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4,5-Diamino-1-methyl-3-(methylthio)pyridazinium Iodide

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Abstract

The structure of the title compound, $C_6H_{11}N_4S^+.I^-$, $M_r = 298{\cdot}15$, has been determined from three-dimensional X-ray diffractometer data. The material crystallizes in the monoclinic space group $P2_1/n$ with four formula units in a cell of dimensions $a = 7{\cdot}549$ (2), $b = 9{\cdot}605$ (2), $c = 14{\cdot}568$ (2) Å, and $\beta = 89{\cdot}11$ (2)°; D_o (flotation in tetrahydrofuran/tribromomethane) = 1·86, $D_c = 1{\cdot}875$ Mg m^{-3}; μ(Mo $K\alpha$) = 3·214 mm^{-1}. The structure was solved by Patterson and difference Fourier methods and refined by least-squares techniques to a final R value (on F) of 0·038 based on 2035 independent data and 120 variables. The pyridazine cation is planar, with apparently more aromatic character than has been observed in other pyridazine derivatives. The net residual electronic charges as calculated by the CNDO/2 approximation suggest that the positive charge is delocalized over the entire ring, as expected for a pseudo-aromatic system.

Introduction

An area of intense recent activity has been the synthesis of nucleic acid base analogues which are designed to react differently in a biological system from their natural counterparts. Changes in the ring structures of the nucleic acid bases were among the first modifications to be made; the report of antineoplastic activity of 8-azaguanine (Kidder & Dewey, 1949; Law, 1950) helped to stimulate this area of research. Among the derivatives with significant biological activities are 5-aza- (anticancer agents and inhibitors of orotidylic acid pyrophosphorylase), 6-aza- (antiviral agents and inhibitors of orotidylic acid decarboxylase), and 3-deazapyrimidine nucleosides (antiviral agents and inhibitors of cytidine 5′-triphosphate synthetase) in addition to the 8-aza- and 3-deazapurine nucleosides (antiviral agents, anticancer agents, and inhibitors of hypoxanthine–guanine phosphoribosyltransferase and inosine 5′-monophosphate dehydrogenase) (Sidwell & Witkowski, 1979; Montgomery, Johnston & Shealy, 1979). Efforts are continuing in this vein to synthesize new compounds which are more active and more selective for the abnormal tissue.

The synthesis of these derivatives is often not straightforward and the composition and structure of the final product is not always known with certainty. For example, according to established trends, methylation of a 3-substituted pyridazine will result in different products depending on the nature of the substituent (Duffin & Kendall, 1959). An electron-withdrawing group, such as methylthio, deactivates the adjacent ring nitrogen, N(2), and promotes methylation at N(1), while a nonwithdrawing group or an electron-donating group, such as methyl, activates N(2). This is in fact what is observed, but the effects of substituents at the other positions on the course of methylation are not known for sure. In order to clear up a number of ambiguities of this sort, we undertook the X-ray crystal structure determination of the dimethylation product of 4,5-diaminopyridazine-3-thione.

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Experimental

The synthesis of the title compound has been reported in the literature (Chen & Panzica, 1981; Graves, Hodgson, Chen & Panzica, 1981); single crystals of the material were generously provided by Professor Raymond P. Panzica.

X-ray data collection and reduction

No preliminary X-ray photographs were taken. A colorless trigonal prismatic crystal (0·08 × 0·08 × 0·43 mm) was mounted on a glass fiber in an arbitrary orientation and placed on an Enraf–Nonius CAD-4 automatic diffractometer. The Enraf–Nonius routine *SEARCH* was employed to locate and center 25 reflections, which indicated that the crystals were in the monoclinic crystal system; a Delauney reduction showed that no cell of higher symmetry was present. ω scans of several axial reflections indicated that the crystal was of high quality. The observed systematic absences are $k = 2n + 1$ for $0k0$ and $h + l = 2n + 1$ for $h0l$, which are consistent only with space group $P2_1/n$, a nonstandard setting of $P2_1/c$. Accurate cell constants (given in the *Abstract*) were obtained by least-squares refinement of the diffractometer settings for the 25 reflections.

