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Structure and Conformation of 6-(4-Nitrobenzyl)thioinosine, $C_{17}H_{17}N_5O_6S$, a Potent Inhibitor of Nucleoside Transport

BY M. SORIANO-GARCIA* AND R. PARTHASARATHY†

Center for Crystallographic Research, Roswell Park Memorial Institute, Buffalo, New York 14263, *USA*

AND B. PAUL‡ AND A. R. P. PATERSON

Cancer Research Group (McEachern Laboratory), University of Alberta, Edmonton, Alberta, Canada T6G 2H7

(*Received* 25 *January* 1984; *accepted* 30 *May* 1984)

Abstract. $M_r = 419{\cdot}4$, monoclinic, $P2_1$, $a = 14{\cdot}718$ (1), $b = 8{\cdot}678$ (1), $c = 7{\cdot}269$ (1) Å, $\beta = 93{\cdot}55$ (1)°, $V = 926{\cdot}6$ (3) Å^3, $Z = 2$, $D_m = 1{\cdot}49$, $D_x = 1{\cdot}503$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 19{\cdot}3$ cm^{-1}, $F(000) = 436$, $T = 294$ K; $R = 0{\cdot}042$ for 2205 observed reflections. The 6-substituent is distal to the imidazole ring; the nucleoside has the *syn* conformation [$\chi_{CN} = -127{\cdot}9$ (4)°] with an intramolecular O(5′)—H(O5′)···N(3) hydrogen bond; the ribose has the C(2′)-*endo* (^2E) pucker with the following pseudorotational parameters: $P = 158{\cdot}9$ (3)° and $\tau_m = 38{\cdot}0$ (2)°; the conformation across C(4′)—C(5′) is g^+ [*i.e.* C(3′)—C(4′)—C(5′)—O(5′) is 53·5 (5)°]. It is suggested that the preferred conformations across the S—C(sp^3) and C(sp^3)—C(sp^2) bridges which link the purine moiety to the substituent on the 6-position of purine are important among the determinants of the nucleoside-transport inhibitory activity.

Introduction. The passage of nucleoside molecules across the plasma membrane of animal cells is mediated by nucleoside-specific transport elements of the membrane. This transport is reversible, non-concentrative, and of broad specificity in that physiological nucleosides and a diverse array of nucleoside analogs are accepted as substrates by transporter elements of a single type (for reviews see Plagemann & Wohlheuter, 1980; Paterson, Kolassa & Cass, 1981; Paterson, Jakobs, Harley, Cass & Robins, 1983). Nucleoside transport in many cell types, but not in all, is powerfully inhibited by 6-(4-nitrobenzyl)thioinosine (NBMPR) and various related compounds. Various cell types in which nucleoside transport is NBMPR-sensitive possess surface sites at which NBMPR is bound with high affinity (K_d 0·1–1 n*M*) (Paterson *et al.*, 1981; Paterson, Jakobs, Harley, Cass & Robins, 1983; Paterson, Jakobs, Harley, Fu, Robins & Cass, 1983). NBMPR occupancy of these sites, which appear to be located on the nucleoside-transporter protein(s) (Jarvis, Janmohamed & Young, 1983), correlates with blockade of transporter function (Cass, Gaudette & Paterson, 1974). The possibility that NBMPR binding sites may be distinct from the transporter sites at which nucleoside molecules interact during the permeation process has been discussed recently (Koren, Paterson & Cass, 1983; Jarvis *et al.*, 1983). The existence of NBMPR-insensitive nucleoside-transport mechanisms has been recognized recently (Belt, 1984; Paterson, Jakobs, Harley, Fu, Robins & Cass, 1983), but their characterization is yet at an early stage.

