Acta Cryst. (1974). B30, 2390

The Crystal and Molecular Structures of Thiosemicarbazones; an Antitumor Agent 5-Hydroxy-2-formylpyridine Thiosemicarbazone Sesquihydrate and the Inactive Acetone Thiosemicarbazone

BY GUS J. PALENIK

Center for Molecular Structures, Department of Chemistry, University of Florida, Gainesville, Florida 32611, *U.S.A.*

AND D. F. RENDLE* AND W. S. CARTER†

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada

(*Received* 10 *October* 1973; *accepted* 21 *May* 1974)

The crystal and molecular structures of two thiosemicarbazones have been determined by X-ray diffraction techniques. The antitumor agent 5-hydroxy-2-formylpyridine thiosemicarbazone sesquihydrate forms pale-yellow, orthorhombic crystals, with $a=13{\cdot}261$ (10), $b=11{\cdot}159$ (5) and $c=13{\cdot}699$ (4) Å, space group *Pbcn*, $Z=8$, ϱ(calc) = 1·466 g cm^{-3} and ϱ(obs) = 1·46 g cm^{-3}. Crystals of acetonethiosemicarbazone are colorless, with $a=7{\cdot}854$ (4), $b=7{\cdot}791$ (4), $c=6{\cdot}307$ (2) Å, $\alpha=111{\cdot}52$ (2), $\beta=109{\cdot}82$ (2) and $\gamma=85{\cdot}12$ (2)°, space group $P\bar{1}$ indicated by the intensity statistics. With two molecules per unit cell ϱ(calc) = 1·282 g cm^{-3} compared to ϱ(obs) = 1·27 g cm^{-3}. In both molecules the sulfur atom is *trans* to the nitrogen atom relative to the C–N bond. The most significant feature is the longer N–N bond [1·398 (6) Å] in acetonethiosemicarbazone compared to the N–N bond [1·379 (6) Å] in the 5-hydroxy-2-formylpyridine thiosemicarbazone. The shorter bond length appears to be related to an interaction with the pyridine ring.

Introduction

Thiosemicarbazones are a large group of organic derivatives whose biological activities are a function of the parent aldehyde or ketone. For example, acetone thiosemicarbazone (ATSC) has no known biological activity while Hagenbach & Gysin (1952) reported that 4-formylpyridine thiosemicarbazone has some antitubercular activity. French & Blanz (1966) found that α-(*N*)-formyl heteroaromatic thiosemicarbazones have antitumor activity but their toxicity has limited their clinical usefulness. However, Blanz & French (1968) found that 5-hydroxy-2-formylpyridine thiosemicarbazone, henceforth 5-OH-2FPTSC, had a much lower toxicity while still retaining favorable antitumor activity. Therefore, a crystal structure study of 5-OH-2FPTSC was undertaken as part of a program devoted to the structures and chelating properties of thiosemicarbazones. We were particularly interested in the crystal structure of an effective antitumor agent for a comparison with our results on other aryl thiosemicarbazones (Restivo & Palenik, 1970; Mathew & Palenik, 1971*a*) and their metal complexes (Mathew & Palenik, 1969, 1971*b*; Palenik, 1973).

A comparison of the structural data on thiosemicarbazones reported by Mathew & Palenik (1971*b*), Restivo & Palenik (1970), and Gabe, Taylor, Glusker, Menken & Patterson (1969) with thiosemicarbazide (Andreetti, Domiano, Gasparri, Nardelli & Sgarabotto, 1970) suggested that an interaction exists between the side-chain and the pyridine or thiophene rings. Therefore, we prepared acetone thiosemicarbazone as an example of a compound in which no interaction with the side chain is possible. A comparison of the results of our studies on 5-OH-2FPTSC and ATSC with the available structural data on other thiosemicarbazones has suggested some generalizations regarding the electronic structures, complexing abilities and biological activities of thiosemicarbazones.

