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2-Formyl-5-benzylpyridine Thiosemicarbazone

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Abstract. $C_{14}H_{14}N_4S$, monoclinic, $C2/c$, a = 27·596 (3), b = 6·056 (1), c = 17·625 (3) Å, β = 110·51 (2)°, M_r = 270·36, Z = 8, D_c = 1·302, D_x = 1·31 g cm^{-3} (by flotation). The molecular conformation is such that both the pyridine N atom and the S atom are *trans* to N(4). The thiosemicarbazone side chain is planar and twisted 6° relative to the pyridine ring.

Introduction. Crystals of the title compound were grown by slowly cooling a sealed ampoule containing a saturated solution in acetonitrile. The ampoule was placed in a Dewar flask initially containing boiling water and cooled to room temperature over a period of approximately four days. A pale yellow, irregularly shaped crystal approximately 0·33 × 0·17 × 0·10 mm was mounted with the [110] axis coincident with the φ axis of a Picker FACS-I computer-controlled diffractometer. Lattice constants were determined by carefully measuring with a narrow slit both plus and minus 2θ values of the Cu $K\alpha_1$, $K\alpha_2$ doublet for 15 reflections with $2\theta > 61°$, curve-fitting the resultant profiles for each reflection, and finally by a least-squares refinement. Three-dimensional intensity data were collected with Ni-filtered Cu $K\overline{\alpha}$ radiation (λ = 1·54178 Å) using a variable scan width (2·4° + 0·72° tan θ), a $\theta/2\theta$ scan (2° min^{-1}), and 10 s background measurements at both extremities of the scan. 2181 independent reflections were measured to a maximum 2θ of 125° (d = 0·87 Å). Intensities of three standard reflections, monitored every block of 50 reflections, remained within 5% of their mean values throughout the entire data collection, indicating both crystal and electronic stability. Structure amplitudes and their estimated errors were calculated from the expressions $|F_o| = (QI_n)^{1/2}$ and $\sigma^2(F_o) = (Q/4I_n)[I_s + (t_s/t_b)^2 I_b + (0{\cdot}02I_n)^2]$, where Q contains corrections for Lorentz–polarization and absorption, I_s and I_b are the scan and background intensities, t_s and t_b are the scan and background times, and I_n is the net integrated intensity. Absorption was corrected for as a function of φ (obtained from a φ scan at $\chi = 90°$) with a maximum deviation of 38% (linear μ = 19·5 cm^{-1} for Cu $K\alpha$ radiation). 1602 (73%) reflections had $|F_o| > 3\sigma(F_o)$ and were used in the structure determination and refinement.

Normalized structure amplitudes, $|E|$'s were calculated from a $K(s)$ curve and rescaled by parity groups (we were unable to solve the structure from $|E|$'s that were normalized, $\langle E^2 \rangle$ = 1·0, as a whole rather than by parity groups). The structure was solved using *MULTAN* (Germain, Main & Woolfson, 1971) and refined by block-diagonal least squares [minimizing $\sum w(\Delta F)^2$]. The scattering factors for all non-hydrogen atoms were taken from the tabulation of Cromer & Waber (1965) while that for H was from Stewart, Davidson & Simpson (1965). After 15 cycles of isotropic refinement of non-hydrogen atoms, the H atom coordinates were determined from a ΔF map (typical peak heights were 0·5 to 0·7 e Å^{-3}). Refinement was terminated after an additional 10 cycles of refinement in which the non-hydrogen atoms were refined with anisotropic temperature factors and the H atoms with isotropic temperature factors. The largest shift was less than 0·1 times its estimated standard

deviation and a final difference electron density map showed a maximum peak height of 0·5 e Å^{-3}. The final R values are $R = 0{\cdot}063$ ($\sum |\Delta F| / \sum |F|$) and $R_w = 0{\cdot}056$ $\{[\sum w(\Delta F)^2 / \sum wF^2]^{1/2}\}$ for observed data and $R = 0{\cdot}086$ and $R_w = 0{\cdot}057$ for all data.*

Discussion. For several years we have been interested in studying the effect of α-(N)-heterocyclic carboxaldehyde thiosemicarbazones on the enzyme ribonucleoside diphosphate reductase. A direct correlation between the growth rate of a series of rat hepatomas and the activity of this enzyme has been established and, since the deoxyribonucleotides are present in relatively low levels in mammalian cells, it seems reasonable that a potent inhibitor of this enzyme will retard the growth of a cancer cell. In order to expand the utility of this class of compounds, one of us has synthesized (Agrawal, Booth, DeNuzzo & Sartorelli, 1976) a large number of derivatives to determine the factors which govern the inhibitory specificity toward the target enzyme and also to produce an agent which is not susceptible to enzymatic degradation in man. To complement the synthetic approach to the structure–activity work, we have also initiated a series of structural investigations to determine more precisely the molecular conformation and electronic distributions necessary for maximum inhibitory activity. In this paper we report the structure of an inactive agent, 2-formyl-5-benzylpyridine thiosemicarbazone (5-BPT), and compare it to both active and inactive structures which have previously been studied.

