1.300 g/cm³ was calculated for four molecules in the cell; the observed density was 1.29 (1) g/cm³ (floatation in aqueous ZnCl_2). Hence, no crystallographic symmetry is imposed on the molecule.

Diffraction data were collected from a crystal bounded by the $(01\bar{1})$, $(0\bar{1}1)$, (011) , $(0\bar{1}\bar{1})$, (100) , and $(\bar{1}00)$ faces. The distances between opposite pairs of faces were as follows: $(01\bar{1})$ to $(0\bar{1}1)$, 0.40 mm; (011) to $(0\bar{1}\bar{1})$, 0.62 mm; (100) to $(\bar{1}00)$, 0.81 mm. The crystal was mounted normal to the (100) face, and in this orientation intensity data were collected on a Picker four-circle automatic diffractometer using $\text{Cu } K\alpha$ 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 1.2° , formed the basis of the least-squares refinement of cell parameters and orientation using the logic documented by Busing and Levy for the PDP-8/L computer.⁵

Intensity data were collected at a takeoff angle of 1.2° ; at this angle the intensity of a typical reflection was approximately 90% of the maximum as a function of takeoff angle. The counter aperture was 5.0×5.0 mm and was positioned 32 cm from the crystal. The radiation was filtered by 0.5-mil nickel foil. The data were collected by the θ - 2θ scan technique at a scan rate of $1.0^\circ \text{ min}^{-1}$. The peaks were scanned from 0.90° in 2θ below the calculated $K\alpha_1$ peak position to 0.90° in 2θ above the calculated $K\alpha_2$ peak position. Stationary-counter, stationary-crystal background counts of 20 s were taken at each end of the scan. The pulse-height analyzer was set for approximately a 90% window, centered on the $\text{Cu } K\alpha$ peak.

A unique data set having $3^\circ \leq 2\theta \leq 120^\circ$ was collected; a total of 2954 intensities were recorded. The intensities of three standard reflections, measured after every 100 reflections, showed no appreciable decline throughout the run.

Solution and Refinement of the Structure. Data processing was carried out as described by Corfield et al.⁶ After correction for background, the intensities were assigned standard deviations according to the formula

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

where 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 for this compound for $\text{Cu } K\alpha$ radiation is 7.20 cm^{-1} ; no correction for absorption was applied. Of the 2954 data collected, 2396 were independent data greater than three times their estimated standard deviations; only these data were used in the subsequent structure analysis and refinement.

The structure was solved by direct methods using the highest 199 normalized structure amplitudes (E 's) in the program MULTAN.^{7,8} The chosen solution, which had an R_{Karle} of 22.58 and an absolute figure of merit of 1.0420, gave an E map that clearly revealed the location of all nonhydrogen positions except C(15) and C(18); these 25 positions were contained in the 47 highest peaks in the map. Isotropic least-squares refinement of these 25 positions led to values of the conventional agreement factors $R_1 = \Sigma |F_o| - |F_c| / \Sigma |F_o| = 0.318$ and $R_2 = [\Sigma w(|F_o| - |F_c|)^2 / \Sigma w F_o^2]^{1/2} = 0.423$. All least-squares refinements in this study 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_o , the atomic scattering factors for nonhydrogen atoms were from International Tables⁹ while those for hydrogen were from Stewart et al.¹⁰ After isotropic least-squares refinement on the 25 nonhydrogen atoms, a difference Fourier map clearly revealed the locations of C(15) and C(18) as the two highest peaks of the map. At this stage of the refinement, 41 reflections with counts greater than 1×10^6 , which were judged to have flooded the counter, were excluded. Hence, 2355 data were used in the subsequent structure refinement. Isotropic least-squares refinement on the 27 nonhydrogen atoms gave $R_1 = 0.195$ and $R_2 = 0.280$. Subsequent anisotropic least-squares refinement on these atoms gave $R_1 = 0.097$