Experimental

A sample of 5-OH-2FPTSC was kindly supplied by F. A. French, Mount Zion Hospital, San Francisco, California. Pale-yellow, rectangular parallelepipeds were grown from a 75% ethanol–water solution. Colorless crystals of ATSC were grown by cooling slowly a water–alcohol solution of the compound. Unit-cell dimensions were obtained from a least-squares fit of 2*θ* values for the Cu $K\beta$ peak ($\lambda=1{\cdot}39218$ Å) measured on General Electric XRD-6 diffractometer. The pertinent crystal data are summarized in Table 1. The intensity measurements for both compounds were made on the same instrument, with the stationary-crystal stationary-counter method. A wide beam of Cu $K\alpha_1$ radiation ($\lambda=1{\cdot}54051$ Å) was used with a nickel foil in front of the scintillation-counter window. Four standard reflections were measured after every 100

* Present address: Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada.

† Present address: Mount Union College, Alliance, Ohio, U.S.A.

reflections and were used to monitor the crystal alignment and stability. The variations of the standards (2% for 5-OH-2FPTSC and 1% for ATSC) were within the expected counting statistics and instrument stability. Multiple measurements (see Table 1) were made for all reflections with $2\theta \leq 135°$. An experimental background curve was derived by measurement of the background in areas of reciprocal space which were known to contain no reflections and which were free from streaking. The values obtained at a given 2θ angle were then averaged. Those reflections which had intensities (I) greater than B (background) $+3\sqrt{I}$ were used in the analyses. The remaining reflections were assigned a value of $\frac{1}{2}(3\sqrt{I})$ and flagged with a minus sign. After a correction for the α_1–α_2 splitting at high 2θ values, these data were then reduced to a set of structure amplitudes on an arbitrary scale.

Table 1. *Crystal data*

	5-OH-2FPTSC	ATSC
Formula	$C_7H_8N_4OS.1{\cdot}5H_2O$	$C_4H_9N_3S$
Crystal system	Orthorhombic	Triclinic
Space group	*Pbcn*	$P\bar{1}$
a(Å)	13·261 (10)	7·854 (4)
b	11·159 (5)	7·971 (4)
c	13·669 (4)	6·207 (2)
α		111·52 (2)
β		109·84 (2)
γ		85·15 (2)
V(Å^3)	2022·7	339·7
Z	8	2
D_c(g cm^{-3})	1·466	1·282
D_m	1·46	1·27
Crystal size (mm)	0·09 × 0·09 × 0·1	0·06 × 0·16 × 0·17
Number of measurements	6146	4261
Number of independent reflections	1830	1288
Number of observed reflections	1096	1152
Final R value	0·056	0·070

Structure determination and refinement

A sharpened, three-dimensional Patterson function was calculated for each compound. The sulphur atom was located and used to calculate phases for a Fourier synthesis. The light atoms were located in successive Fourier syntheses which were also used to refine the atomic positions. After the final Fourier synthesis, the R value, $R=\sum||F_o|-|F_c||\sum|F_o|$, was 0·22 for 5-OH-2FPTSC and 0·25 for ATSC.

Further refinement was carried out by full-matrix least-squares methods in each case. Employing individual isotropic thermal parameters reduced R to 0·17 for ATSC after three cycles and to 0·14 for 5-OH-2FPTSC after four cycles. Converting the thermal parameters to their anisotropic equivalent and continuing the refinement reduced R to 0·08 for 5-OH-2FPTSC after four cycles and to 0·12 for ATSC after three cycles. A difference Fourier synthesis was used to locate the hydrogen atoms in each compound. The hydrogen atoms contributions were included in the subsequent calculations but their parameters were not varied. Two additional least-squares cycles reduced R to 0·056 for 5-OH-2FPTSC while three least-squares cycles reduced R to 0·070 for ATSC. At this point all the shifts were less than 0·1 times their estimated standard deviations and therefore the refinement was considered complete. Two reflections 210 and $21\bar{1}$ were given zero weight in the ATSC refinement since they appeared to suffer from extinction. The weighting scheme used in the least-squares refinement was:

$$\sqrt{w}=|F(\text{obs})|/F(\text{low}) \text{ if } F(\text{obs})<F(\text{low})$$
$$\sqrt{w}=1 \text{ if } F(\text{low})\leq F(\text{obs})\leq F(\text{high})$$
$$\sqrt{w}=F(\text{high})/F(\text{obs}) \text{ if } F(\text{obs})>F(\text{high})$$

where $F(\text{low})=12{\cdot}0$ for 5-OH-2FPTSC and 6·0 for ATSC and $F(high)=40{\cdot}0$ for 5-OH-2FPTSC and 18·0 for ATSC. The scattering factors were taken from the