Various NBMPR congeners have been evaluated for their ability to inhibit a transport-dependent aspect of cellular nucleoside metabolism (Paul, Chen & Paterson,

* Present address: Depto. de Química, UAM-Iztapalapa, Apdo Postal 55-534, México 13, DF.
† Address correspondence to this author.
‡ Present address: Grace Cancer Drug Center, Roswell Park Memorial Institute, Buffalo, NY 14263, USA.

0108-2701/84/111897-05$01.50

1975), nucleoside transport and NBMPR binding (Paterson, Naik & Cass, 1977; Paterson, Jakobs, Harley, Cass & Robins, 1983), and although structure–activity relationships have not been explored systematically, the inhibition site appears to be purine-specific, and the glycosyl and S(6) substituents are important determinants of the ligand-binding-site interaction. The contribution of the S(6) substituents to binding may be through hydrophobic interactions with the binding site. Of a series of N(6)-substituted adenine nucleosides recently evaluated as competitive inhibitors of high affinity, site-specific binding of NBMPR to cultured cells, 6-(4-nitrobenzyl)-2′-deoxyadenosine was the most tightly bound (K_d 2 nM) (Paterson, Jakobs, Harley, Fu, Robins & Cass, 1983). Like NBMPR, this compound is a potent inhibitor of adenosine transport. From the variety of nucleoside derivatives that are transport inhibitory, it is evident that general features of the inhibiting molecules such as hydrophobicity, dimensions and conformations are important determinants of transport inhibitory activity. It was in this context that the present study of the conformation of NBMPR was undertaken.

Experimental. Crystals of NBMPR by slow evaporation from ethyl alcohol solutions: D_m measured by flotation (bromoform–benzene); crystal dimensions 0·23 × 0·36 × 0·18 mm; X-ray data from GE XRD5 manual diffractometer equipped with Cu $K\alpha$ radiation and Ross filters; lattice parameters refined using 54 reflections at high 2θ angles (60 to 140°) where α_1 and α_2 are separated; 2375 unique reflections measured to the limit $2\theta < 164°$ using stationary-crystal–stationary-counter technique; range of hkl: $h \pm 18$, k 0→11, l 0→9; 2205 significant with $I \geq 2\sigma(I)$; three standard reflections monitored periodically showed less than 5% variation in intensity during course of data collection; Lorentz–polarization, α_1–α_2 and anisotropy of absorption (using φ scan) corrections applied; structure solved using *MULTAN* (Germain, Main & Woolfson, 1971); structural parameters refined by least-squares method on $|F|$ with block-diagonal approximation; difference electron-density maps used to locate all 17 H atoms included in the refinement with individual isotropic thermal parameters; final R for 2205 reflections 0·042; differential synthesis weighting $w = 1/f_C$ used, f_C being the scattering factor for C (Cochran, 1948); (Δ/σ_{max}) for shifts 0·01 for non-H atoms; largest features in $\Delta\rho$ map about ±0·3 e Å^{-3}; atomic scattering factors and anomalous-dispersion corrections for S, O, N and C from *International Tables for X-ray Crystallography* (1974); scattering factor for H from Stewart, Davidson & Simpson (1965). Fourier and torsion-angle programs by Dr S. T. Rao; *ORTEP* by Johnson (1965); *BDLS*-6, a locally modified version of least-squares programs of P. K. Gantzel, R. A. Sparks and K. N. Trueblood (ACA old program No. 317).

Table 1. *Positional parameters and equivalent isotropic temperature factors for non-*H *atoms and isotropic temperature factors for* H *atoms with their e.s.d.'s*

$B_{eq} = \frac{4}{3}\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$. Coordinate values for non-H atoms have been multiplied by 10^4, and for H atoms by 10^3. The thermal parameters have been multiplied by 10^2 for non-H and by 10 for H atoms.