Table I. Positional Parameters for 9-Diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine

atom	x	y	z
N(1)	-0.2911 (2)	0.3329 (1)	0.4662 (1)
C(2)	-0.3451 (3)	0.4123 (1)	0.4292 (1)
N(3)	-0.4436 (2)	0.4156 (1)	0.3584 (1)
C(4)	-0.4834 (3)	0.3323 (1)	0.3281 (1)
C(5)	-0.4346 (3)	0.2492 (1)	0.3605 (1)
C(6)	-0.3272 (3)	0.2452 (1)	0.4375 (1)
O(6)	-0.2688 (3)	0.1794 (1)	0.4764 (1)
N(7)	-0.5027 (3)	0.1826 (1)	0.3091 (1)
N(8)	-0.5921 (3)	0.2209 (1)	0.2461 (1)
N(9)	-0.5813 (2)	0.3130 (1)	0.2563 (1)
C1P	-0.2871 (2)	0.4987 (1)	0.4694 (1)
C2P	-0.2031 (3)	0.5060 (1)	0.5484 (1)
C3P	-0.1516 (3)	0.5898 (1)	0.5804 (1)
C4P	-0.1842 (3)	0.6671 (1)	0.5356 (1)
C5P	-0.2658 (3)	0.6612 (1)	0.4577 (1)
C6P	-0.3170 (3)	0.5782 (1)	0.4253 (1)
OP	-0.1769 (2)	0.4281 (1)	0.5903 (1)
C(10)	-0.1021 (3)	0.4297 (1)	0.6726 (1)
C(11)	-0.1034 (4)	0.3339 (2)	0.7009 (1)
C(12)	-0.0312 (4)	0.3254 (2)	0.7868 (1)
C(13)	-0.6902 (3)	0.3732 (1)	0.2004 (1)
O(13)	-0.8450 (2)	0.3884 (1)	0.2085 (1)
N(14)	-0.6057 (2)	0.4049 (1)	0.1457 (1)
C(15)	-0.7057 (4)	0.4680 (2)	0.0882 (1)
C(16)	-0.7854 (5)	0.4226 (2)	0.0138 (2)
C(17)	-0.4138 (4)	0.3850 (2)	0.1401 (2)
C(18)	-0.2853 (4)	0.4555 (2)	0.1802 (2)
H(1) ^a	-0.217	0.338	0.515
H3P	-0.096	0.597	0.638
H4P	-0.141	0.730	0.559
H5P	-0.286	0.717	0.421
H6P	-0.383	0.573	0.371
H10A	-0.183	0.470	0.699
H10B	0.025	0.457	0.682
H11A	-0.236	0.318	0.688
H11B	-0.032	0.294	0.666
H12A	0.101	0.355	0.806
H12B	-0.048	0.264	0.804
H12C	-0.097	0.362	0.818
H15A	-0.784	0.507	0.114
H15B	-0.634	0.504	0.082
H16A	-0.851	0.457	-0.023
H16B	-0.875	0.390	0.020
H16C	-0.694	0.398	-0.012
H17A	-0.389	0.324	0.160
H17B	-0.415	0.386	0.078
H18A	-0.145	0.445	0.169
H18B	-0.313	0.522	0.161
H18C	-0.277	0.450	0.237

^a Hydrogen atom parameters were not varied.

and $R_2 = 0.169$. The hydrogen atoms were then located in a difference Fourier map. The positions for the hydrogen atoms were not varied in subsequent refinement. Least-squares refinement in which the isotropic thermal parameters of the hydrogen atoms were refined while the nonhydrogen atoms were refined anisotropically gave final values of $R_1 = 0.046$ and $R_2 = 0.070$. In the final cycle of least-squares refinement, no parameter experienced a shift of more than 0.06σ , which is taken as evidence of convergence. A final difference Fourier map was featureless, with no peak higher than $0.31 \text{ e } \text{Å}^{-3}$. The atomic positions, along with their standard deviations as estimated from the inverse matrix, are listed in Table I. A compilation of observed and calculated structure amplitudes and the atomic thermal parameters are available as supplementary material.