Table 2. *Final positional and thermal parameters* ($\times 10^4$) *and their estimated standard deviations in parentheses for 5-hydroxy-2-formylpyridine thiosemicarbazone*

The temperature factor for an atom is of the form $\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+\beta_{12}hk+\beta_{13}hl+\beta_{23}kl)]$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
S	1541 (1)	1987 (1)	828 (1)	26 (1)	57 (1)	79 (1)	23 (2)	−12 (2)	−11 (2)
N(1)	4139 (3)	375 (4)	1074 (3)	27 (2)	55 (4)	51 (3)	23 (5)	10 (5)	3 (6)
N(2)	3406 (3)	1246 (3)	1000 (4)	27 (2)	43 (4)	67 (4)	7 (5)	−1 (5)	−6 (6)
N(3)	2253 (2)	−226 (4)	709 (4)	31 (3)	57 (4)	80 (4)	1 (5)	−8 (6)	−18 (7)
N(4)	6737 (3)	429 (4)	1681 (3)	26 (3)	46 (3)	51 (3)	3 (5)	5 (5)	−1 (6)
C(1)	2454 (4)	910 (5)	834 (4)	28 (3)	65 (4)	46 (3)	9 (6)	−6 (6)	0 (8)
C(2)	5016 (4)	759 (4)	1277 (4)	28 (3)	58 (4)	42 (3)	−2 (7)	−4 (5)	4 (7)
C(3)	5857 (4)	−74 (5)	1417 (4)	24 (3)	52 (4)	36 (3)	−7 (6)	2 (5)	7 (7)
C(4)	5756 (4)	−1296 (5)	1310 (4)	28 (3)	56 (5)	58 (4)	−20 (6)	−14 (6)	4 (7)
C(5)	6573 (4)	−2035 (5)	1495 (4)	39 (3)	41 (4)	60 (4)	−14 (7)	0 (7)	4 (7)
C(6)	7472 (4)	−1528 (5)	1783 (4)	27 (3)	42 (4)	50 (3)	0 (6)	10 (6)	5 (7)
C(7)	7522 (4)	−289 (4)	1861 (4)	24 (3)	53 (5)	55 (4)	−13 (6)	−3 (7)	4 (8)
O(1)	8304 (3)	−2154 (3)	2004 (3)	31 (2)	46 (3)	74 (3)	26 (4)	−22 (4)	0 (5)
O(2)	272 (3)	−1266 (4)	816 (4)	41 (3)	102 (5)	91 (4)	−28 (5)	0 (5)	17 (7)
O(3)	0 (0)*	542 (6)	2500 (0)*	48 (4)	87 (6)	130 (7)	0 (0)*	2 (9)	0 (0)*

* Indicates a position fixed by the space group.

International Tables for X-ray Crystallography (1962). The final, non-hydrogen parameters for 5-OH-2FPTSC are given in Table 2, the hydrogen-atom parameters are given in Table 3. For ATSC the final non-hydrogen atom parameters are given in Table 4, the hydrogen-atom parameters in Table 5.*

Results and discussion

The atomic numbering, bond distances, and bond angles are shown in Fig. 1 for 5-OH-2FPTSC and in Fig. 2 for ATSC. The bond distances found in the thiosemicarbazide side chain of various thiosemicarbazones have been tabulated in Table 6, together with the distances reported for thiosemicarbazide, 4-phenyl thiosemicarbazide and 1-phenyl thiosemicarbazide. Excluding ATSC, the weighted average of the N(1)–N(2) distance in the various thiosemicarbazones is 1·372 (3) Å, which is significantly shorter than the average of 1·404 (8) Å for the N(1)–N(2) bond in ATSC and the various thiosemicarbazides. The most obvious explanation for the shortened N(1)–N(2) bond would involve an interaction with the group on C(2). Therefore, our study of ATSC suggests that aryl thiosemicarbazones can be treated as extensively delocalized systems. This conclusion is important in considering the reaction of thiosemicarbazones with Cu(II) and Fe(III).

