testing ET theories.

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Antiallergenic 8-Azapurines. 3. Structural Characterization of 2-(2-Propoxyphenyl)-8-azahypoxanthine, 2-(2-Propoxy-5-(propylsulfonyl)phenyl)-8-azahypoxanthine, and 2-(2-Propoxy-5-(*N*-methyl-*N*-isopropylsulfamoyl)phenyl-8-azahypoxanthine

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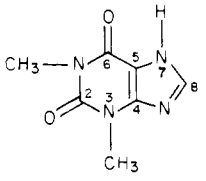
Contribution from the Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514, and the Research Laboratories, May & Baker Ltd., Dagenham, Essex, England. *Received May 26, 1981. Revised Manuscript Received August 11, 1981*

Abstract: The crystal and molecular structures of 2-(2-propoxyphenyl)-8-azahypoxanthine, $C_{13}H_{13}N_5O_2$, 2-(2-propoxy-5-(propylsulfonyl)phenyl)-8-azahypoxanthine methanolate, $C_{16}H_{19}N_5O_4S{\cdot}CH_4O$, and 2-(2-propoxy-5-(*N*-methyl-*N*-isopropylsulfamoyl)phenyl)-8-azahypoxanthine, $C_{17}H_{22}N_6O_4S$, have been determined from three-dimensional counter X-ray data using Mo Kα radiation. The 2-propoxyphenyl compound crystallizes in the orthorhombic space group *Pnma* with four molecules in a cell of dimensions a = 9.293 (2) Å, b = 6.671 (2) Å, c = 21.020 (7) Å; the structure has been refined to a final value of the conventional R factor (on F) of 0.043 based on 1029 independent intensities. The propylsulfonyl derivative, which crystallizes with 1 mol of methanol/mol of purine in the monoclinic space group $P2_1/c$ with four molecules in a cell of dimensions a = 12.521 (15) Å, b = 5.816 (8) Å, c = 28.388 (40) Å, β = 108.21 (5)°, has been refined to an R factor of 0.105 based on 918 observations. The *N*-methyl-*N*-isopropylsulfamoyl derivative also crystallizes in space group $P2_1/c$ with four molecules in a cell of dimensions a = 12.129 (8) Å, b = 10.680 (9) Å, c = 16.958 (11) Å, β = 116.74 (4)° and has been refined to an R factor of 0.050 based on 1771 observations. In the 2-propoxyphenyl and propylsulfonyl derivatives, the entire ring systems are held approximately planar (exactly planar in the former case) by a strong N(1)–H···O(2) intramolecular hydrogen bond, where O(2) is the oxygen atom of the propoxy group. In the *N*-methyl-*N*-isopropylsulfamoyl derivative, the purine and phenyl rings are inclined at an angle of 52.6°. The 2-propoxy and *N*-methyl-*N*-isopropylsulfamoyl derivatives are present as the N(9)-H tautomers, but the propylsulfonyl compound exhibits the N(8)-H tautomer. CNDO/2 molecular orbital calculations show that, in all three cases, atom N(3) is very electron rich while the triazole atoms have smaller residual charges.

As a result of the discovery that common methylxanthines such as theophylline (I) and caffeine (II) show certain antiallergic



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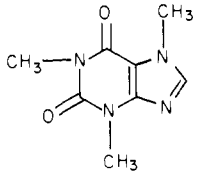

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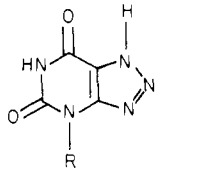

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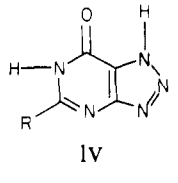

IV

properties,[2] efforts are being made to determine the structural basis for the biochemical properties of these compounds in order to facilitate the production of more potent antiallergic drugs.[3,4] Substitution of a nitrogen atom for the carbon atom in the 8-position of the imidazole ring to yield 8-azaxanthines (III) has been shown to consistently increase the potency of the drugs with respect to their xanthine analogues;[5] this observation is especially true with bulky substituents at the 3-position of the pyrimidine ring. Numerous 8-azahypoxanthines with exocylic substituents at the 2-position of the pyrimidine ring (IV) were examined,[3-5] and the compounds with the most potent antiallergic properties were found to be those with ortho-substituted phenyl groups at C(2). It has been postulated that activity of the drugs is increased when the 2-substituent contains a group that is capable of forming a hydrogen bond to the N(1)–H group of the purine ring.[3,4] In order to test this hypothesis, we have undertaken the X-ray crystallographic investigation of three compounds of type IV, 2-(2-propoxyphenyl)-8-azahypoxanthine (V), 2-(2-propoxy-5-(propylsulfonyl)phenyl)-8-azahypoxanthine (VI), and 2-(2-propoxy-5-(*N*-methyl-*N*-isopropylsulfamoyl)phenyl)-8-azahypoxanthine (VII), all of which show marked antiallergenic activity.[4] We also anticipated that this study would provide us with additional information on the relative basicities of the nitrogen atoms

(1) (a) University of North Carolina. (b) May & Baker, Ltd.
(2) Orange, R. P.; Kaliner, M. A.; Laraia, P. J.; Austen, K. F. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1971**, *30*, 1725.
(3) Holland, A.; Jackson, D. S.; Chaplen, P.; Lunt, E.; Marshall, S. M.; Pain, D. L.; Wooldridge, K. R. H. *Eur. J. Med. Chem.* **1975**, *10*, 447.
(4) Broughton, B. J.; Chaplen, P.; Knowles, P.; Lunt, E.; Marshall, S. M.; Pain, D. L.; Wooldridge, K. R. H. *J. Med. Chem.* **1975**, *18*, 1117.
(5) Coulson, C. J.; Ford, R. E.; Lunt, E.; Marshall, S.; Pain, D. L.; Rogers, I. H.; Wooldridge, K. R. H. *Eur. J. Med. Chem.* **1974**, *9*, 313.