Diffraction data were collected on the CAD-4 diffractometer with Mo radiation [λ(Mo $K\bar{\alpha}$) = 0·7107 Å] and a graphite monochromator. A unique set of data ($+h,+k,\pm l$) in the range $2 \le 2\theta \le 60°$ was collected by the ω–2θ scan technique. Reflections were scanned at a variable rate ranging from 1·25 to 10° (2θ) min^{-1}. A prescan was performed for every reflection to determine if a final scan was warranted and, if so, to select an appropriate scan rate. The maximum allowable time for a final scan was 60 s. Background counts were obtained by extending the final scan by 25% at each end. Hence, the time spent collecting the backgrounds is always 50% of the peak scan time. These data-collection parameters are summarized in Table 1. Intensity checks on three standard reflections were made after every 3 h of X-ray exposure time and orientation checks on three different standard reflections were made after every 300 reflections. No systematic variation in these standards was encountered throughout data collection.

Table 1. *Data-collection parameters*

Radiation	Mo $K\alpha$
Take-off angle	2·6°
Monochromator angle	12·2°
Prescan rate	10·00° (2θ) min^{-1}
Scan mode	ω–2θ
Scan range	$2 \le 2\theta \le 60°$
Scan width	$2(A + B \tan\theta)$
A	0·80°
B	0·35°
Scan rate	$1·25 \le S \le 10·00°$ (2θ) min^{-1}
Background counts	25% of peak scan width

A small data set to be used for the empirical absorption correction was also collected. These consisted of ψ scans for nine reflections with $\chi \ge 80°$. For each reflection, scans were started at $\psi = 0°$ and continued at 10° intervals so that a total of 37 scans were taken.

Data reduction was carried out in the usual fashion. Raw intensities were calculated using the formula $I = S \times \mathrm{ATN}(C - RB)$ where C is the total count of the scan, B is the total background count ($BH + BL$), R is the ratio of the scan time to the background scan time (t_s/t_b) and is always equal to 2, ATN is the attenuator factor and equals one if the attenuator was not used and 17·42 if it was, and S is the scan rate. These intensities were assigned standard deviations according to the formula

$$\sigma(I) = [(S \times \mathrm{ATN})^2(C + R^2B) + (pI)^2]^{1/2}$$

where the quantities have the same definitions as above and the correction factor, p, was assigned a value of 0·04. The intensities and their standard deviations were then corrected for Lorentz–polarization effects and absorption. The absorption coefficient for this compound with Mo $K\alpha$ radiation (3·214 mm^{-1}) is sufficient to warrant correction of the data. The transmission factors range from 0·943 to 1·000 with an average of 0·973. A total of 2904 independent reflections were processed of which 2035 had $I \ge 3\sigma(I)$. Only these latter data were considered observed and used in subsequent calculations.

Structure solution and refinement

The structure was solved by the heavy-atom method. The position of the iodide ion was determined from a three-dimensional Patterson map. All other nonhydrogen atoms were located in a subsequent difference Fourier map. Isotropic, least-squares refinement of these positions gave values of the usual agreement factors $R = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$ of 0·103 and 0·133, respectively. All least-squares calculations were carried out on F, the function minimized being $\sum w(|F_o| - |F_c|)^2$ where the weights, w, are assigned as $4F_o^2/\sigma^2(F_o^2)$. In the calculation of the structure factors, F_c, the neutral-atom scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The effects of the anomalous dispersion of all atoms were included. The values of f' and f'' were also taken from *International Tables* (1974). Anisotropic refinement of the 12 nonhydrogen atom positions lowered the values of R and R_w to 0·044 and 0·057, respectively. A subsequent difference Fourier map revealed the positions of all 11 H atoms. Attempts to refine the H

atom positional parameters were unsuccessful, but isotropic thermal parameters for all the H atoms were successfully refined.