* Tables of observed and calculated structure factors for ATSC and 5-OH-2FPTSC have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30508 (18 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

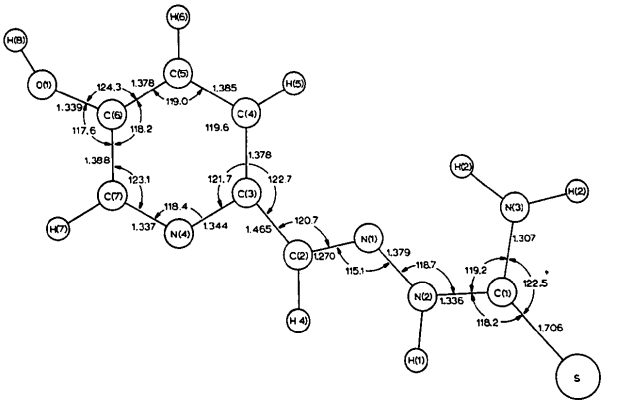

Fig. 1. Atomic numbering, bond distances and angles in 5-hydroxy-2-formylpyridine thiosemicarbazone. The angle C(2)–C(3)–N(4) of 115·5° was not included for clarity. The estimated standard deviations on bond angles is 0·5° and 0·006 Å for C(1)–S, N(1)–N(2) and C(6)–O(1) and 0·007 Å for the remaining distances.

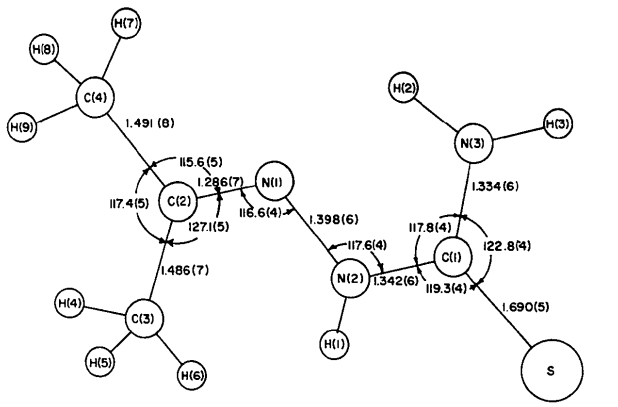

Fig. 2. Atomic numbering, bond distances and angles in acetonethiosemicarbazone. The estimated standard deviations are given in parentheses.

Table 3. *Hydrogen atom positions in 5-hydroxy-2-formylpyridine thiosemicarbazone*

The hydrogen atom is given followed by the atom to which it is bonded in brackets, the bond distance in Å, the positional parameters × 10^3 and the isotropic thermal parameter used in the structure-factor calculation.

Atom [bonded to]	Distance (Å)	x	y	z	B(Å^2)
H(1)[N(2)]	0·99	342	213	106	3·3
H(2)[N(3)]	0·90	168	−62	57	3·7
H(3)[N(3)	0·95	277	−78	54	3·7
H(4)[C(2)]	1·06	522	168	129	2·9
H(5)[C(4)	1·03	504	−165	129	3·2
H(6)[C(5)]	1·00	644	−292	141	3·4
H(7)[C(7)]	1·01	814	22	196	3·3
H(8)[O(1)]	0·82	848	−285	192	3·3
H(9)[O(2)]	0·93	−035	−133	50	5·4
H(10)[O(2)]	1·05	35	−106	156	5·4
H(11)[O(3)]	0·94	37	115	218	6·3

Table 4. *Final positional and thermal parameters* ($\times 10^4$) *and their estimated standard deviations in parentheses for acetone thiosemicarbazone*