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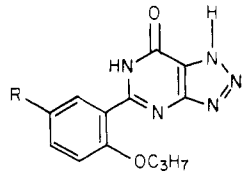


V, R = H
VI, R = $SO_2C_3H_7$
VII, R = $SO_2N(CH_3)(i\text{-}C_3H_7)$

in the 8-azapurine ring, a topic which has been of concern to these laboratories in recent years.[6] Consequently, molecular orbital calculations were performed on these three molecules in order to gain information concerning the relative basicities of the nitrogen atoms in the 8-azapurine ring.

Experimental Section

X-ray Data Collection. (a) 2-(2-Propoxyphenyl)-8-azahypoxanthine. A powdered sample of the compound was recrystallized from hot methanol. The colorless hexagonal prisms were examined by precession and Weissenberg photography, which revealed that they belong to the orthorhombic system; the observed systematic absences of $0kl$ for $k + l$ odd and $hk0$ for h odd suggest that the space group is either D_{2h}^{16}—*Pnma* or C_{2v}^{9}—$Pn2_1a$. Successful refinement was taken as proof that the centrosymmetric choice of *Pnma* was correct. Intensity statistics also suggested a centric distribution, but this indication is not expected to be reliable in the present case of a planar molecule lying on a mirror (or *pseudo-mirror*) plane. The cell constants, obtained by least-squares procedures, are a = 9.293 (2) Å, b = 6.671 (2) Å, and c = 21.020 (7) Å. Observations were made at ambient temperature by using Mo $K\alpha_1$ with an assumed wavelength of 0.7093 Å. The observed density of 1.37 g cm^{-3} was in good agreement with the calculated value of 1.383 g cm^{-3} assuming four molecules per unit cell. This imposes no restriction if the space group is $Pn2_1a$, but if *Pnma* is the correct choice, the entire molecule is constrained to lie on the crystallogrphic mirror plane in order for there to be four formula units per cell.

Diffraction data were collected on a hexagonal prismatic crystal mounted roughly parallel to the crystallographic b axis. Intensity data were collected on a Picker four-circle automatic diffractometer equipped with a graphite monochromator and using Mo $K\alpha$ radiation. Data were collected in the $\theta/2\theta$ scan mode from 0.9° below the calculated Mo $K\alpha_1$ position to 0.9° above the calculated Mo $K\alpha_2$ position at a rate of 1°/min with stationary-counter stationary-crystal background counts of 20 s duration at both ends of the scan. A unique data set having $3° < 2\theta < 53°$ was collected; a total of 1442 independent intensities were recorded. The three standard reflections which were monitored at intervals of 100 reflections showed no systematic decline as a function of exposure time. The data were processed by using the formula of Ibers and co-workers[7] for the estimated standard deviation

$$\sigma(I) = [C + 0.25(ts/tb)^2(B_H + B_L) + p^2I^2]^{1/2}$$

The value of p was assigned as 0.045.[8] The values of I and σ(I) were corrected for Lorentz-polarization effects.[9] The linear absorption coefficient for this compound using Mo $K\alpha$ radition was 0.919 cm^{-1} and no correction for absorption was made. Of the 1442 measured intensities, 1029 were greater than three times their estimated standard deviations, and only these were used in the subsequent structure analysis and refinement.

(b) 2-(2-Propoxy-5-(propoxysulfonyl)phenyl)-8-azahypoxanthine. Colorless, rectangular needle-shaped crystals were grown by the evaporation of a methanol solution. The crystals were assigned to the monoclinic system on the basis of X-ray photographic investigation, the observed systematic absences of l odd for $(h0l)$ and k odd for $(0k0)$ reflections being consistent only with the space grup $P2_1/c$ (C_{2h}^5, No. 14). The cell constants, obtained by least-squares methods from the diffractometer angular settings of 12 reflections, are a = 12.521 (15) Å, b = 5.816 (8) Å, c = 28.388 (40) Å, and β = 108.21 (5)°. The crystals showed a marked tendency to decompose in all solvents used for density determination, presumably because of the presence of solvated methanol in the lattice (vide infra). Consequently, we were unable to determine the density of the crystals, but the value of 1.385 g cm^{-3} calculated on the basis of four molecules per cell (including one molecule of methanol per molecule of azapurine) is similar to the value of 1.383 g cm^{-3} calculated above for the related molecule 2-(2-propoxyphenyl)-8-azahypoxanthine. Hence, in space group $P2_1/c$ no symmetry is imposed on the molecules.

Intensity data were collected from a crystal bounded by the faces {100}, {010}, and {001}, the crystal dimensions being 0.05 × 1.32 × 0.15 mm in the a^*, b^*, and c^* directions, respectively. The crystal chosen, like all others examined previously, was of very poor quality, virtually all peaks examined showing two peaks in the ω scan, but it was determined that even from a crystal of this quality the salient features of the structure should be obtainable. The crystal was mounted approximately parallel to the b (needle) axis, and intensity data were collected as described above.

A data set having 2θ(Mo) ≤ 45° was collected; at values of 2θ(Mo) ≥ 45° very few data were observable. A total of 3067 data (including space group extinct data and standards) were gathered, of which only 918 were independent data with $I > 3\sigma(I)$; only these latter data were used in the subsequent structural analysis. The intensities of three standard reflections, monitored after every 100 reflections, showed pronounced decline as a function of X-ray exposure time such that at the end of the data set a typical standard reflection had only 54% of its original intensity. The data were corrected for this decline by the application of an isotropic correction which was assumed to be linear with accumulated exposure time. Absorption effects (μ = 1.94 cm^{-1}) were again neglected.

(c) 2-(2-Propoxy-5-(*N*-methyl-*N*-isopropylsulfamoyl)phenyl)-8-azahypoxanthine. Hexagonal plate-shaped crystals were obtained from a hot methanol solution of the compound. X-ray photographic examination showed that they belong to the monoclinic system, the observed systematic absences being consistent only with space group $P2_1/c$ (C_{2h}^5, No. 14). The cell constants, obtained as above, are a = 12.129 (8) Å, b = 10.680 (9) Å, c = 16.958 (11) Å, and β = 116.74 (4)°. The observed density of 1.38 g cm^{-3} is in good agreement with the value of 1.377 g cm^{-3} calculated for four molecules in the cell. Hence, no symmetry is imposed on the molecules.

