into pairs of long axial and short equatorial bonds of a t.b.p. (1·798 and 1·833 *versus* 1·798 and 1·793 Å). The average deviation of the four O atoms from coplanarity divided by $\frac{1}{4}$ of the 'equatorial' bond lengths is a sensitive criterion for classifying every geometry between t.b.p. and r.p. (Wunderlich, 1978). The average distance of the four O atoms from their least-squares plane is 0·116 Å; thus the geometry is 0·116/0·449 = 0·26 away from the ideal r.p. and can be called a 74% r.p. Because of enlarged bond lengths (average difference 0·15 Å) at the As atom, the steric hindrance of the methyl group in this arsorane is reduced in comparison with the analogous phosphorane which was described as an 86% r.p. (Wunderlich, 1976). A similar spiroarsorane (Goldwhite, Grey & Teller, 1976) containing a phenyl group as the fifth ligand is described as intermediate between t.b.p. and r.p. This could not be evaluated by the above criterion, since atomic parameters were not reported. However, by consideration of the central angles (axial 169·8, equatorial 117·4, 118·0, 124·6°) the geometry is 75% t.b.p. [angle criterion according to Holmes (1974)].

Compared with spirocyclic oxyphosphoranes the organic moiety of the molecule shows no unusual features although several deviations from standard basic geometries do occur. The six-membered rings are squeezed toward the centre of the molecule and are planar within 0·017 Å. The five-membered rings are planar within 0·033 Å and are coplanar with the benzene rings within 2·5°.

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2-Formyl-4-morpholinopyridine Thiosemicarbazone

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(*Received* 31 *August* 1977; *accepted* 12 *November* 1977)

Abstract. $C_{11}H_{15}N_5OS$, $P2_1/c$, monoclinic, a = 7·458 (1), b = 11·653 (1), c = 15·732 (1) Å, β = 109·51 (1)°, D_x = 1·37 g cm^{-3}, Z = 4. The conformation of the molecule is similar to that observed in related thiosemicarbazone derivatives and suggests that the overall conformation of the thiosemicarbazone moiety is not responsible for increased or decreased biological activity.

Introduction. Several studies, which have been reviewed recently (Agrawal & Sartorelli, 1975) have shown that α-(*N*)-heterocyclic carboxaldehyde thiosemicarbazones possess significant antineoplastic activity against a wide variety of transplanted tumors. It is believed that these compounds inhibit the biosynthesis of DNA by blocking the conversion of ribonucleotides to deoxyribonucleotides. Kinetic data support an inhibitory mechanism in which either a preformed Fe chelate of the molecule interacts with the target enzyme, ribonucleoside-diphosphate reductase, or the ligand itself coordinates to the Fe-charged enzyme (Sartorelli, Agrawal & Moore, 1971). Among the initial

molecules studied in man was 2-formyl-5-hydroxypyridine thiosemicarbazone (5-HP) which, although effective against transplanted murine neoplasms, found little utility in man since it was shown to be rapidly metabolized and excreted as an *O*-glucuronide. In order to expand the utility of this class of molecules, one of us has synthesized (Agrawal, Booth, DeNuzzo & Sartorelli, 1976) a large number of derivatives to determine the bulk tolerance for the interaction between the enzyme, inhibitor, and the Fe^{2+} ion and to design an agent which might (*a*) not be as susceptible to enzymatic degradation in man and (*b*) possess a greater inhibitory activity towards the target enzyme.

To complement the synthetic approach to the structure–activity relation already in progress and to determine more precisely the molecular conformations and electronic distributions necessary in these compounds for maximum biological activity, we have begun a series of single-crystal X-ray diffraction studies on both biologically active and inactive molecules of this class. We have previously reported the structure of 2-formyl-4-phenylpyridine thiosemicarbazone (4-PPT) (Brown & Agrawal, 1977), an agent possessing borderline biological activity. We now report the structure of 2-formyl-4-morpholinopyridine thiosemicarbazone (4-MPT), an agent which is significantly superior to 5-HP as an antineoplastic agent in mice bearing Sarcoma 180 ascites cells.