The temperature factor for an atom is of the form $\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+\beta_{12}hk+\beta_{13}hl+\beta_{23}kl)]$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
S	566 (2)	2856 (2)	1864 (2)	220 (3)	142 (2)	271 (5)	98 (4)	153 (6)	152 (5)
N(1)	2618 (5)	−173 (5)	5773 (7)	193 (9)	165 (8)	301 (16)	62 (14)	122 (20)	230 (19)
N(2)	1990 (5)	421 (5)	3792 (7)	206 (10)	137 (8)	265 (15)	97 (13)	124 (19)	153 (17)
N(3)	1339 (6)	3049 (5)	6470 (7)	226 (10)	159 (8)	275 (16)	104 (14)	192 (20)	119 (18)
C(1)	1323 (6)	2072 (6)	4197 (8)	141 (10)	144 (9)	288 (18)	51 (15)	108 (21)	171 (21)
C(2)	3364 (6)	−1705 (6)	5389 (9)	139 (10)	161 (10)	355 (20)	38 (16)	133 (23)	241 (23)
C(3)	3641 (8)	−2913 (7)	3069 (10)	258 (13)	170 (10)	387 (21)	130 (19)	272 (28)	197 (25)
C(4)	4045 (8)	−2296 (8)	7538 (11)	289 (15)	258 (13)	450 (25)	145 (23)	257 (31)	461 (31)

Table 5. *Probable hydrogen-atom positions in acetone thiosemicarbazone*

The hydrogen atom is given followed by the atom to which it is bonded in brackets, the bond distance in Å, the positional parameters $\times 10^3$ and the isotropic thermal parameter used in the least-squares calculations.

Atom [bonded to]	Distance	x	y	z	B
H(1)[N(2)]	0·78	198	−23	250	4·0
H(2)[N(3)]	1·04	195	233	761	4·5
H(3)[N(3)]	1·13	76	443	683	4·5
H(4)[C(3)]	1·21	308	−412	250	5·5
H(5)[C(3)]	0·98	479	−400	337	5·5
H(6)[C(3)]	0·92	381	−263	185	5·5
H(7)[C(4)]	1·09	354	−140	897	5·5
H(8)[C(4)]	1·31	582	−233	821	5·5
H(9)[C(4)]	1·28	434	−398	674	5·5

The C(2)–N(1) distance of 1·286 (7) Å found in ATSC must be an upper limit for a C–N double bond. Although an interaction between C(2) and the methyl groups is impossible, any interaction between C(2) and the side chain will decrease the C(2)–N(1) bond order. The value of 1·30 (4) Å has been proposed by Trefonas, Flurry, Majeste, Meyers & Copeland (1966), but the relatively large estimated standard deviation limits the usefulness of the value. However, if one compares ATSC with TSC, the differences in the bond lengths in the two compounds can be rationalized by the inclusion of resonance forms involving C(2)–N(1)=N(2) which lengthen C(2)–N(1) and shorten N(1)–N(2). Under these conditions, C(2)–N(1) must be slightly longer than a pure C–N double bond.

Table 6. *A comparison of the distances found in various thiosemicarbazones*

	C(2)–N(1)	N(1)–N(2)	N(2)–C(1)	C(1)–S	C(1)–N(3)
4-FPYTSC	1·275 (3)	1·365 (3)	1·354 (3)	1·678 (2)	1·329 (3)
2-FTTSC	1·282 (4)	1·369 (4)	1·343 (4)	1·698 (3)	1·306 (4)
	1·290 (4)	1·380 (3)	1·346 (4)	1·691 (3)	1·327 (4)
KTS	1·285 (6)	1·371 (6)	1·351 (6)	1·692 (4)	1·310 (6)
	1·294	1·371	1·359	1·687	1·305
	1·284	1·379	1·351	1·689	1·314
	1·290	1·365	1·352	1·682	1·311
5OH-2FPTSC	1·270 (7)	1·379 (6)	1·336 (7)	1·706 (6)	1·307 (7)
ATSC	1·286 (7)	1·398 (6)	1·342 (6)	1·690 (5)	1·344 (6)
TSC		1·411 (2)	1·326 (2)	1·707 (2)	1·316 (3)
4-PTS		1·431 (6)	1·357 (7)	1·685 (5)	1·349 (7)
1-PTS		1·395 (2)	1·330 (2)	1·696 (2)	1·320 (2)

4-FPYTSC: 4-formylpyridine thiosemicarbazone (Restivo & Palenik, 1970).
2-FTTSC: 2-formylthiophene thiosemicarbazone (Mathew & Palenik, 1971*b*).
KTS: 2-keto-3-ethoxybutyraldehyde thiosemicarbazone (Gabe *et al.*, 1969).
TSC: thiosemicarbazide (Andreetti *et al.*, 1970).
4-PTS: 4-phenyl thiosemicarbazide (Kálmán, Argay & Czugler, 1972).
1-PTS: 1-phenyl thiosemicarbazide (Czugler, Kálmán & Argay, 1973).