	x	y	z	B_{eq}/B(Å^2)
S(6)	5272 (1)	2316	8644 (1)	397 (3)
O(4′)	8786 (1)	7346 (3)	7284 (3)	281 (4)
O(2′)	10120 (2)	4514 (3)	9786 (4)	400 (6)
O(3′)	10847 (1)	7166 (3)	8662 (3)	368 (6)
O(5′)	9115 (1)	5602 (3)	3980 (3)	341 (5)
O(14*a*)	1855 (2)	5974 (4)	2520 (5)	770 (10)
O(14*b*)	2400 (2)	4861 (5)	218 (5)	830 (10)
N(1)	6272 (2)	2971 (3)	5788 (3)	301 (5)
N(3)	7648 (2)	4484 (3)	5894 (3)	277 (5)
N(7)	6843 (2)	4579 (4)	10423 (3)	362 (7)
N(9)	8028 (2)	5520 (3)	8958 (3)	271 (5)
N(14)	2374 (2)	5069 (3)	1869 (6)	556 (9)
C(2)	7000 (2)	3608 (4)	5052 (4)	306 (6)
C(4)	7513 (2)	4695 (4)	7676 (4)	243 (5)
C(5)	6786 (2)	4121 (4)	8601 (4)	273 (6)
C(6)	6168 (2)	3211 (4)	7574 (4)	276 (5)
C(8)	7593 (2)	5401 (5)	10566 (4)	349 (7)
C(1′)	8894 (2)	6291 (4)	8754 (4)	246 (5)
C(2′)	9661 (2)	5234 (3)	8261 (4)	265 (6)
C(3′)	10288 (2)	6338 (4)	7351 (4)	281 (6)
C(4′)	9629 (2)	7464 (4)	6369 (4)	285 (6)
C(5′)	9421 (2)	7131 (5)	4343 (5)	354 (7)
C(10)	4678 (2)	1357 (5)	6698 (5)	357 (7)
C(11)	4103 (2)	2410 (5)	5471 (4)	321 (6)
C(12)	3454 (2)	3379 (5)	6153 (5)	420 (9)
C(13)	2898 (2)	4257 (5)	5000 (6)	450 (9)
C(14)	2988 (2)	4166 (5)	3129 (6)	404 (8)
C(15)	3640 (2)	3264 (5)	2394 (5)	413 (9)
C(16)	4199 (2)	2381 (5)	3588 (5)	371 (7)
H(O2′)	975 (2)	378 (5)	1023 (5)	52 (11)
H(O3′)	1106 (3)	658 (6)	934 (7)	93 (16)
H(O5′)	862 (3)	530 (6)	457 (6)	90 (15)
H(C2)	707 (2)	336 (4)	368 (4)	18 (6)
H(C8)	784 (2)	576 (3)	1171 (3)	15 (6)
H(C1′)	906 (2)	693 (4)	997 (4)	30 (8)
H(C2′)	933 (3)	455 (5)	741 (5)	58 (11)
H(C3′)	1067 (2)	576 (3)	644 (3)	11 (5)
H(C4′)	989 (2)	844 (4)	653 (4)	19 (6)
H(C5′*a*)	998 (2)	728 (5)	369 (4)	44 (9)
H(C5′*b*)	889 (2)	793 (4)	374 (4)	24 (7)
H(C10*a*)	431 (2)	68 (4)	726 (4)	36 (8)
H(C10*b*)	522 (2)	99 (5)	611 (4)	40 (9)
H(C12)	340 (2)	350 (4)	743 (4)	34 (8)
H(C13)	243 (2)	493 (4)	526 (5)	44 (9)
H(C15)	363 (2)	338 (5)	92 (5)	50 (10)
H(C16)	470 (2)	171 (4)	310 (5)	46 (10)

Discussion. The final positional and isotropic thermal parameters for all the atoms are given in Table 1.* The bond distances, bond angles and the conformation of the molecules are shown in Fig. 1. The thioinosine moiety, unlike the usual inosines, does not carry an H atom at N(1) because of the substitution of S(6). The bond lengths and angles, especially around N(1), reflect this difference in the tautomers. The C(6)–S(6) bond distance in NBMPR compared to the corresponding bond distances in 6-thioinosine (Shefter, 1968) and 6-mercaptopurine monohydrate (Sletten, Sletten & Jensen, 1969; Brown, 1969) is longer by 0·09 and