In the final cycle of least squares there were 2035 observations and 120 variables; no parameter shifted by more than 0·3 times its estimated standard deviation, which is taken as evidence of convergence. The final values of R and R_w were 0·038 and 0·046, respectively. Comparison of the values of $|F_o|$ and $|F_c|$ in the later stages of refinement indicated that no correction for the effects of secondary extinction was necessary, and none was made. A final difference Fourier map contained peaks as high as 0·73 e Å^{-3}. The top nine peaks were all associated with the iodide ion. Other than this residual electron density, the map was featureless. The atomic positional parameters derived from the last cycle of least squares, along with their standard deviations, as estimated from the inverse matrix, are presented in Table 2.*

Molecular orbital calculations

Net residual electronic charge densities were calculated for the pyridazinium cation in its crystallographic conformation using the CNDO/2 approximation (Pople & Beveridge, 1970). The net residual atomic charge is defined as the number of valence electrons minus the nuclear charge, which is calculated as the sum of the diagonal elements in the density matrix for the particular atom.

* Lists of observed and calculated structure amplitudes and of anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36244 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Atomic positional parameters and U_{eq} values*

For anisotropic atoms, U_{eq} was calculated from the expression $U_{eq} = (1/6\pi^2) \sum_i \sum_{j>i} \beta_{ij} \mathbf{a}_i . \mathbf{a}_j$. H atom positional parameters were not refined.

	x	y	z	U_{eq} or U (Å^2)
I	−0·11879 (4)	−0·05199 (3)	0·80980 (2)	0·0512 (1)
S(3)	0·3440 (2)	0·6837 (1)	1·0493 (1)	0·0472 (3)
N(1)	0·1510 (5)	0·5170 (4)	0·8276 (2)	0·0428 (5)
N(2)	0·2253 (5)	0·6088 (4)	0·8851 (2)	0·0397 (6)
C(3)	0·2559 (5)	0·5649 (4)	0·9699 (3)	0·0367 (6)
C(4)	0·2185 (5)	0·4281 (4)	1·0028 (3)	0·0362 (6)
C(5)	0·1445 (5)	0·3354 (4)	0·9377 (3)	0·0386 (7)
C(6)	0·1105 (6)	0·3868 (5)	0·8498 (3)	0·0431 (7)
C(1)	0·1167 (7)	0·5720 (5)	0·7342 (3)	0·0574 (10)
C(7)	0·3647 (8)	0·8363 (5)	0·9804 (4)	0·0629 (10)
N(4)	0·2516 (5)	0·3906 (4)	1·0890 (2)	0·0458 (7)
N(5)	0·1139 (6)	0·2005 (4)	0·9585 (3)	0·0547 (7)
H(11)	0·1994	0·5514	0·7013	0·08 (2)
H(12)	0·0293	0·5430	0·7129	0·12 (3)
H(13)	0·1118	0·6557	0·7375	0·11 (2)
H(71)	0·5180	0·8984	1·0215	0·13 (3)
H(72)	0·2510	0·8723	0·9616	0·11 (2)
H(73)	0·4357	0·8233	0·9265	0·12 (2)
H(41)	0·2820	0·4277	1·1250	0·07 (2)
H(42)	0·1855	0·3202	1·1136	0·12 (3)
H(51)	0·1096	0·1879	1·0090	0·06 (1)
H(52)	0·0610	0·1551	0·9334	0·02 (1)
H(6)	0·0477	0·3363	0·8034	0·04 (1)

Results and discussion

The crystal structure consists of columns of parallel-stacked pyridazinium rings. The columns are parallel to the crystallographic a axis and the stacking distance is 3·78 Å ($a/2$), which is larger than that reported for interactions of this type in many nucleic acid bases. However, this is not surprising since the molecule is charged. The columns of pyridazinium cations are shielded from one another by the presence of iodide ions. A view of this arrangement is given in Fig. 1.