A single crystal of the title compound, grown from methanol and measuring 0·40 × 0·33 × 0·20 mm, was mounted with the [10$\bar{6}$] axis coincident with the φ axis of a Picker computer-controlled four-circle diffractometer. Examination of the reciprocal lattice showed $2/m$ symmetry with systematic extinctions $k = 2n + 1$ for $0k0$ and $l = 2n + 1$ for $h0l$ reflections, uniquely characterizing the space group as $P2_1/c$. Lattice constants were determined by carefully measuring the Cu $K\alpha_1$–$K\alpha_2$ doublet for 18 reflections with $2\theta > 60°$.

Three-dimensional intensity data were collected with Ni-filtered Cu $K\bar{\alpha}$ radiation to $2\theta = 125°$ with a fixed θ:2θ scan rate of 2° min^{-1}. A variable scan width, 2·4° + 0·72° tan θ, with 10 s background measurements at both extremities of the scan, was used to measure 2067 independent reflections. Periodic measurements of three reference reflections showed a systematic decay of 1·2% and a random variation of approximately 2%. Intensities were corrected for absorption as a function of φ (maximum deviation of 19% in a φ scan at $\chi = 90°$; linear $\mu = 21{\cdot}5$ cm^{-1} for Cu $K\alpha$), for linear decay, for Lorentz and polarization effects in the usual manner, and then converted to structure amplitudes. 1833 reflections (88%) for which $|F| > 3\sigma(F)$ were considered statistically observed and used in the subsequent calculations.

The structure was solved by straightforward application of *MULTAN* (Germain, Main & Woolfson, 1971). Isotropic refinement of the 18 non-hydrogen atoms by block-diagonal least squares with $1/\sigma^2$ weights [minimizing $\Sigma w(\Delta F)^2$] led to $R = 0{\cdot}14$ ($\Sigma|\Delta F|/\Sigma|F|$). Scattering factors for non-hydrogen atoms were taken from Cromer & Waber (1965) while those for H were from Stewart, Davidson & Simpson (1965). All H atoms were easily located in a subsequent ΔF synthesis. The final R values after 20 cycles of refinement (non-hydrogen atoms, anisotropic; H atoms, isotropic) are $R = 0{\cdot}046$ and $R_w = 0{\cdot}056$ $\{[\Sigma w(\Delta F)^2/\Sigma wF^2]^{1/2}\}$ for observed data and $R = 0{\cdot}051$ and $R_w = 0{\cdot}057$ for all data. A final difference electron density map showed no peak greater than 0·5 e Å^{-3}. The shifts in all parameters were less than 0·05 times their respective estimated standard deviation.*

Discussion. The final fractional coordinates for 4-MPT are listed in Table 1 along with their estimated standard deviations. Bond distances and angles among non-hydrogen atoms are listed in Table 2. Fig. 1 is an *ORTEP* drawing of the molecule.

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33174 (12 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* (×10^5; *for* H ×10^4) *and estimated standard deviations*

	x	*y*	*z*
N(1)	8486 (35)	82490 (18)	20610 (14)
C(2)	2212 (37)	88695 (21)	13201 (16)
N(3)	4426 (34)	84388 (18)	5657 (14)
N(4)	12258 (31)	73754 (17)	5706 (14)
C(5)	11981 (36)	70072 (21)	−1959 (16)
C(6)	18516 (34)	58526 (20)	−3027 (15)
C(7)	25625 (36)	51215 (21)	4256 (16)
C(8)	30326 (35)	39908 (20)	2874 (16)
C(9)	28526 (42)	37092 (21)	−5981 (18)
C(10)	21714 (43)	44955 (22)	−12723 (17)
N(11)	16452 (33)	55705 (18)	−11581 (13)
N(12)	35479 (31)	31957 (18)	9796 (14)
C(13)	40938 (44)	36141 (23)	19099 (18)
C(14)	41842 (49)	26531 (27)	25598 (20)
O(15)	53464 (30)	17264 (17)	24627 (13)
C(16)	45734 (44)	12777 (24)	15780 (21)
C(17)	45791 (44)	21531 (22)	8666 (19)
S	−8624 (12)	101511 (6)	12634 (5)
H(1)	894 (36)	8576 (21)	2617 (17)
H′(1)	1314 (35)	7625 (20)	2063 (17)
H(3)	126 (38)	8872 (22)	85 (17)
H(5)	651 (35)	7428 (18)	−737 (16)
H(7)	2715 (34)	5412 (19)	1010 (16)
H(9)	3017 (40)	2989 (22)	−742 (19)
H(10)	2086 (37)	4314 (21)	−1923 (17)
H(13)	3171 (37)	4128 (20)	1991 (17)
H′(13)	5282 (39)	3979 (23)	2036 (19)
H(14)	2899 (43)	2385 (23)	2484 (20)
H′(14)	4841 (42)	3013 (24)	3185 (20)
H(16)	3169 (42)	1044 (23)	1522 (19)
H′(16)	5375 (40)	647 (22)	1515 (18)