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33390 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *Fractional atomic coordinates with estimated standard deviations* (×10^4)

	x	y	z
N(1)	2141 (1)	9693 (6)	4426 (2)
C(2)	2535 (1)	9451 (7)	4152 (2)
N(3)	2506 (1)	7716 (6)	3667 (2)
N(4)	2090 (1)	6314 (6)	3454 (2)
C(5)	2097 (1)	4770 (7)	2979 (2)
C(6)	1695 (1)	3115 (6)	2715 (2)
C(7)	1286 (1)	2968 (7)	3015 (2)
C(8)	933 (1)	1309 (8)	2743 (2)
C(9)	979 (1)	−232 (7)	2190 (2)
C(10)	1398 (1)	43 (7)	1933 (2)
N(11)	1745 (1)	1643 (6)	2179 (2)
C(12)	607 (1)	−2104 (7)	1882 (3)
C(13)	69 (1)	−1484 (7)	1320 (2)
C(14)	−53 (1)	558 (7)	954 (2)
C(15)	−547 (2)	1017 (8)	423 (2)
C(16)	−924 (1)	−577 (9)	253 (2)
C(17)	−810 (2)	−2616 (9)	613 (3)
C(18)	−317 (2)	−3064 (8)	1151 (3)
S	3043 (0)	11166 (2)	4388 (1)
H(1)	1878 (13)	8477 (64)	4251 (22)
H(1)′	2140 (11)	10842 (61)	4693 (19)
H(3)	2788 (17)	7332 (83)	3546 (27)
H(5)	2395 (12)	4490 (63)	2826 (20)
H(7)	1283 (11)	4068 (57)	3355 (18)
H(8)	628 (14)	1390 (69)	2862 (23)
H(10)	1446 (11)	−1270 (56)	1641 (18)
H(12)	582 (14)	−2914 (14)	2325 (23)
H(12′)	767 (12)	−3142 (59)	1627 (20)
H(14)	212 (10)	1836 (50)	1078 (17)
H(15)	−646 (11)	2449 (57)	182 (18)
H(16)	−1298 (12)	−125 (64)	−150 (19)
H(17)	−1073 (13)	−3776 (69)	463 (23)
H(18)	−205 (11)	−4608 (59)	1431 (18)

Table 2. *Bond distances* (Å) *and bond angles* (°)

S–C(2)	1·675 (4)	C(10)–N(11)	1·325 (5)
N(1)–C(2)	1·345 (5)	N(11)–C(6)	1·343 (5)
C(2)–N(3)	1·338 (5)	C(9)–C(12)	1·498 (6)
N(3)–N(4)	1·372 (4)	C(12)–C(13)	1·516 (6)
N(4)–C(5)	1·261 (6)	C(13)–C(14)	1·381 (6)
C(5)–C(6)	1·447 (6)	C(13)–C(18)	1·385 (6)
C(6)–C(7)	1·407 (5)	C(14)–C(15)	1·384 (6)
C(7)–C(8)	1·363 (6)	C(15)–C(16)	1·373 (6)
C(8)–C(9)	1·387 (6)	C(16)–C(17)	1·373 (7)
C(9)–C(10)	1·391 (5)	C(17)–C(18)	1·386 (6)
S–C(2)–N(1)	123·7 (3)	C(10)–C(9)–C(12)	121·0 (4)
S–C(2)–N(3)	120·3 (3)	C(9)–C(10)–N(11)	124·7 (4)
N(1)–C(2)–N(3)	116·1 (3)	C(10)–N(11)–C(6)	118·3 (3)
C(2)–N(3)–N(4)	121·2 (3)	C(9)–C(12)–C(13)	116·0 (4)
N(3)–N(4)–C(5)	115·7 (3)	C(12)–C(13)–C(14)	123·4 (4)
N(4)–C(5)–C(6)	122·6 (3)	C(12)–C(13)–C(18)	118·2 (4)
C(5)–C(6)–C(7)	123·4 (3)	C(14)–C(13)–C(18)	118·3 (4)
C(5)–C(6)–N(11)	115·4 (3)	C(13)–C(14)–C(15)	121·2 (4)
C(7)–C(6)–N(11)	121·2 (3)	C(14)–C(15)–C(16)	119·8 (4)
C(6)–C(7)–C(8)	118·7 (4)	C(15)–C(16)–C(17)	119·9 (4)
C(7)–C(8)–C(9)	121·0 (3)	C(16)–C(17)–C(18)	120·2 (4)
C(8)–C(9)–C(10)	116·0 (4)	C(17)–C(18)–C(13)	120·6 (4)
C(8)–C(9)–C(12)	123·0 (3)		

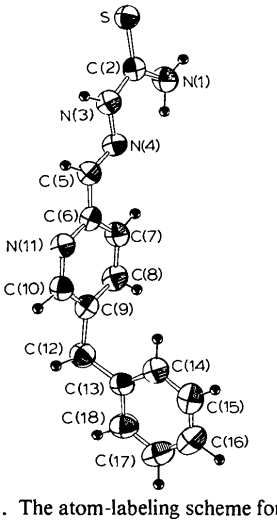

Fig. 1. The atom-labeling scheme for 5-BPT.