Molecular Orbital Calculations. The MO calculations were performed by the CNDO/2 self-consistent field method.¹¹ The calculations utilized the Quantum Chemistry Exchange Program No. 141 (University of Indiana, Bloomington, Ind.) as modified locally by Professor L. G. Pedersen. The molecular geometry of 9-diethylcarbamoyl-(2-propoxyphenyl)-8-azahypoxanthine was taken from the

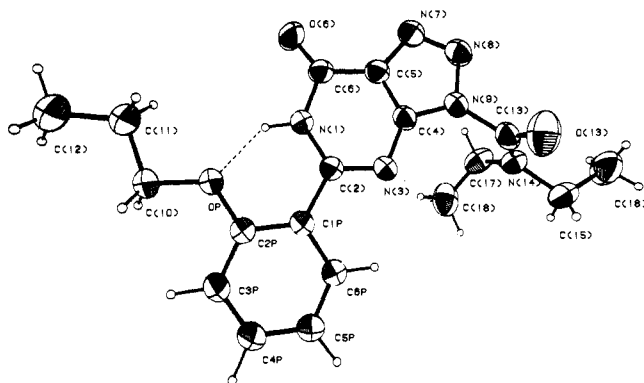


Figure 1. View of a single molecule of 9-diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine. Hydrogen atoms are shown as open circles of arbitrary size; other thermal ellipsoids are drawn at the 50% probability level.

Table II. Intramolecular Distances (Å)

atoms	distance	atoms	distance
N(1)-C(2)	1.367 (2)	C(10)-C(11)	1.503 (3)
N(1)-C(6)	1.401 (2)	C(10)-H10A	1.02
N(1)-H(1) ^a	0.93	C(10)-H10B	1.02
C(2)-N(3)	1.317 (2)	C(11)-C(12)	1.504 (3)
C(2)-C1P	1.485 (2)	C(11)-H11A	1.00
N(3)-C(4)	1.355 (2)	C(11)-H11B	1.06
C(4)-C(5)	1.376 (3)	C(12)-H12A	1.07
C(4)-N(9)	1.359 (2)	C(12)-H12B	0.97
C(5)-C(6)	1.434 (3)	C(12)-H12C	0.97
C(5)-N(7)	1.368 (2)	C(13)-O(13)	1.207 (3)
C(6)-O(6)	1.221 (2)	C(13)-N(14)	1.321 (3)
N(7)-N(8)	1.306 (2)	N(14)-C(15)	1.471 (3)
N(8)-N(9)	1.376 (2)	N(14)-C(17)	1.480 (3)
N(9)-C(13)	1.455 (3)	C(15)-C(16)	1.486 (4)
C1P-C2P	1.410 (3)	C(15)-H15A	0.98
C1P-C6P	1.403 (3)	C(15)-H15B	0.78
C2P-C3P	1.388 (3)	C(16)-H16A	0.90
C2P-OP	1.360 (2)	C(16)-H16B	0.85
C3P-C4P	1.383 (3)	C(16)-H16C	0.95
C3P-H3P	1.02	C(17)-C(18)	1.501 (4)
C4P-C5P	1.386 (3)	C(17)-H17A	0.97
C4P-H4P	1.04	C(17)-H17B	1.07
C5P-C6P	1.378 (3)	C(18)-H18A	1.11
C5P-H5P	1.04	C(18)-H18B	1.05
C6P-H6P	0.98	C(18)-H18C	0.99
OP-C(10)	1.443 (2)	OP...H(1)	1.86
		N(1)...OP	2.594 (2)

^a No esd is given for distances involving hydrogen atoms since these atoms were not varied in the least-squares procedure.