Table 2. *Bond distances* (Å) *and bond angles* (°) *among non-hydrogen atoms*

C(2)–N(1)	1·318 (3)	C(10)–N(11)	1·343 (3)
C(2)–S	1·687 (3)	N(11)–C(6)	1·344 (3)
C(2)–N(3)	1·349 (3)	C(8)–N(12)	1·383 (3)
N(3)–N(4)	1·369 (3)	N(12)–C(13)	1·466 (3)
N(4)–C(5)	1·274 (3)	C(13)–C(14)	1·503 (4)
C(5)–C(6)	1·460 (3)	C(14)–O(15)	1·425 (4)
C(6)–C(7)	1·384 (3)	O(15)–C(16)	1·417 (4)
C(7)–C(8)	1·399 (3)	C(16)–C(17)	1·516 (4)
C(8)–C(9)	1·394 (4)	C(17)–N(12)	1·481 (3)
C(9)–C(10)	1·365 (4)		
N(1)–C(2)–S	123·7 (2)	C(9)–C(8)–N(12)	122·6 (2)
N(1)–C(2)–N(3)	117·6 (2)	C(8)–C(9)–C(10)	120·4 (2)
S–C(2)–N(3)	118·7 (2)	C(9)–C(10)–N(11)	124·9 (2)
C(2)–N(3)–N(4)	120·6 (2)	C(10)–N(11)–C(6)	114·9 (2)
N(3)–N(4)–C(5)	115·3 (2)	C(8)–N(12)–C(13)	118·4 (2)
N(4)–C(5)–C(6)	121·3 (2)	C(8)–N(12)–C(17)	118·3 (2)
C(5)–C(6)–C(7)	121·5 (2)	C(13)–N(12)–C(17)	114·3 (2)
C(5)–C(6)–N(11)	114·2 (2)	N(12)–C(13)–C(14)	111·5 (2)
C(7)–C(6)–N(11)	124·3 (2)	C(13)–C(14)–O(15)	112·5 (3)
C(6)–C(7)–C(8)	119·9 (2)	C(14)–O(15)–C(16)	108·8 (2)
C(7)–C(8)–C(9)	115·6 (2)	O(15)–C(16)–C(17)	112·1 (2)
C(7)–C(8)–N(12)	121·8 (2)	C(16)–C(17)–N(12)	109·5 (2)

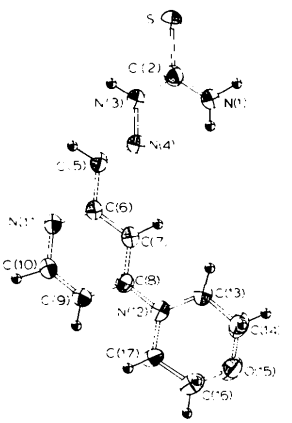

Fig. 1. *ORTEP* drawing with atomic numbering.

The structure determination of 4-MPT represents the first structure determination of a free α-(*N*)-heterocyclic carboxaldehyde thiosemicarbazone which has significantly superior antineoplastic activity against transplanated murine neoplasm, Sarcoma 180, than does 5-HP. 4-MPT possesses an additional advantage over 5-HP in that the tertiary N, attached at position 4 of pyridine ring, would be expected to be minimally or not susceptible to metabolic inactivation and yet may be readily formylated for clinical use as a water-soluble salt.