The most important feature of this structure is the confirmation that the ring methyl group is located at N(1) rather than N(2). A view of the pyridazinium cation is presented in Fig. 2. Thus, the course of methylation is apparently dictated by the substituent on C(3) and is not materially affected by the substituents at C(4) and C(5). This same trend is likely to hold for the ring-closure product of 4,5-diaminopyridazine-3-thione: imidazo[4,5-*d*]pyridazine-4-thione (Chen & Panzica, 1981). Another note of stereochemical interest is that the C atom of the methylthio group lies in the plane of the pyridazine ring and away from the amino group at C(4). Presumably, this is to minimize steric and electrostatic interactions. Overall, the bond distances and angles, which are given in Fig. 2, reveal no uncharacteristic features: the values are very close to those observed in other pyridazine structures (Carlisle & Hossain, 1966; Ottersen, 1973, 1974, 1975; Ottersen & Seff, 1973; Cucka, 1963; Ohsawa, Akomoto, Tsuji, Igeta & Iitaka, 1978; Graves, Hodgson, Katz, Wise & Townsend, 1978; Graves & Hodgson, 1981).

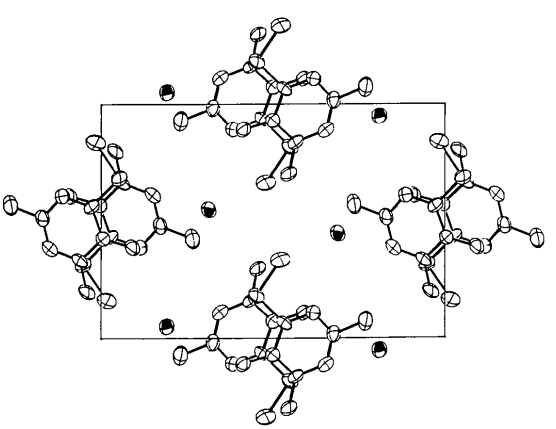

Fig. 1. The unit-cell contents as projected on to the *bc* plane; the *c* axis is horizontal and the *b* axis is vertical.

The bond distances within the ring are indicative of greater aromatic character than is present in most of the other structures, which more clearly have alternating long and short bonds. The bond lengths to the amino groups are typical of corresponding bonds in adenine (Kistenmacher & Shigematsu, 1974), guanine (Thewalt, Bugg & Marsh, 1971), cytosine (McClure & Craven, 1973) and various derivatives. An interesting feature of the bond angles is the comparison of the internal angles at the two ring N atoms. The N atom with the substituent has a significantly larger internal angle. The same is true for all of the pyridazine derivatives regardless of whether the substituent is an alkyl group or an H atom. This effect was first noted by Singh (1965) for the pyrimidines and was later generalized by Ringertz (1972).

The pyridazine ring is planar with no atom deviating from the six-atom, least-squares plane by more than 0·013 (4) Å (this is further evidence of the aromaticity of the pyridazine moiety). The substituent atoms also lie very close to this plane, the maximum deviation being 0·098 (4) Å. There are no base–base hydrogen bonds in the crystal. The only hydrogen bonds are between the amino groups and the iodide ions. As indicated in Table 3 and Fig. 3, all four amino H atoms participate in these interactions. With an ionic radius of 2·20 Å (Bondi, 1964), the iodide ion can interact with distant protons. The geometry of these interactions is typical of I···H–N interactions in other systems (Havighurst, Mack & Blake, 1924; Copeland & Hodgson, 1973; Lee & Richardson, 1976; Sheldrick & Sheldrick, 1970; Hartl, 1975). The N–I–N angles do not conform to any regular geometry but they are closest to a tetrahedral arrangement. The shortest I–I contact is 5·49 Å and is obviously much larger than the van der Waals contact distance.