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39544 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

0·08 Å respectively. Further, the two C—S bonds are unequal; the C(6)—S(6) is shorter by 0·06 Å than the S(6)—C(10) bond. The latter [1·817 (4) Å] corresponds to a single bond between an S atom and an sp^3-hybridized C. The shortening of the former compared to the C(10)—S(6) bond may be attributed to the (p–p) orbital overlap between the C(6) and S(6) atoms. In esters, the analogous C(sp^2)—O— and —O—C(sp^3) bonds differ by 0·1 Å, presumably because of electron delocalization between the carbonyl and ester O atoms, so that the C(sp^2)—O— bond possesses some double-bond character (Dexter, 1972).

The bond distances and angles in the ribose moiety agree in general with the values found in several recent structure determinations. The two ring C—O bonds C(1′)—O(4′) 1·409 (4) and C(4′)—O(4′) 1·448 (3) Å, differ in length, as in other nucleoside and nucleotide structures. The glycosidic bond length falls within the usual range for inosine, inosine monophosphate (IMP) and their derivatives.

Fig. 1 illustrates the conformation in the solid state and shows that the S(6) substituent is 'distal' (Parthasarathy, Ohrt & Chheda, 1974) to the imidazole ring. The plane of the nitrobenzyl group is inclined at 104·4 (5)° to the plane of the base. The conformation across the glycosidic bond is *syn*, with χ_{CN} [O(4′)—C(1′)—N(9)—C(8)] being −127·9 (4)° (Table 2). In this structure, added conformational stabilization is derived through an intramolecular hydrogen bond, the O(5′)—H···N(3) bond [H(O5′)···N(3) 1·91 (5) Å, O(5′)—H(O5′)···N(3) 174 (4)°]. The ribose has the C(2′)-*endo* (^2E) conformation; the conformation across the C(4′)—C(5′) bond is *gauche–gauche*. Table 2 shows that in inosine molecules the most common puckering of the ribosyl portion is C(2′)-*endo* with the exception of the monoclinic inosine which has the C(3′)-*endo* (^3E) and *gauche–trans* conformation. There is a striking correlation between the intramolecular O(5′)—H···N(3) hydrogen bond and the *syn* conformation of purine nucleosides (Rao & Sundaralingam, 1970). However, there are several guanosine or inosine derivatives that assume the *syn* conformations without such O(5′)—H···N(3) hydrogen bonds (Ginell & Parthasarathy, 1978). Inosine and thioinosine may assume a variety of distinctly different conformations even in the crystalline state. However, the phosphorylation of inosine seems to change the conformation from *syn* to *anti* and restrict its conformational freedom, as seen from the range of conformations assumed by IMP and its derivatives (Table 2).