Data were collected as described above with $2 \le 2\theta \le 50°$. A total of 2729 data were gathered, of which 1771 were independent data with $I > 3\sigma(I)$; only these data were used in the refinement. Absorption effects (μ = 1.92 cm^{-1}) were neglected.

Solution and Refinement of the Structures. All least-squares refinements in these analyses were carried out on F, the function minimized being $\sum w(|F_o| - |F_c|)^2$ where the weights w were assigned as $4F_o^2/\sigma^2(I)$. In all calculations of F_c the atomic scattering factors for nonhydrogen atoms were from ref 10 and those for hydrogen were from Stewart, Davidson, and Simpson.[11] The effects of the anomalous dispersion of sulfur were included in the calculation of F_c for compounds VI and VII, the values of $\Delta f'$ and $\Delta f''$ being taken from ref 10.

(a) 2-(2-Propoxy)-8-azahypoxanthine. The structure was solved by direct methods[12] using the multiple solution program MULTAN.[13] Isotropic least-squares refinement of the positions of all 20 nonhydrogen atoms as obtained from an E map yielded values for the conventional agreement factors of $R_1 = \sum||F_o| - |F_c||/\sum|F_o| = 0.168$ and $R_2 = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2} = 0.221$.

Subsequent anisotropic refinement of the same 20 atoms yielded R_1 = 0.099 and R_2 = 0.132. The positions of all hydrogen atoms except one methyl hydrogen atom were then located in a difference Fourier map; the position of the missing atom was calculated by assuming tetrahedral angles about carbon and an H-C bond length of 0.95 Å.[14] Least-squares refinement in which these hydrogen atom positions were varied isotropically and the nonhydrogen atoms were varied anisotropically led to final values of R_1 = 0.043 and R_2 = 0.056. No correction for secondary extinction was necessary.

Two unsuccessful attempts were made to refine the structure in the noncentrosymmetric space group $Pn2_1a$, one including all atoms and one including nonhydrogen atoms only; this confirmed that the centrosymmetric space group was correct. In the final cycle of least-squares refinement, the ratio of data to variables was 6.68:1 and no atom parameter changed more than 0.52 times its estimated standard deviation, indicating that refinement had converged. The final difference Fourier contained

(6) Hodgson, D. J.; Singh, P. In "Environmental Effects on Molecular Structure"; Pullman, B., Ed.; D. Reidel Publishing Co.: Dordrecht, Holland, 1976.
(7) Corfield, P. W. R.; Doedens, R. J.; Ibers, J. A. *Inorg. Chem.* **1967**, *6*, 197.
(8) Busing, W. R.; Levy, H. A. *J. Chem. Phys.* **1967**, *26*, 563.
(9) Goldfield, S. A.; Raymond, K. N. *Inorg. Chem.* **1971**, *10*, 2604.
(10) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, England, 1974; Vol. IV.
(11) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.
(12) Hauptman, H.; Karle, J. "American Crystallographic Association", Monograph No. 3, 1953.
(13) Main, P.; Woolfson, M. M.; Germain, G. "MULTAN: A Computer Program for Automatic Solution of Crystal Structures", Department of Physics, University of York, York, England.
(14) Churchill, M. R. *Inorg. Chem.* **1973**, *12*, 1213.

no peak higher than 0.197 e A^{-3}. The positional and thermal parameters for 2-(2-propoxy)-8-azahypoxanthine and a table of observed and calculated structure amplitudes are available as supplementary material.

(b) 2-(2-Propoxy-5-propylsulfonylphenyl)-8-azahypoxanthine. The structure was solved as described above. Isotropic refinement of the nonhydrogen atoms (including the C and O atoms of the methanol molecule) yielded values of R_1 and R_2 of 0.175 and 0.180, respectively. Anisotropic refinement of these atoms lowered the values of R_1 and R_2 to 0.116 and 0.131, respectively. The positions of all hydrogen atoms except that of the methanol alcoholic hydrogen atom were located in two subsequent difference Fourier summations. The positions of all hydrogen atoms which could be calculated on the basis of anticipated geometries at C or N atoms were constrained to these calculated values, based on C-H and N-H distances of 0.95 and 0.90Å, respectively,[14] and tetrahedral or trigonal geometry as appropriate. No attempt was made to refine any hydrogen atom parameter, but hydrogen atoms were included as contributors to F_c with isotropic thermal parameters assigned as 1.5 $Å^2$ greater than the isotropic thermal parameter of the C or N atom to which they were attached. The final least-squares calculation involved anisotropic refinement of the 28 nonhydrogen atoms with 918 observations 253 variables; no parameter shifted by more than 0.02σ, which is taken as evidence of convergence. The anisotropic thermal parameters of atoms C(2) and C(6) converged to values which are insignificantly nonpositive definite. The final values of R_1 and R_2 are 0.105 and 0.119, respectively. The final difference Fourier map was featureless, with numerous peaks in the range of 0.25–0.49 e $Å^{-3}$. With data of this quality, no correction for secondary extinction was deemed appropriate, and none was applied. The atomic positional and thermal parameters, along with their standard deviations as estimated from the inverse matrix, and a listing of observed and calculated structure amplitudes are available as supplementary material.

(c) 2-(2-Propoxy-5-(*N*-methyl-*N*-isopropylsulfamoyl)phenyl)-8-azahypoxanthine. The structure was solved as described above. Isotropic refinement of the nonhydrogen atoms yielded values of 0.230 and 0.303 for R_1 and R_2, respectively; anisotropic refinement lowered these values to 0.145 and 0.221, respectively. All hydrogen atoms were located in subsequent difference Fourier maps, and each was assigned a fixed isotropic thermal parameter of 1.5 $Å^2$ greater than that of the atom to which it was attached. In subsequent cycles of least-squares, the nonhydrogen atoms were refined anisotropically but no hydrogen parameter was varied. The final cycle, therefore, was based on 1771 observations and 253 variables and converged to final values of R_1 and R_2 of 0.050 and 0.062, respectively. A final difference Fourier map was featureless, with no peak higher than 0.23 e $Å^{-3}$. No correction for secondary extinction was required. The atomic positional and thermal parameters and a listing of observed and calculated structure amplitudes are available as supplementary material.