Table 3. *Intermolecular hydrogen bonds and non-bonded contacts less than* 3·5 Å

D—H···*A*	Equivalent position of acceptor	*D*—H	H—*A*	*D*—*A*	∠*D*—H···*A*
N(1)—H(1)′···S	$(\frac{1}{2}-x, \frac{5}{2}-y, 1-z)$	0·84 Å	2·60 Å	3·42 Å	165°
N(3)—H(3)···N(11)	$(\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z)$	0·90	2·16	3·01	159

Atom 1	Atom 2	Equivalent position of atom 2	Distance
N(1)	N(3)	$(\frac{1}{2}-x, \frac{3}{2}-y, 1-z)$	3·48 Å
N(1)	C(2)	$(\frac{1}{2}-x, \frac{3}{2}-y, 1-z)$	3·44
N(1)	C(7)	$(x, 1+y, z)$	3·40
N(11)	C(5)	$(\frac{1}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z)$	3·49

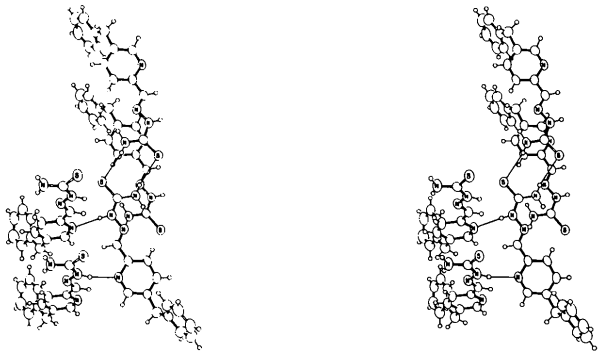

Fig. 2. Intermolecular hydrogen bonding between the molecule described in Table 1 and its neighbors.

The fractional atomic coordinates and their estimated standard deviations for 5-BPT are listed in Table 1. Table 2 lists the non-hydrogen bond distances and bond angles. 5-BPT has been shown to be inactive against mice bearing Sarcoma 180 ascites cells. However, the overall conformation of the thiosemicarbazone side chain and the pyridine ring (as shown in Fig. 1) closely resembles both the marginally active derivative 2-formyl-4-phenylpyridine thiosemicarbazone (4-PPT) (Brown & Agrawal, 1977) and active derivatives 2-formyl-5-hydroxypyridine thiosemicarbazone (5-HP) (Palenik, Rendle & Carter, 1974) and 2-formyl-4-morpholinopyridine thiosemicarbazone (4-MPT) (Brown & Agrawal, 1978). In the crystalline state there seem to be no significant differences in bond distances among the four molecules.

The relative inactivity of 5-BPT as compared to 4-PPT may be a consequence of the bulk tolerance of the enzyme ribonucleoside diphosphate reductase toward the chelating derivatives. Since 4-PPT is essentially a planar molecule (as are 5-HP and 4-MPT) and 5-BPT is not planar, the active site of the enzyme may require a relatively planar ligand. The structure–activity-relationship studies also seem to support this argument.

The pyridine ring and benzyl moiety show no unusual features. The least-squares plane of the pyridine ring [atoms C(6) through N(11); $0{\cdot}0216x - 0{\cdot}0958y + 0{\cdot}0455z = 3{\cdot}22$; standard deviation of 0·003 Å] makes an angle of 78·2° to the least-squares plane of the phenyl ring [atoms C(13) through C(18); $-0{\cdot}0100x + 0{\cdot}0538y + 0{\cdot}0461z = 1{\cdot}722$; standard deviation of 0·004 Å]. The average C—C distance and C—C—C angle within the phenyl ring are 1·380 ± 0·005 Å and 120·0 ± 0·6° respectively.

Table 3 lists the intermolecular contacts and hydrogen bonds for 5-BPT and Fig. 2 illustrates the hydrogen bonds from one molecule to its neighbors. The hydrogen bond between H(1)′ and S at 2·60 Å is almost identical to the hydrogen bond observed in 4-MPT. H(1) does not intermolecularly hydrogen bond as it does in other molecules but does remain in the best position for intramolecular hydrogen bonding to N(4) [N(1)—H(1)···N(4) = 108°, H(1)···N(4) = 2·15 Å]. The moiety consisting of H(1), N(1), C(2), S, N(3), and N(4) has a standard deviation of 0·02 Å for a least-squares plane. N(11) is the acceptor in a strong hydrogen bond with H(3) on N(3).

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