The electronic charge densities listed in Table 4 are not abnormal. N(1), which formally holds the positive charge of the molecule, is indeed positively charged but it is evident that the charge is delocalized over the entire ring. All ring atoms are slightly positively charged with the exception of N(2), and even it is less negative than corresponding N atoms in purines and pyrimidines (Graves & Hodgson, 1981; Singh & Hodgson, 1974, 1977). The amino N atoms have a small negative charge which is similar to those calculated for the amino groups in adenosine, 8-azaadenosine, cytidine, and 6-azacytidine (Singh & Hodgson, 1974, 1977). The one surprising feature of this calculation is that the C atom of the methylthio group is slightly negatively charged and is actually more so than the S atom. This may be as important as steric factors in determining the conformation of the molecule at S(3).

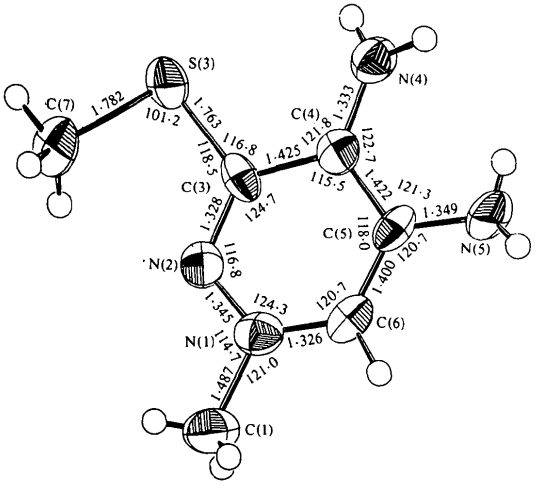

Fig. 2. The pyridazinium cation as viewed along **a*** including the numbering scheme employed and the interatomic bond distances and angles. The estimated standard deviation for all bond distances is 0·005 Å and for the bond angles it is 0·3°.

Table 3. *Hydrogen-bonding interactions involving iodide*

			I···H (Å)	I···N (Å)	I···H–N (°)
I	H(41)	N(4^{i})	3·046	3·712 (3)	168·7
I	H(42)	N(4^{ii})	2·856	3·710 (3)	156·6
I	H(51)	N(5^{ii})	2·950	3·668 (3)	162·5
I	H(52)	N(5^{iii})	3·016	3·708 (3)	171·7

Symmetry code: (i) $-\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z$; (ii) $-x, -y, 2-z$; (iii) x,y,z.

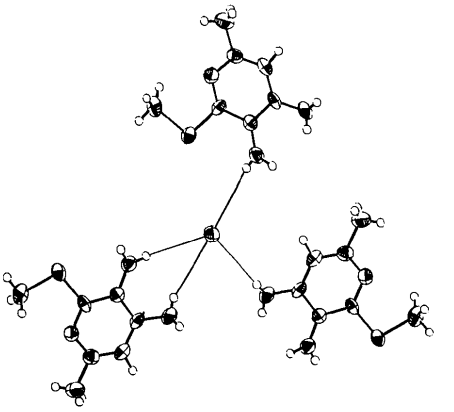

Fig. 3. The four N–H···I interactions as shown along the a^* axis.

Table 4. *Net residual atomic charges* (e^-)

The e.s.d. for these charges is 0·02 e^-.

S(3)	−0·03	C(6)	0·07	H(12)	0·05	H(42)	0·13
N(1)	0·11	C(1)	0·05	H(13)	0·06	H(51)	0·12
N(2)	−0·02	C(7)	−0·06	H(71)	0·07	H(52)	0·14
C(3)	0·03	N(4)	−0·19	H(72)	0·05	H(6)	0·06
C(4)	0·19	N(5)	−0·20	H(73)	0·05		
C(5)	0·11	H(11)	0·05	H(41)	0·16		

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