Molecular Orbital Calculations. The MO calculations were performed by the CNDO/2 self-consistent field method.[15] 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 geometries were taken from the X-ray diffraction results described in this paper. For the two larger molecules (the 5-substituted compounds) the molecules were modified in order to fit the 38-atom, 99-orbital dimensions of the program. For the 5-propylsulfonyl compound, the propoxy group was replaced by a hydroxy group; in so doing, a hydrogen atom was placed in a calculated position based on the position of the displaced carbon atom [C01] of the propoxy moiety. Similarly, the propyl group of the propylsulfonyl was replaced by a methyl group. For the 5-*N*-methyl-*N*-isopropylsulfamoyl compound, the propoxy group was replaced by hydroxy as above and the methyl and isopropyl groups were replaced by hydrogen atoms. All C-H and N-H bond lengths in the molecules were changed to 1.08 and 1.01 Å, respectively, keeping their bond directions the same as those observed in the X-ray study. The validity of this slightly truncated model used in two of the three compounds has been established by LeMay and Hodgson.[16]

Infrared Spectra. Solid-state infrared spectra of V, VII, and the related compound 9-(diethyl-carbamoyl)-2-(2-propoxyphenyl)-8-azahypoxanthine were obtained on a Beckman IR 4250 infrared spectrophotometer, using the potassium bromide pellet technique.

Results and Discussion

The molecular structures of single molecules of V, VI, and VII are shown in Figures 1, 2, 3, respectively. The bond distances and angles for the three compounds are compared in Tables I and II, respectively. Necessarily, as was noted above, the metrical parameters derived from the structure of compound VI are relatively imprecise because of the poor quality of the data.

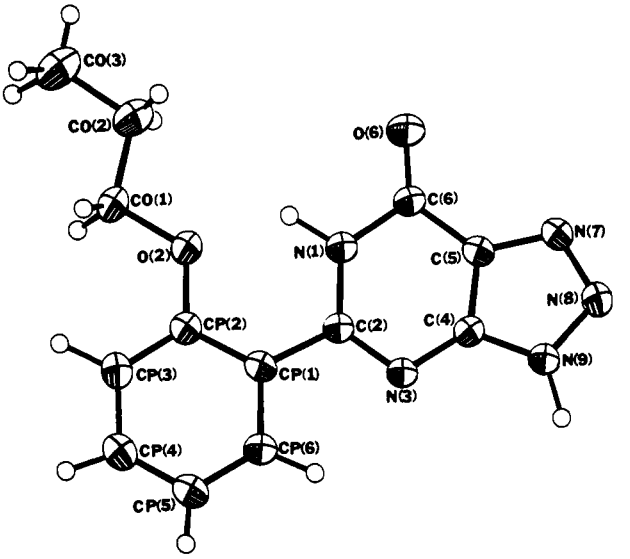


Figure 1. A view of a single molecule of 2-(2-propoxyphenyl)-8-azahypoxanthine. Hydrogen atoms are shown as spheres of arbitrary size.

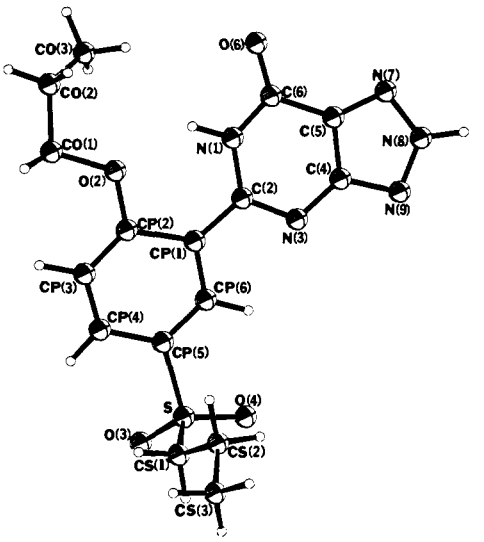


Figure 2. A view of a single molecule of 2-(2-propoxy-5-(propylsulfonyl)phenyl)-8-azahypoxanthine. Hydrogen atoms are shown as spheres of arbitrary size.

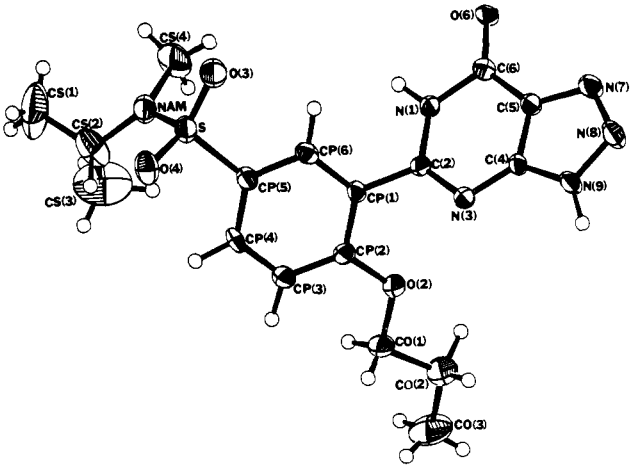


Figure 3. A view of a single molecule of 2-(2-propoxy-5-(*N*-methyl-*N*-isopropylsulfamoyl)phenyl)-8-azahypoxanthine.

(15) Pople, J. A.; Segal, G. A. *J. Chem. Phys.* **1966**, *44*, 3289.
(16) LeMay, H. E.; Hodgson, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 6474.