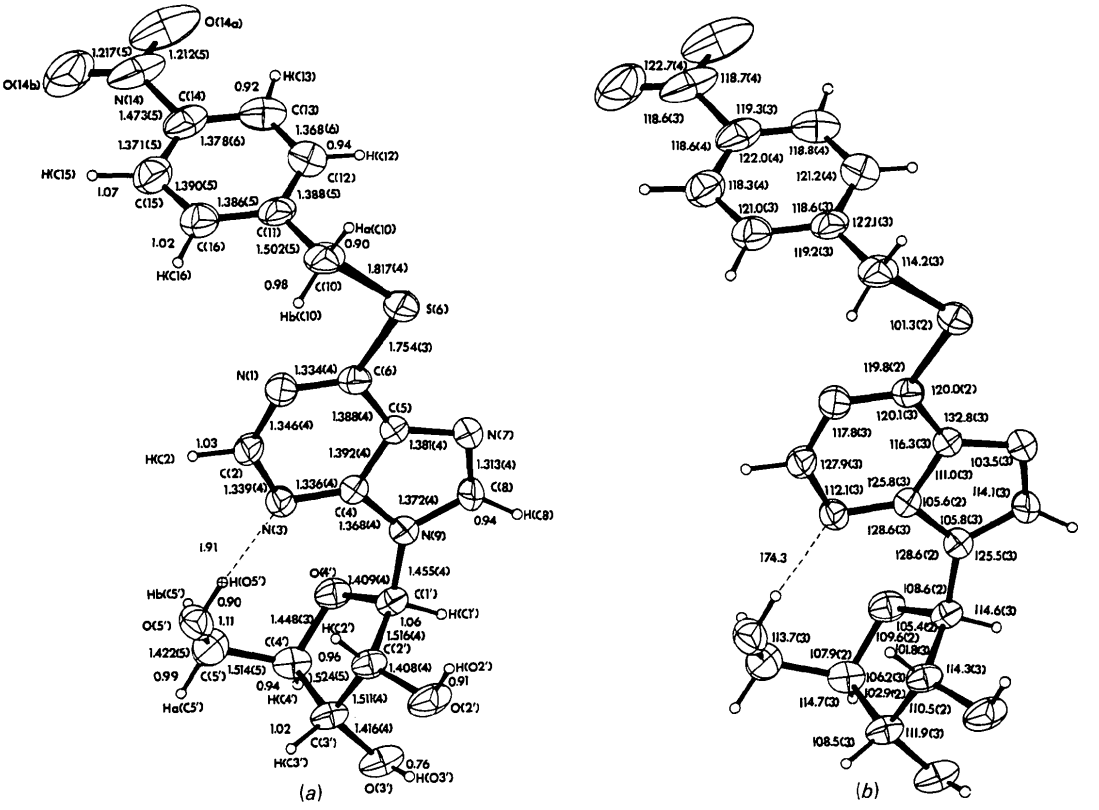

Fig. 1. (*a*) Covalent bond distances (Å) and (*b*) covalent bond angles (°). The numbers in parentheses denote the corresponding e.s.d.'s. The e.s.d.'s for bond distances involving H atoms range from 0·02 to 0·05 Å.

Table 2. *Conformational data (°) for inosine and inosine monophosphate in different crystal structures*

Structure	χ_{CN}		Pucker of ribose	Conformation about C(4′)–C(5′) φ_{OO}	φ_{OC}	References
Nucleosides						
6-(4-Nitrobenzyl)thioinosine	−127·9 (4)	(*syn*)	C(2′)-*endo*	−64·6 (5) (*g*)	53·5 (5) (*g*)	Present study
Inosine dihydrate						
Molecule 1	−121	(*syn*)	C(2′)-*endo*	−55 (*g*)	64 (*g*)	(*a*)
Molecule 2	−48	(*anti*)	C(2′)-*endo*	−73 (*g*)	47 (*g*)	
Inosine (monoclinic)	−12	(*anti*)	C(3′)-*endo*	−75 (*g*)	169 (*t*)	(*b*)
Inosine (orthorhombic)						
Molecule 1	−122	(*syn*)	C(2′)-*endo*	−63 (*g*)	57 (*g*)	(*c*)
Molecule 2	−125	(*syn*)	C(2′)-*endo*	−58 (*g*)	64 (*g*)	
6-Thioinosine						
Molecule 1	−135	(*syn*)	C(2′)-*endo*	−63 (*g*)	55 (*g*)	(*d*)
Molecule 2	−144	(*syn*)	C(2′)-*endo*	−63 (*g*)	57 (*g*)	
2-Ethylthio-8-methylinosine	−110	(*syn*)	C(2′)-*endo*	62 (*g*)	182 (*t*)	(*e*)
Nucleotides						
Inosine-5′-phosphate	−20	(*anti*)	C(3′)-*endo*	−66 (*g*)	52 (*g*)	(*f*)
Inosine-5′-phosphate (Ba)						
Molecule 1	−46	(*anti*)	C(2′)-*endo*	−58 (*g*)	49 (*g*)	(*g*)
Molecule 2	−34	(*anti*)	C(2′)-*endo*	−57 (*g*)	51 (*g*)	
Inosine-5′-phosphate (2Na)	−43	(*anti*)	C(2′)-*endo*	−61 (*g*)	56 (*g*)	(*h*)