X-ray diffraction results described in this paper. The molecule was modified in order to fit the 38-atom, 99-orbital dimensions of the program. The propoxy group was replaced with a methoxy group; in so doing, a hydrogen atom was placed in a calculated position based on the position of the displaced central carbon, C(11), of the propoxy moiety. Similarly, the two N-bound ethyl groups of the molecule were replaced by hydrogen atoms. All C-H, N-H, and O-H bond lengths in the molecule were then changed to 1.08, 1.01, and 0.97 Å, respectively, keeping their bond directions the same as those observed in the X-ray work. The total electronic energy in the modified molecule was taken as having converged when successive calculations differed by less than 7.5×10^{-6} au (5 cal/mol). More drastic modification of the title compound, achieved by replacing N(14) and C(10) with hydrogen atoms, was used to determine the effects of truncating the molecule on the MO result. In that calculation electronic energy was assumed to have converged when successive calculations differed by less than 5.0×10^{-6} au (3 cal/mol).

The electronic charge density on each atom is defined as the number of valence-shell electrons for that atom minus the net charge on the atom calculated using the CNDO/2 approximation. As expected,

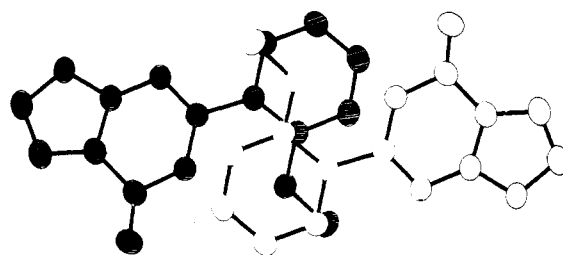


Figure 2. The stacking interactions in 9-diethylcarbamoyl-2-(2-propoxyphenyl)-8-azahypoxanthine, showing only the overlapping portions of the molecules.

Table III. Selected Bond Angles (deg)

atoms	angle	atoms	angle
C(2)-N(1)-C(6)	127.5 (2)	C(2)-C1P-C6P	117.5 (2)
C(2)-N(1)-H(1)	116	C2P-C1P-C6P	118.0 (2)
C(6)-N(1)-H(1)	116	C1P-C2P-C3P	120.2 (2)
N(1)-C(2)-N(3)	122.7 (2)	C1P-C2P-OP	117.0 (2)
N(1)-C(2)-C1P	118.9 (2)	C3P-C2P-OP	122.8 (2)
N(3)-C(2)-C1P	118.4 (2)	C2P-C3P-C4P	120.5 (2)
C(2)-N(3)-C(4)	112.1 (2)	C3P-C4P-C5P	120.1 (2)
N(3)-C(4)-C(5)	129.2 (2)	C4P-C5P-C6P	119.8 (2)
N(3)-C(4)-N(9)	126.5 (2)	C5P-C6P-C1P	121.4 (2)
C(5)-C(4)-N(9)	104.3 (2)	C2P-OP-C(10)	120.8 (2)
C(4)-C(5)-C(6)	118.9 (2)	OP-C(10)-C(11)	106.6 (2)
C(4)-C(5)-N(7)	109.7 (2)	C(10)-C(11)-C(12)	112.5 (2)
C(6)-C(5)-N(7)	131.4 (2)	N(9)-C(13)-O(13)	117.7 (2)
N(1)-C(6)-C(5)	109.5 (2)	N(9)-C(13)-N(14)	114.9 (2)
N(1)-C(6)-O(6)	121.0 (2)	O(13)-C(13)-N(14)	127.4 (2)
C(5)-C(6)-O(6)	129.4 (2)	C(13)-N(14)-C(15)	118.0 (2)
C(5)-N(7)-N(8)	108.0 (2)	C(13)-N(14)-C(17)	124.7 (2)
N(7)-N(8)-N(9)	108.3 (2)	C(17)-N(14)-C(15)	117.2 (2)
C(4)-N(9)-N(8)	109.7 (2)	N(14)-C(15)-C(16)	112.4 (2)
N(8)-N(9)-C(13)	128.9 (2)	N(14)-C(17)-C(18)	111.9 (2)
C(2)-C1P-C2P	124.5 (2)	N(1)-H(1)...OP	134

^a No esd is given for angles involving hydrogen atoms since these atoms were not varied in the least-squares procedure.

replacement of C(10) with a hydrogen atom made a small change in charge density at OP (from -0.22 e to -0.26 e) while replacement of N(14) with a hydrogen atom produced small changes at C(13) (from $+0.45$ e to $+0.32$ e), O(13) (from -0.35 e to -0.22 e), and N(9) (from -0.10 e to -0.08 e). Charge densities at the other atoms in the structure were unaffected by this truncation.