Table I. Selected Intramolecular Distances (Å) in Molecules V, VI, and VII

atoms	V	VI	VII
N(1)-C(2)	1.372 (3)	1.40 (2)	1.367 (4)
N(1)-C(6)	1.402 (3)	1.28 (2)	1.383 (5)
C(2)-N(3)	1.311 (3)	1.32 (2)	1.317 (4)
N(3)-C(4)	1.350 (3)	1.33 (2)	1.346 (5)
C(4)-C(5)	1.377 (3)	1.42 (3)	1.360 (5)
C(5)-C(6)	1.434 (3)	1.48 (3)	1.440 (5)
C(6)-O(6)	1.207 (3)	1.24 (2)	1.217 (4)
C(5)-N(7)	1.361 (3)	1.29 (2)	1.354 (5)
N(7)-N(8)	1.307 (3)	1.32 (2)	1.304 (4)
N(8)-N(9)	1.350 (3)	1.31 (2)	1.352 (4)
N(9)-C(4)	1.352 (3)	1.34 (2)	1.349 (4)
C(2)-CP(1)	1.479 (3)	1.44 (2)	1.459 (5)
CP(1)-CP(2)	1.412 (3)	1.54 (3)	1.399 (5)
CP(2)-CP(3)	1.384 (3)	1.37 (3)	1.380 (5)
CP(3)-CP(4)	1.388 (4)	1.32 (3)	1.383 (6)
CP(4)-CP(5)	1.368 (4)	1.43 (3)	1.377 (5)
CP(5)-CP(6)	1.378 (3)	1.35 (3)	1.382 (5)
CP(6)-CP(1)	1.406 (3)	1.37 (3)	1.396 (5)
CP(2)-O(2)	1.370 (3)	1.38 (2)	1.352 (4)
O(2)-CO(1)	1.443 (3)	1.47 (2)	1.448 (5)
CO(1)-CO(2)	1.502 (4)	1.53 (3)	1.494 (6)
CO(2)-CO(3)	1.496 (4)	1.49 (3)	1.513 (7)
S-O(3)		1.45 (1)	1.417 (3)
S-O(4)		1.45 (1)	1.424 (3)
S-CP(5)		1.76 (2)	1.758 (4)
CS(1)-CS(2)		1.35 (4)	1.477 (8)
CS(2)-CS(3)		1.65 (4)	1.499 (9)
S-CS(1)		1.69 (3)	
S-N			1.610 (3)
N-CS(2)			1.443 (3)
N-CS(4)			1.466 (5)

Table II. Selected Intramolecular Angles (Deg) in Compounds V, VI, and VII

atoms	V	VI	VII
C(6)-N(1)-C(2)	127.2 (2)	129 (2)	126.1 (3)
N(1)-C(2)-N(3)	123.0 (2)	120 (2)	123.7 (4)
N(3)-C(2)-CP(1)	119.0 (2)	116 (2)	119.5 (3)
N(1)-C(2)-CP(1)	118.0 (2)	124 (2)	116.6 (3)
C(2)-N(3)-C(4)	112.4 (2)	115 (2)	112.3 (3)
N(3)-C(4)-N(9)	127.0 (2)	124 (2)	126.7 (3)
N(3)-C(4)-C(5)	128.8 (2)	127 (2)	128.1 (3)
C(5)-C(4)-N(9)	104.2 (2)	109 (2)	105.1 (3)
C(4)-C(5)-N(7)	109.1 (2)	110 (2)	109.4 (3)
C(6)-C(5)-N(7)	131.6 (2)	134 (3)	130.7 (4)
C(4)-C(5)-C(6)	119.3 (2)	116 (2)	119.8 (4)
N(1)-C(6)-O(6)	121.8 (2)	123 (2)	121.0 (3)
C(5)-C(6)-O(6)	128.9 (2)	124 (2)	129.1 (4)
N(1)-C(6)-C(5)	109.3 (2)	112 (2)	109.9 (3)
C(5)-N(7)-N(8)	108.1 (2)	100 (2)	107.4 (3)
N(7)-N(8)-N(9)	108.2 (2)	122 (2)	109.1 (3)
N(8)-N(9)-C(4)	110.4 (2)	98 (2)	108.9 (3)
C(2)-CP(1)-CP(6)	117.0 (2)	122 (2)	118.2 (3)
CP(2)-CP(1)-CP(6)	117.5 (2)	110 (2)	119.6 (4)
C(2)-CP(1)-CP(2)	125.5 (2)	128 (2)	122.0 (3)
CP(3)-CP(2)-O(2)	122.5 (2)	126 (2)	124.1 (4)
CP(3)-CP(2)-CP(1)	120.4 (2)	123 (2)	119.5 (4)
CP(1)-CP(2)-O(2)	117.1 (2)	110 (2)	116.4 (4)
CP(2)-CP(3)-CP(4)	119.9 (2)	122 (2)	120.3 (4)
CP(3)-CP(4)-CP(5)	121.0 (2)	117 (2)	120.7 (4)
CP(4)-CP(5)-CP(6)	119.5 (2)	122 (2)	119.8 (4)
CP(6)-CP(5)-S		120 (2)	119.5 (3)
CP(4)-CP(5)-S		117 (2)	120.7 (3)
CP(1)-CP(6)-CP(5)	121.7 (2)	125 (2)	120.0 (3)
CP(2)-O(2)-CO(1)	119.6 (2)	116 (2)	117.6 (3)
O(2)-CO(1)-CO(2)	107.6 (2)	108 (2)	108.2 (4)
CO(1)-CO(2)-CO(3)	111.0 (3)	115 (2)	110.5 (4)
CP(5)-S-O(3)		107 (1)	107.4 (2)
CP(5)-S-O(4)		107 (1)	107.4 (2)
CP(5)-S-X[a]		109 (2)	107.2 (2)
O(3)-S-X[a]		108 (1)	107.8 (2)
O(3)-S-O(4)		115 (1)	118.9 (2)
O(4)-S-X[a]		110 (1)	107.6 (2)
S-CS(1)-CS(2)		119 (3)	
CS(1)-CS(2)-CS(3)		112 (3)	111.3 (5)
S-N-CS(2)			121.8 (3)
S-N-CS(4)			116.4 (3)
CS(2)-N-CS(4)			118.2 (4)
N-CS(2)-CS(1)			110.0 (5)
N-CS(2)-CS(3)			113.1 (5)

[a] X = CS(1) in VI; X = N in VII.