References: (*a*) Thewalt, Bugg & Marsh (1970). (*b*) Munns & Tollin (1970). (*c*) Subramanian, Madden & Bugg (1973). (*d*) Shefter (1968). (*e*) Nagashima & Wakabayashi (1974). (*f*) Sletten *et al.* (1969). (*g*) Nagashima, Wakabayashi, Matsuzaki & Iitaka (1974). (*h*) Nagashima & Iitaka (1968).

The torsion angle χ_{CN} is given by C(8)–N(9)–C(1′)–O(4′). φ_{OO} and φ_{OC} represent the O(4′)–C(4′)–C(5′)–O(5′) and C(3′)–C(4′)–C(5′)–O(5′) torsion angles respectively. The symbols '*g*' and '*t*' refer to '*gauche*' and '*trans*' respectively.

Fig. 2 shows the hydrogen bonding and molecular packing in crystalline NBMPR. The nucleoside molecules are packed with no intra- or intermolecular overlap of the base rings. Distances and angles for the intra- and intermolecular hydrogen bonding are given in the legend for Fig. 2. N(1) does not take part in hydrogen bonding, evidently because of the distal conformation of the S(6) substituent. O(3′)–H is not involved in any hydrogen bonding, but makes two long H···O contacts of 2·58 (5) and 2·52 (5) Å, respectively, with neighboring O(14*a*) and O(14*b*).

The activity of the purine-nucleoside class of nucleoside-transport inhibitors appears to depend upon the physicochemical properties of the purine 6-position substituent (Paul *et al.*, 1975) as in the cytokinin structure–activity relationships (Skoog *et al.*, 1967; Soriano-Garcia & Parthasarathy, 1975). Potent inhibitory activity is conferred by the presence of the –HN(6)–(4-nitrobenzyl) group or by –S(6)–*R* groups where *R* is 4-nitrobenzyl, benzyl or cyclohexyl. That conformational flexibility in these 6-position groups is a requirement for inhibitory activity is suggested by the observation that inhibitory activity is much reduced by the presence of methyl groups on C(10) (Paul *et al.*, 1975). The preferred conformation of the NH–CH_2–*R* group was studied previously (Soriano-Garcia & Parthasarathy, 1975) and the conformation of the S–CH_2–*R* group is expected to be similar, corresponding to a range of torsional angles of ±(70–110°) around S(6)–C(10) and C(10)–C(11) bonds. The values observed are respectively −76·9 (3) and −52·9 (3)°. The 6-(phenylthio) derivatives are less potent than 6-(benzylthio) derivatives, reflecting the inability of the former compounds to assume conformations similar to those of the latter. Molecular models show that such a favorable conformation could be further stabilized in compounds such as 6-(2-hydroxy-5-nitrobenzyl)thio-9-β-ribofuranosylpurine which have