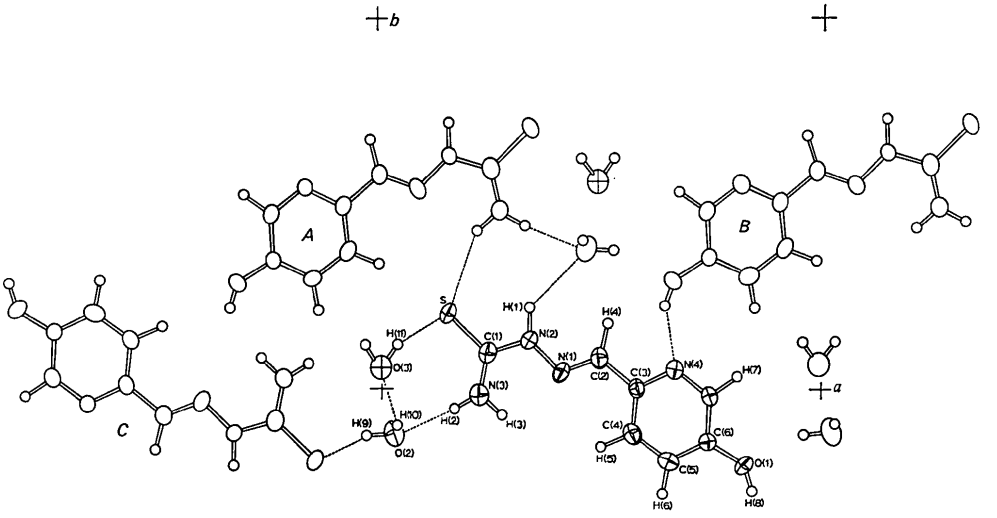

Fig. 3. A packing diagram for 5-hydroxy-2-formylpyridine thiosemicarbazone. The numbered model corresponds to the coordinates given in Tables 2 and 3. Molecule *A* is at $\frac{1}{2}-x, \frac{1}{2}+y, z$; molecule *B* is at $\frac{3}{2}-x, \frac{1}{2}+y, z$ and molecule *C* is at $-x, -y, -z$. The probable hydrogen bonds are shown by broken lines.

There is a large variation (1·678 to 1·706 Å) in the C–S distances in the various thiosemicarbazones given in Table 6. Apparently, the parent aldehyde or ketone has a strong influence on the C–S bond distance. A strong substituent-chain interaction might give rise to a long C–S bond correlated with a short C(2)–N(1) bond. We might also anticipate that the N(1)–N(2) bond length would be related to the C–S and C(2)–N(1) bond distances. Unfortunately, no obvious correlation exists between any of the various bond lengths. However, hydrogen bonds are important in all the thiosemicarbazones and therefore, small differences in bond lengths may be perturbed by the different hydrogen-bonding patterns.

In the thiosemicarbazones, excluding ATSC, the C(1)–N bonds in the chain are significantly different. The weighted averages are: C(1)–N(2) is 1·350 (4) Å and C(1)–N(3) is 1·318 (4) Å. This difference is reasonable since in the case of N(3), we have an NH_2 group while for N(2), we have an NH attached to another nitrogen atom. In addition, the most reasonable resonance forms for thiosemicarbazones all have greater double-bond character in the C(1)–N(3) bond. Although there should be an approximate correlation between a long C–S bond and a short C(1)–N(3) bond, the relationship is not exact. The NH_2 group is invariably involved in hydrogen-bonding which slightly perturbs the C(1)–N(3) bond distance.

In summary, therefore, we see that certain thiosemicarbazones (usually those containing aryl groups) can be considered as delocalized systems. There are approximate correlations between the distances in these molecules which support the delocalization hypothesis. In addition, the dimensions found in ATSC, where two CH_3 groups limit the resonance forms, are consistent with a delocalized system in the other cases.