Nonetheless, the salient features of this structure are readily discernible and can be compared with those of the other compounds.

One feature of interest is the observation that these three related molecules do not all exhibit the same tautomer in the solid state. As can be seen in Figures 1, 2, and 3, compounds V and VII have the triazole proton on N(9) while compound VI exhibits the N(8)-H tautomer. This difference between V and VII on the one hand and VI on the other is substantiated by an examination of the bond lengths and angles in the triazole rings. As expected for the N(9)-H tautomer, compounds V and VII have the N(7)–N(8) bond [1.307 (3) and 1.304 (4) Å] much shorter than N(8)–N(9) [1.350 (3) and 1.352 (4) Å], since the former is a formal double bond while the latter is a single bond. In VI, these two bond lengths are approximately equal [1.32 (2) and 1.31 (2) Å], as expected for the N(8)-H tautomer, although the large esd's on these lengths do not allow any firm chemical conclusion. Moreover, the similarity of the internal angles in VI at C(4) and C(5) [109 (2) and 110 (2)°] and at N(7) and N(9) [100 (2) and 98 (2)°] are indicative of the N(8)-H tautomer. In V and VII, the angle at N(9) is larger than that at N(7) and that at C(5) is larger than at C(4). Qualitatively, the values of the internal angles at N(7) and N(9) are consistent with the predictions of Singh[17] and of Ringertz,[18] who have noted that protonation leads to an increase of approximately 5° in the internal angle at the site of protonation. Equally convincingly, all of the internal angles in the triazole in VI are comparable to those in other H(8) azapurines, including 8-azaguanine cation,[19] 3-methyl-8-azaguanine cation,[20] 8-azaxanthine,[21] 8-aza-2,6-diaminopurine cation,[22] and 2-phenyl-8-methyl-8-azahypoxanthine,[23] while those in V and VII are comparable to those in which protonation (or substitution) is known to be at N(9) such as 8-azaguanine,[24] 8-azaadenosine,[25] and 9-(diethylcarbamoyl)-2-(2-propoxyphenyl)-8-azahypoxanthine.[16] Similar effects have been noted for other 1,2,3-triazoles by Nielsen and Søtofte.[26-29]

Another feature of great interest in these structures is the planarity (or near planarity) of two of the compounds. In V, the entire molecule is constrained to be planar; this forces the average of the interior angles in the benzene ring and the six-membered portion of the purine ring to be exactly 120° and imposes the trans-extended conformation on the propoxy side chain of the phenyl ring. This rigid coplanarity is stabilized by the presence of a strong intramolecular hydrogen bond involving N(1) and HN(1) of the purine ring and O(2), the exocyclic oxygen atom

(17) Singh, C. *Acta Crystallogr.* **1965**, *19*, 861.
(18) Ringertz, H. G. In "The Purines - Theory and Experiment"; Bergmann, E. D., Pullman, B., Eds.; Israel Academy of Sciences and Humanities: Jerusalem, 1972.
(19) Kozlowski, D. L.; Singh, P.; Hodgson, D. J. *Acta Crystallogr., Sect. B* **1974**, *B30*, 2806; **1975**, *B31*, 1751.
(20) Singh, P.; Hodgson, D. J. *Acta Crystallogr., Sect B* **1978**, *B34*, 318.
(21) Nowacki, W.; Burki, H. *Z. Kristallogr.* **1955**, *106*, 339. Mez, H. C.; Donohue, J. *Ibid.* **1969**, *130*, 376.
(22) Singh, P.; Hodgson, D. J. *Acta Crystallogr., Sect. B.* **1975**, *B31*, 845.
(23) Cline, S. J.; Hodgson, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 6285.
(24) Macintyre, W. M.; Singh, P.; Werkema, M. W. *Biophys. J.* **1965**, *5*, 697. Sletten, J.; Sletten, E.; Jensen, L. H. *Acta Crystallogr., Sect. B* **1968**, *B24*, 1692.
(25) Singh, P.; Hodgson, D. J. *J. Am. Chem. Soc.*, **1977**, *99*, 4807.
(26) Nielsen, K. *Acta Chem. Scand., Ser. A* **1975**, *A29*, 647.
(27) Søtofte, I.; Nielsen, K. *Acta Chem. Scand., Ser. A.* **1979**, *A33*, 687.
(28) Nielsen, K.; Schepper, L.; Søtofte, I. *Acta Chem. Scand., Ser. A* **1979**, *A33*, 693.
(29) Nielsen, K.; Søtofte, I. *Acta Chem. Scand. Ser. A* **1979**, *A33*, 697.

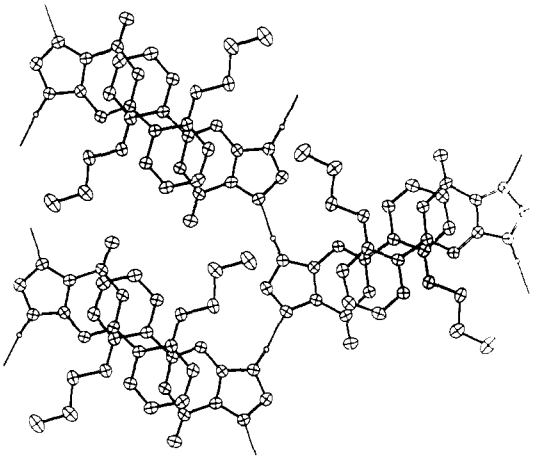


Figure 4. The molecular packing and hydrogen bonding in 2-(2-propoxyphenyl)-8-azahypoxanthine viewed normal to the crystallographic *ac* plane. Hydrogen bonds are shown as thin lines.