Results and Discussion

The molecular structure of the title compound is shown in Figure 1. The diethylcarbamoyl group is clearly attached to N(9). The bond distances are listed in Table II, the bond angles in Table III. Figure 2 shows how the closest planes, related via an inversion center, are arranged relative to one another.

The Azapurine. The intramolecular bond lengths in the six-membered heterocyclic portion of the molecule agree very closely with those reported by Ringertz for a variety of 9-substituted purines.¹² The C(5)-C(6) distance in the present compound is slightly longer (1.434 Å) than the corresponding distances in 7-methyl-8-azadenine (1.423 Å)¹³ and 8-azadenosine (1.421 Å);¹⁴ however, the value agrees quite well with that for 8-azaguanine (1.430 Å).¹⁵ The N(1)-C(6) bond length (1.401 Å) is also slightly longer than the average for substituted guanines (1.393 Å)¹² and 8-azaguanine (1.385 Å). Paralleling the apparent small decrease in the bond order of the C(5)-C(6) and N(1)-C(6) bonds in the title compound compared to 9-substituted guanines is an apparent increase in the bond order of the exocyclic carbonyl, C(6)-O(6). In the title compound this distance is 1.221 Å, while the average value for the 9-substituted guanines reported by Ringertz is 1.234

Å¹² and the value in 8-azaguanine is 1.224 Å.¹⁵

The bond lengths in the five-member triazole ring agree very closely with those reported for 8-azaadenosine¹⁴ and 8-azaguanine,¹⁵ which like the title compound have exocyclic atoms attached to N(9). The ranges of bond lengths for these three compounds are as follows: C(5)-N(7), 1.361–1.368 Å; N(7)-N(8), 1.293–1.306 Å; N(8)-N(9), 1.359–1.380 Å; N(9)-C(4), 1.350–1.359 Å; and C(4)-C(5), 1.376–1.386 Å. The widest range is found for the formally single N(8)-N(9) bond; this length is shortest for 8-azaguanine, which has a proton on N(9) while the other two compounds have a carbon atom at the 9 position (1.376–1.380 Å). By way of further comparison, the formally single N(7)-N(8) bond in 7-methyl-8-azaadenine has a bond length of 1.346 Å,¹³ the formally double N(8)-N(9) in this latter compound is 1.306 Å, in excellent agreement with the N(7)-N(8) distance in the title compound.

The bond angles in the azapurine correspond well to the suggestions of Ringertz¹² and of Singh,¹⁶ who have noted that the internal angles in the purine ring are dependent on the nature of the exocyclic substituent atoms. For example, based on Ringertz's tabulations of earlier purine structures, we would expect that replacement of the exocyclic NH₂ group on C(2) in guanine with a sp²-hybridized carbon atom, as in the title compound, should produce a small decrease in the N(1)-C(2)-N(3) bond angle. This conclusion follows Ringertz's observation that an increase in the double-bond character of the exocyclic bond decreases the angle within the ring at the site of the attachment of the exocyclic atom. The average value of this angle in guanine and 9-substituted guanines is 123.7°,¹² while 123.2° is reported for 8-azaguanine.¹⁵ The angle in the title compound is 122.7°. However, the N(1)-C(6)-C(5) bond angle in the title compound (109.5°) is smaller than those in guanine and 9-substituted guanine derivatives (111.4) and in 8-azaguanine (110.7°). Corresponding to this decrease there is an increase in the angle at N(1) (127.5°) compared to the guanines (125.2°) and 8-azaguanine (126.2°).