In both ATSC and 5-OH-2FPTSC the molecules are hydrogen-bonded in the solid state. The molecular packing is illustrated in Figs. 3 and 4, and the probable hydrogen bonds are tabulated in Table 7. In ATSC the two N–H···S hydrogen bonds are across centers of symmetry at 0,0,0 and $0,\frac{1}{2},\frac{1}{2}$, resulting in a zigzag chain of ATSC molecules in the crystal. The methyl groups in ATSC form the outside of the chain, and the contacts between chains involve only van der Waals forces. The geometry of the N–H···S bonds found in ATSC is typical of the hydrogen bonding found in other thiosemicarbazones by Restivo & Palenik (1970) and Mathew & Palenik (1971*a*).

In 5-OH-2FPTSC the hydrogen bonding is somewhat more complicated because of the water molecules and OH group on the pyridine ring. Of the seven hydrogen atoms capable of forming hydrogen bonds, five definitely are involved in hydrogen bonding. The remaining two hydrogen atoms, H(10) and H(1), have two contacts which are possibly weak hydrogen bonds. One interesting feature of the hydrogen-bonding in 5-OH-2FPTSC in the absence of N–H···S hydrogen bonds across a center of symmetry; these bonds are present in other thiosemicarbazones, see above. In addition, the S atom in 5-OH-2FPTSC is the acceptor for three hydrogen bonds involving H(1), H(9) and the H(11) and the C–S distance is one of the longest observed in thiosemicarbazone. This observation points out the difficulties in comparing bond distances in solids when hydrogen bonds are present.

Biological implications

Thiosemicarbazones which are active antitumor agents are also potent inhibitors of the mammalian form of the enzyme ribonucleoside diphosphate reductase. The

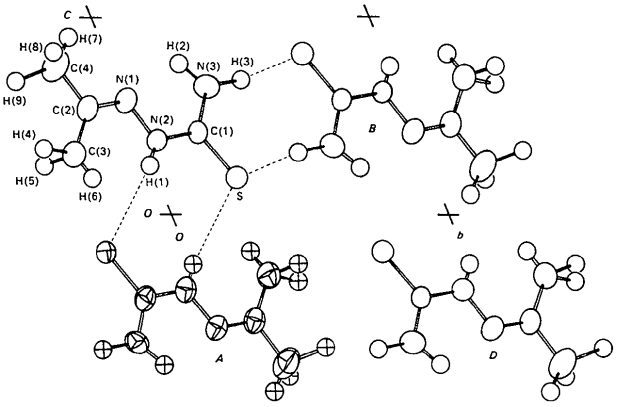

Fig. 4. A packing diagram for acetone thiosemicarbazone showing the possible hydrogen bonds by a broken line. Molecule *A* is at $-x,-y,-z$; molecule *B* at $-x,1-y,1-z$ and molecule *D* at $-x,1-y,-z$.

Table 7. *Hydrogen bonds*

D–H···*A*	Position of *A*	*D*–H	H···*A*	*D*···*A*	∠*D*–H···*A*	∠H–*D*···*A*
5-Hydroxy-2-formylpyridine thiosemicarbazone						
O(1)–H(8)···N(4)	$\frac{3}{2}-x,-\frac{1}{2}+y,z$	0·82	1·972 Å	2·734 Å	154·3°	18·2°
O(2)–H(9)···S	$-x,-y,-z$	0·93	2·515	3·388	155·8	17·7
O(2)–H(10)···O(3)	x,y,z	1·05	2·246	3·082	134·9	31·1
O(3)–H(11)···S	x,y,z	0·95	2·584	3·464	154·4	18·8
N(3)–H(2)···O(2)	x,y,z	0·90	2·026	2·874	156·1	16·6
N(3)–H(3)···S	$\frac{1}{2}-x,-\frac{1}{2}+y,z$	0·96	2·677	3·501	144·6	26·3
N(2)–H(1)···O(2)	$\frac{1}{2}-x,\frac{1}{2}+y,z$	0·99	2·515	3·294	134·9	32·8
Acetone thiosemicarbazone						
N(2)–H(1)···S	$-x,-y,-z$	0·78	2·930	3·543	137·6	25·8
N(3)–H(3)···S	$-x,1-y,1-z$	1·13	2·309	3·423	169·4	7·1