on the phenyl ring. The O(2)···NH(1)–N(1) angle is 136°. The significance of this hydrogen bond is manifested not only in the planarity of the molecule as a whole but also in the bonding in the purine ring as well. In most purines and azapurines containing a C(6)—O(6) bond, there is at least some keto–enol tautomerism involving HN(1), N(1), C(6), and O(6). In V, however, the presence of the strong intramolecular hydrogen bond involving HN(1) prevents the migration of HN(1) from N(1) to O(6) and causes a concomitant increase in the C(6)—O(6) bond order. This is shown by the relatively short C(6)—O(6) bond, the absence of any intermolecular hydrogen bonding involving O(6), and by the position of the –C=O stretching frequency at 1715 cm^{-1} in the solid-state infrared spectrum of this compound. This latter value compares with that of 1713 cm^{-1} in 9-(diethylcarbamoyl)-2-(2-propoxyphenyl)-8-azahypoxanthine [which also contains a strong intramolecular hydrogen bond to N(1)][16] and is much higher than the value of 1697 cm^{-1} in VII, in which there is no N(1)···O(2) intramolecular hydrogen bond. Thus, while the significance of the intramolecular hydrogen bond in the biological activity of this compound cannot be determined from this study, such a hydrogen bond does exist and has a strong influence on the structure and bonding of this molecule.

In VI the 8-azapurine ring is approximately planar, with no atom deviating from the least-squares plane by more than 0.02 Å. This result is not surprising, of course, but is in contrast to the commonly observed puckered geometry in which a purine is best viewed as being formed by a planar six-membered ring fused to a planar five-membered ring with a dihedral angle of 2–3° between these two planes. Similarly, the phenyl ring is approximately planar, with no atom deviating from the least-squares plane by more than 0.03 Å. More significantly, the entire ring system in nearly planar, with no phenyl or azapurine ring atom deviating from the 15-atom least-squares plane by more than 0.07 Å. Alternatively, the dihedral angle between the azapurine plane and the phenyl plane is only 5.4°; this result is comparable with that observed in the related and more precisely determined 2-(2-propoxyphenyl)-8-azahypoxanthine structure. Here again, the apparent cause of this planarity (or near planarity) is the presence of an intramolecular hydrogen bond between N(1) of the azapurine and the oxygen atom of the 2-propoxy group. In the present case, the N(1)···O(2) and H(1)···O(2) distances are 2.72 (2) and 1.98 Å, respectively, while the N(1)–H(1)···O(2) angle is 134°.

In the related molecule VII, however, a different situation obtains. The azapurine is again planar, with no atom deviating from the least-squares plane by more than 0.03 Å, and the phenyl ring is planar with no atom deviating from the least-squares plane by more than 0.02 Å. As can be seen in Figure 3, however, the azapurine and phenyl planes are not coplanar, the dihedral angle between them being 52.6°. In VII, there is no N(1)···O(2) hydrogen bond; hence, the C(6)—O(6) bond is slightly longer than

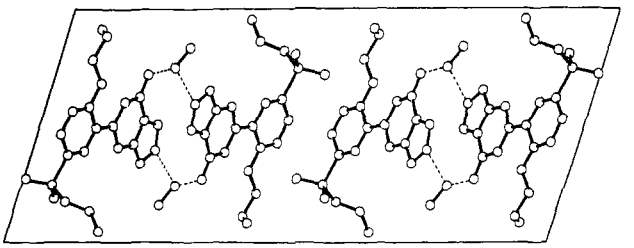


Figure 5. The molecular packing and hydrogen bonding in 2-(2-propoxy-5-(propylsulfonyl)phenyl)-8-azahypoxanthine–methanol viewed along the crystallographic *b* axis. Hydrogen bonds involving the methanol molecule are depicted by dashed lines.

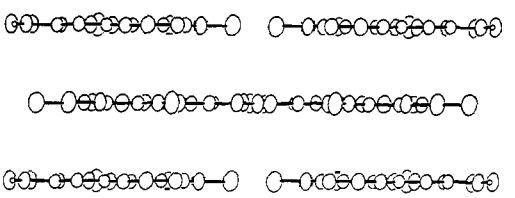


Figure 6. A view perpendicular to the crystallographic *bc* plane showing the packing and stacking in 2-(2-propoxyphenyl)-8-azahypoxanthine.

in V [1.217 (4) vs. 1.207 (3) Å], the -C=O stretching frequency is lower than in V (vide supra), and O(6) participates in hydrogen bonding (vide infra).

While O(6) does not participate in intermolecular hydrogen bonding in V, such bonding does exist between H(9) and N(7) of an adjacent molecule, linking molecules together in nonlinear chains in which all atoms have the same crystallographic *b* coordinate, and two adjacent molecules in the chain are related by the symmetry operation $^1/_2 + x, y, ^1/_2 - z$. The N(9)···N(7) and H(9)···N(7) distances and associated N(9)-H(9)···N(7) angle are 2.783 (3) Å, 1.80 (3) Å, and 171 (3)°, respectively. A view of the molecular packing is given in Figure 4. In VI, the two remaining potential donors participate in intermolcular hydrogen bonding involving the methanol molecule. Thus, N(8) forms a hydrogen bond to the methanolic oxygen atom, with N(8)···O(5) and H(8)···O(5) distances of 2.76 (2) and 1.86 Å, respectively, and N(8)–H(8)···O(5) angle of 160°. The methanol molecule also apparently forms a donor hydrogen bond to O(6) of an adjacent screw-related azapurine, with an O(5)···O(6) separation of 2.70 (2) Å; unfortunately, further details of this interaction are obscured by our inability to locate the proton on O(5). The spatial relationship between the methanol molecules and the azapurine is depicted in Figure 5.