The bond angles in the five-member triazole ring also reflect the point of attachment of the exocyclic group and compare favorably with the corresponding angles in analogous compounds. For example, none of the angles in the title compound differs by more than 0.7° from those reported for 8-azaguanine,¹⁵ and all angles were well within the ranges tabulated by Purnell and Hodgson for 8-azapurines.¹⁷

Of greater interest is the effect of extraannular attachment at N(9) on the exocyclic bond angles. It has been pointed out by Singh and Hodgson¹⁴ that the exocyclic angles around N(9) in 8-azaadenosine are distorted relative to those in adenosine and in 9-alkylpurines. In 9-alkylpurines the "inside" exocyclic angle (toward the six-member ring of the purine) is an average of 2.5° smaller than the "outside" exocyclic angle. In adenosine, the inside angle is 124.3° while the outside angle is 130.0°. In contrast, these angles are 128.4 and 121.8°, respectively, in 8-azaadenosine.¹⁴ In the present compound the inside angle, C(4)-N(9)-C(13), is 128.9° while the outside angle, N(8)-N(9)-C(13), is 120.6°. These angles not only agree with those in 8-azaadenosine, but also with the attachment of the proton at N(9) in 8-azaguanine, the only other 8-azapurine structure we know of with a substituent at N(9). In 8-azaguanine the inside angle is 128.2° while the outside angle is 121.5°. Thus replacement of the 8-position methine group of a purine with a nitrogen atom seems to generally decrease the "outer" exocyclic bond angle at N(9). In the case of 8-azaadenosine, this change in angle has been shown to cause a reduction in the barrier to rotation around the glycosyl bond.¹⁴

As shown in Table IV, the 8-azapurine portion of the molecule is planar, no atom deviating from the least-squares plane through the nine atoms by more than 0.005 Å. The exocyclic O(6) and C1P atoms are 0.013 and 0.041 Å above the plane,

Table IV. Deviations (Å) from Least-Squares Planes^a

atoms	plane 1	atoms	plane 2	atoms	plane 3
N(1)*	-0.001	N(1)*	-0.027	N(9)*	0.000
C(2)*	0.003	C(2)*	-0.091	C(13)*	-0.001
N(3)*	0.001	C1P*	0.055	O(13)*	0.001
C(4)*	-0.005	C2P*	0.052	N(14)*	0.000
C(5)*	-0.002	OP*	-0.120	C(15)	-0.034
C(6)*	0.001	H(1)*	0.131	C(17)	-0.030
N(7)*	0.003	C(6)	-0.105		
N(8)*	-0.001	N(3)	-0.250		
N(9)*	0.002	C3P	0.214		
O(6)	0.013	C6P	0.218		
C1P	0.041	C(10)	-0.218		
OP	-0.375				
C(13)	-0.197				

^a An asterisk indicates atom included in the calculation of the least-squares plane.

respectively, while the exocyclic atom C(13) is 0.197 Å below the plane.

Other Aspects of the Structure. The bond lengths within the phenyl ring range from 1.378 to 1.410 Å (for C5P-C6P and C1P-C2P, respectively), and they average 1.391 Å. The angles range from 118.0° (at C1P) to 121.4° (at C6P) and average 120.0°. The six atoms deviate a maximum of 0.005 Å from the least-squares plane through the phenyl ring. The exocyclic OP and C(2) atoms lie 0.015 Å below and 0.012 Å above the plane, respectively. The C(10), C(11), and C(12) atoms lie roughly in this same plane, being situated 0.099, 0.180, and 0.295 Å, respectively, below the plane of the phenyl ring.