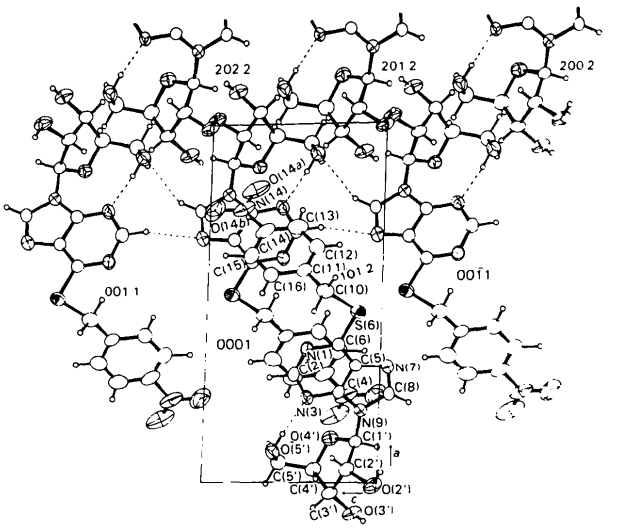

Fig. 2. A view of the hydrogen bonding in the crystal structure. There is one intramolecular O(5′)–H···N(3) and three intermolecular O(2′)–H···O(3′), C(8)–H···O(5′) and C(2)–H···N(7) hydrogen bonds. The *D*···*A*, H···*A* and *D*–H···*A* values are, respectively [2·813 (5), 2·767 (4), 3·244 (4), 3·463 (4) Å], [1·91 (5), 1·86 (4), 2·42 (3), 2·59 (3) Å] and [174 (4), 171 (4), 145 (2) and 142 (2)°].

good biological activity by the formation of an intramolecular O—H···N(1) bond analogous to the intramolecular hydrogen bonds in ureido purines (Parthasarathy *et al.*, 1974).

This work was supported by grants CA23704 and GM24864 from the National Institutes of Health. MS-G gratefully acknowledges a fellowship from the Consejo Nacional de Ciencia y Tecnologia de México (CONACYT).

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A Thermal Molecular Migration in the Solid State. Structures of Isomeric 5-Amino-4-(2,6-dichlorophenyl)-1-(2-nitrophenyl)-1*H*-1,2,3-triazole (Yellow Form I) and 4-(2,6-Dichlorophenyl)-5-(2-nitroanilino)-2*H*-1,2,3-triazole (Red Form II), $C_{14}H_9Cl_2N_5O_2$

BY NIRUPA SEN (NÉE U. KAMATH) AND K. VENKATESAN

Department of Organic Chemistry, Indian Institute of Science, Bangalore-560 012, India

(*Received* 9 *May* 1984; *accepted* 2 *July* 1984)

Abstract. Yellow form (I): $M_r = 350{\cdot}09$, monoclinic, $P2_1/n$, $Z = 4$, $a = 9{\cdot}525$ (1), $b = 14{\cdot}762$ (1), $c = 11{\cdot}268$ (1) Å, $\beta = 107{\cdot}82$ (1)°, $V = 1508{\cdot}3$ Å^3, D_m(flotation in aqueous KI) = 1·539 (2), $D_x = 1{\cdot}541$ (2) g cm^{-3}, μ(Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å) = 40·58 cm^{-1}, $F(000) = 712$, $T = 293$ K, $R = 8{\cdot}8\%$ for 2054 significant reflections. Red form (II): $M_r = 350{\cdot}09$, triclinic, $P\bar{1}$, $Z = 2$, $a = 9{\cdot}796$ (2), $b = 10{\cdot}750$ (2), $c = 7{\cdot}421$ (1) Å, $\alpha = 95{\cdot}29$ (2), $\beta = 70{\cdot}18$ (1), $\gamma = 92{\cdot}76$ (2)°, $V = 731{\cdot}9$ Å^3, D_m(flotation in KI) = 1·585 (3), $D_x = 1{\cdot}588$ (3) g cm^{-3}, μ(Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å) = 40·58 cm^{-1}, $F(000) = 356$, $T = 293$ K, $R = 5{\cdot}8\%$ for 1866 significant reflections. There are no unusual bond distances or angles. The triazole and two phenyl rings are planar. On the basis of packing considerations the possibility of intermolecular interactions playing a role in the reactivity of the starting material is ruled out.

0108-2701/84/111901-05$01.50