In the absence of intramolecular hydrogen bonding in VII, the two potential donors participate in intermolecular hydrogen bonds. Atom N(1) forms a hydrogen bond to the ketonic oxygen atom O(6) of a neighboring molecule with N(1)···O(6) and H(1)···O(6) distances and associated N(1)–H(1)···O(6) angle of 2.827 (4) Å, 1.94 Å, and 178°, respectively. Atom N(9) forms a hydrogen bond to ring atom N(3) of an adjacent molecule with N(9)···N(3), H(9)···N(3), and N(9)–H(9)···N(3) parameters of 2.893 (4) Å, 1.93 Å, and 158°, respectively. The presence of a hydrogen bond to N(3) suggests that this atom may be very electron rich in VII: a similar result was observed in another 8-azapurine, 7-methyl-8-azaadenine.[30]

As might be expected for these coplanar molecules, there are intermolecular stacking interactions in V and VI. In V, the stacking is along the crystallographic *b* axis, the interplanar separation being *b*/2 (3.335 Å). A view of this stacking pattern is shown in Figure 6. In VI, the closest intermolecular approach is between molecules related to each other by translation along the crystallographic *b* axis; two such molecules are depicted in Figure 7. As can be seen, these molecules sit above one another, with the least-squares planes through the azapurine rings separated by 3.37 Å. Base stacking in purine structures is very common,

(30) Shoemaker, A. L.; Hodgson, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 4119.

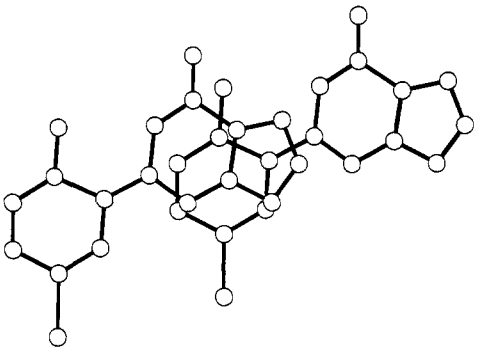
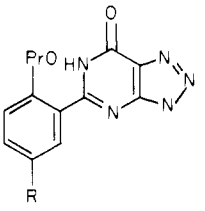


Figure 7. Stacking interactions in 2-(2-propoxy-5-(propylsulfonyl)-phenyl)-8-azahypoxanthine viewed perpendicular to the molecular plane.

Table III. Net Atomic Charge Densities (Electrons) for the Azahypoxanthine Atoms



	R		
atom	H	$SO_2C_3H_7$	$SO_2N(CH_3)\cdot(i\text{-}C_3H_7)$
N(1)	−0.22	−0.17	−0.20
C(2)	+0.28	+0.24	+0.29
N(3)	−0.28	−0.23	−0.27
C(4)	+0.21	+0.16	+0.22
C(5)	−0.10	−0.04	−0.09
C(6)	+0.36	+0.35	+0.35
O(6)	−0.36	−0.39	−0.36
N(7)	−0.07	−0.06	−0.06
N(8)	−0.06	+0.07	−0.06
N(9)	−0.07	−0.15	−0.07
H(1)	+0.14	+0.13	+0.12
H(8)		+0.08	
H(7)	+0.11		+0.12
O(2)	−0.24	−0.25	−0.25

of course, and Bugg[31] has noted that the molecules usually sit such that the polar regions of one molecule overlap with the polarizable ring system of an adjacent molecule. In VI, the three relatively polar bonds centered on C(4) [C(4)-N(3), C(4)–C(5), C(4)-N(9) (vide infra)] overlap with the polarizable phenyl ring of the compound below, while in V a similar interaction involving the polar N(1)–C(2) bond and the polarizable phenyl ring is apparent.

(31) Bugg, C. E., in ref 18.

Thus, while there are no base-stacking interactions in the present compounds, the results found here are entirely consistent with Bugg's general picture. Moreover, the stacking here is very similar to that observed[23] in 2-phenyl-8-methyl-8-azahypoxanthine and in 2-phenyl-7-methyl-8-azahypoxanthine.

Atomic Charge Densitites. The net atomic charges as calculated by the CNDO/2 method[15] are shown in Table III. The net atomic charge is defined as the difference between the number of valence electrons and the nuclear charge, the latter being calculated as the sum of the diagonal elements in the density matrix for the atom under consideration. The calculations indicate that the most electron-rich site in the azapurine rings is N(3) in all cases, with net atomic charges of −0.28, −0.23, and −0.27 e^- in V, VI, and VII, respectively. These charge densities are very similar to those found in a wide variety of 8-azapurines studied in these laboratories[16,23,25,30] and again underscore the contention[19] that one impact of the 8-aza substitution is an increase in the basicity of N(3) relative to that of other sites. The crystallographic data are also consistent with this hypothesis. The second highest peak (0.16 e A^{-3}) in the final difference Fourier of V (the most precisely refined molecule) lies outside the ring in the molecular plane approximately 0.8 Å from N(3); moreover, the U_{ij}'s for atom N(3) are smaller than those for all other nitrogen atoms, as would be expected if there is a buildup of negative charge on this atom. Another noteworthy feature in Table III is the very low residual charge at N(8) in all three compounds, which is actually calculated to be slightly positive in VI. It has been noted[6] that this site is never very electron rich, and the positive residual charge in VI [+0.07 e^-] compares well with that of +0.05 e^- calculated[23] for another example of this tautomer, 2-phenyl-8-methyl-8-azahypoxanthine. Hence, it appears that the effect of substitution at N(8) is to reduce further the already low electron density at N(8).

Conclusion. The present crystallographic study conclusively demonstrates that the presence of a 2-propoxy group (and by implication any other 2-alkoxy group) can give rise to strong intramolecular hydrogen bonding to N(1) of the purine and that this in turn leads to a planar compound; while this study cannot show that it is this conformational feature which brings about the enhanced reactivity of these systems, the emergence of such structures will be of assistance in directing future research efforts in this field.

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Registry No. V, 37762-06-4; VI, 61627-04-1; VII, 55122-37-7.

Supplementary Material Available: Atomic positional and thermal parameters, tabulations of least-squares planes, and listings of observed and calculated structure amplitudes for all three structures (30 pages). Ordering information is given on any current masthead page.