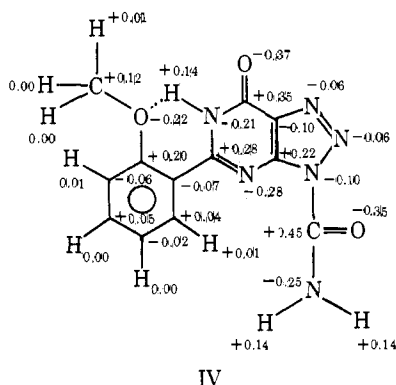
While the phenyl and azapurine rings are not entirely coplanar, the interplanar angle between these two moieties is only 10.1°. This close approach to coplanarity is attributable to the presence in the structure of a strong intramolecular hydrogen bond of 2.594 (2) Å between the purine atom N(1) and the exocyclic phenyl oxygen atom OP. The associated H(1)...OP distance and N(1)-H(1)...OP angle are 1.86 Å and 134°, respectively. These values are consistent with those reported by other workers for N-H...O hydrogen bonds.¹⁸ The deviations from planarity for the atoms in the six-membered ring containing the hydrogen bond (i.e., N(1), H(1), C(2), C1P, C2P, and OP) are documented in Table IV (plane 2). Thus, while the present structural analysis cannot assess the biological significance of the presence of such a hydrogen bond, it does demonstrate that this intramolecular hydrogen bonding is available to the system.

The C(13), O(13), and N(13) atoms sit nearly perpendicular to the purine ring; the least-squares plane through these atoms and N(9) makes an angle of 89.52° with the least-squares plane through the purine. As shown in Table IV (plane 3), the C(15) and C(17) atoms are nearly in the plane of C(13), O(13), and N(13), being situated 0.034 and 0.030 Å, respectively, below the plane. The C(13)-O(13) and C(13)-N(14) distances (1.207 and 1.321 Å, respectively) agree well with the average values for corresponding distances in polypeptides, 1.23 and 1.325 Å.¹⁹ Other intramolecular bond lengths and bond angles within the compound are normal.

The closest intermolecular approach between molecules is between molecules related by a center of inversion. These molecules sit above one another as shown in Figure 2 with the least-squares planes through the azapurine rings situated 3.45 Å apart. Stacking of purine and pyrimidine molecules in crystals is common.²⁰ The molecules usually stack in such a way that the polar regions of one molecule overlap with the polarizable ring system of an adjacent base. Thus the base stacking appears to be largely governed by polarization forces. The present substance fits this general pattern, but does not correspond to any of the stacking patterns summarized by Bugg.²⁰

Instead, the molecules stack so as to place the polar oxygen OP above the phenyl ring, so there are no base stacking interactions in the crystal. The distance from OP to the least-squares plane through the phenyl ring is 3.66 Å. This particular arrangement might be forced on the system by the packing demands of the large exocyclic substitutions at C(2) and N(9), since OP is not the most polar portion of the molecule (see IV, below).

Electronic Charge Density. The net atomic charge densities, as calculated by the CNDO/2 method,¹¹ are shown below, IV, for a truncated version of the title compound. The calculation indicates that the most electron-rich site in the azapurine ring



IV

is at N(3), -0.28 e. This charge density is very similar to those found in 8-azaadenosine¹⁴ (-0.26 e), 7-methyl-8-azaadenine¹³ (0.23 e) and 9-methyladenine²¹ (-0.24 e). The electron density at N(9) in IV, -0.10 e, is close to that in 8-azaadenosine, -0.08 e, and is lower than that in 7-methyl-8-azaadenine, -0.16 e. Thus carbon substitution at N(9) reduces the electron density of this atom as expected. However, the electron density at N(9) remains higher than at N(7) and N(8). For the three compounds we have compared in the preceding sentences, electron density at N(7) ranges from 0.00 to -0.08 e, while at N(8) it ranges from -0.01 to -0.06 e. Singh and Hodgson¹⁴ have pointed out that substitution of a nitrogen for the methine group in the 8 position of a purine leaves the N(7) and N(9) with considerably less negative charge than in the unsubstituted case, which is consistent with the present observations. Moreover, the enhanced electron density at N(3) relative to that at the triazole nitrogen atoms provides further evidence for our contention²² that N(3) is relatively more basic in the 8-azapurines than in the purines, and helps to explain why protonation at N(3) is frequently observed in 8-azapurine cations.²²⁻²⁴

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Supplementary Material Available: A listing of observed and calculated structure amplitudes and a table of atomic thermal parameters (15 pages). Ordering information is given on any current masthead page.

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