blocking of the conversion of ribonucleotides to deoxyribonucleotides results in an inhibition of the synthesis of DNA, the mechanism proposed by French, Blanz, Shaddix & Brockman (1974) to explain the antitumor activities of thiosemicarbazones. There are indications that either an iron chelate is the active inhibitor agent or that the thiosemicarbazones coordinate to the iron atom in the enzyme thereby blocking the active site. In either case the coordinating ability of the thiosemicarbazone is of prime concern. However, both acetone thiosemicarbazone which can function as a neutral bidentate ligand and benzaldehyde thiosemicarbazone which can function as a mononegative bidentate chelate (Palenik, 1973), are devoid of any antitumor activity. Therefore, the *planar mono-negative tridentate* nature of the active thiosemicarbazones appears to be an essential feature for antitumor activity.

One possible explanation for the high activity of thiosemicarbazones as inhibitors of the enzyme involves our observation that there is extensive delocalization involving the aryl group and the thiosemicarbazide side chain. The result is a change in the reducing properties of the thiosemicarbazone so that complexes with Cu(II), for example, can be formed in some cases while a reduction of Cu(II) to Cu(I) occurs with alkyl thiosemicarbazones. The net effect might be compared to a tuning of the sulfur atom to a particular combination of ligands and metal ions. Under these circumstances, the thiosemicarbazone could function by removing the iron atom from the enzyme and hence rendering the enzyme inactive. The possibility is supported by the observation of French, Lewis, Blanz & Sheena (1965) that thiosemicarbazones cause urinary and fecal excretion of iron as a green ferrous complex. Studies are in progress on other possible tridentate, sulfur-containing ligands which might be useful antitumor agents.

We should like to thank Fred French for the sample of 5-hydroxy-2-formylpyridine thiosemicarbazone, the National Research Council of Canada, the U. S. Public Health Service, National Cancer Institute for Financial Support through Grant CA-12390, and the Northeast Regional Data Center of the University of Florida for a grant of computer time.

References

ANDREETTI, G. D., DOMIANO, P., GASPARRI, G. F., NARDELLI, M. & SGARABOTTO, P. (1970). *Acta Cryst.* B**26**, 1005–1009.

BLANZ, E. J. JR & FRENCH, F. A. (1968). *Cancer Res.* **28**, 2419–2422.

CZUGLER, M., KÁLMÁN, A. & ARGAY, G. (1973). *Cryst. Struct. Commun.* **2**, 655–658.

FRENCH, F. A. & BLANZ, E. J. JR (1966). *J. Med. Chem.* **9**, 585–589.

FRENCH, F. A., BLANZ, E. J. JR, SHADDIX, S. C. & R. W. BROCKMAN (1974). *J. Med. Chem.* **17**, 172–181.

FRENCH, F. A., LEWIS, A. E., BLANZ, E. J. JR & SHEENA, A. H. (1965). *Fed. Proc. Fed. Amer. Soc. Exp. Biol.* **24**, 402.

GABE, E. J., TAYLOR, M. R., GLUSKER, J. P., MENKEN, J. A. & PATTERSON, A. L. (1969). *Acta Cryst.* B**25**, 1620–1631.

HAGENBACH, R. E. & GYSIN, H. (1952). *Experientia*, **8**, 184–185.

International Tables for X-ray Crystallography (1962). Vol. III, p. 201. Birmingham: Kynoch Press.

KÁLMÁN, A., ARGAY, G. & CZUGLER, M. (1972). *Cryst. Struct. Commun.* **1**, 375–378.

MATHEW, M. & PALENIK, G. J. (1969). *J. Amer. Chem. Soc.* **91**, 6310–6314.

MATHEW, M. & PALENIK, G. J. (1971*a*). *Acta Cryst.* B**27**, 59–66.

MATHEW, M. & PALENIK, G. J. (1971*b*). *Inorg. Chem. Acta*, **5**, 349–353.

PALENIK, G. J. (1973). Unpublished results.

RESTIVO, R. & PALENIK, G. J. (1970). *Acta Cryst.* B**26**, 1397–1402.

TREFONAS, L. M., FLURRY, R. L. JR, MAJESTE, R., MEYERS, E. A. & COPELAND, R. F. (1966). *J. Amer. Chem. Soc.* **88**, 2145–2149.