The activity of any drug is a complex combination of steric, electronic, and pharmokinetic factors. Palenik, Rendle & Carter (1974) have suggested that the delocalization of the heterocyclic ring into the thiosemicarbazone side chain is responsible for the enhanced activity of 5-HP over aliphatic derivatives (which are void of activity). Such delocalization was suggested to tune the S atom for a specific set of ligands and metal atom and therefore act as a specific agent for the Fe atom of the enzyme ribonucleoside-diphosphate reductase. Since the structure of 4-PPT, which has marginal antineoplastic activity, and of 4-MPT, which possesses superior activity, has side-chain parameters almost identical with those of 5-HP, the bond distances and angles of the thiosemicarbazone moiety are probably not the structural features which characterize enhanced activity. In fact, the only distance in the entire side chain which possibly can be correlated with antineoplastic activity is that for C(2)–N(1). In both 5-HP and 4-MPT this distance [1·307 (6) and 1·318 (3) Å respectively] is statistically significantly shorter than in 4-PPT [1·345 (8) Å]. However, since C(2)–N(1) distances in the range 1·305 to 1·350 Å are found for thiosemicarbazides, it is unlikely that this parameter affects activity.

The conformation of the side chain for 4-MPT is identical with that of 5-HP and 4-PPT; *i.e. trans* about C(5)–N(4) and S *trans* to N(4). This conformation places N(1) *cis* to N(4) and in the best orientation for intramolecular hydrogen bonding to N(4). If the molecule were rotated 180° about N(3)–C(2), a lone pair from S would be adjacent to the lone pair on N(4) producing a conformation of higher energy. Such an energy barrier would have to be overcome when the ligand chelates to a metal ion. Tridentate chelation will also require a 180° rotation about C(5)–C(6). This latter rotational barrier is probably small but would be influenced by the degree of delocalization into the C(6)–C(5) bond. Dihedral angles about C(5)–C(6) of 9° for 4-MPT, 7° for 5-HP, and 0° for 4-PPT suggest that the twist about this bond might be correlated with antineoplastic activity. Such a correlation of biological activity with the twist of the angle of C(5)–C(6) will be examined in other agents of this series.

There are no particularly unusual bond distances or bond angles within the morpholinopyridine ring system. Enlargement of the interior bond angles *ortho* to the pyridine N(11) is typical of this class of compounds as is the reduction of the interior angles at N(11) and the *para* C(8). The pyridine ring itself is planar to ±0·012 Å (equation of the best least-squares plane is $0{\cdot}1327X + 0{\cdot}0266Y + 0{\cdot}0094Z = 3{\cdot}505$) and the morpholine ring is in a distorted chair conformation.

4-MPT is involved in an extensive hydrogen-bonding network as illustrated in Fig. 2 and tabulated in Table 3. The molecule, as described in Table 1, forms a pair of hydrogen bonds about the center of symmetry (at 0,1,0) between S and N(3) at 3·42 Å. This distance is within the range of distances, 3·2 to 3·5 Å, previously observed for thiosemicarbazones. N(11) is strongly hydrogen bonded to H(1) on N(1). For 4-PPT this

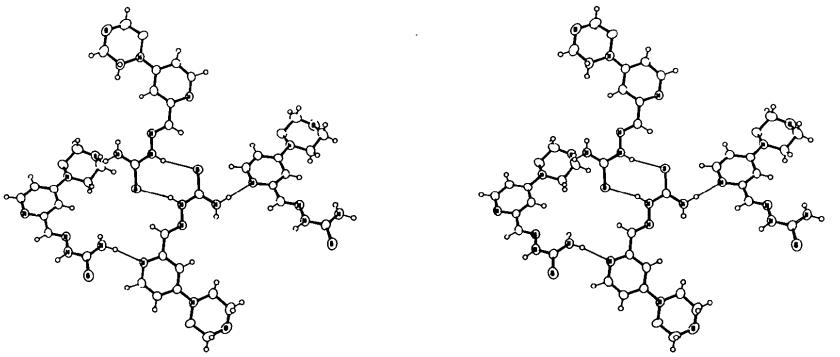

Fig. 2. Stereodrawing of 4-MPT showing the hydrogen-bonding scheme. Only the hydrogen bonds from one molecule to its neighbors are indicated.

Table 3. *Intermolecular hydrogen bonds and nonbonded contacts less than* 3·5 Å

D–H···*A*	*D*–H	H–*A*	*D*–*A*	Angle
N(1)–H(1)···N(11^{i})	0·95 Å	2·07 Å	3·00 Å	166°
N(1)–H(1)′···O(15^{ii})	0·80	2·57	3·22	138
N(3)–H(3)···S^{iii}	0·87	2·62	3·42	152

N(4)···(8^{iv})	3·40 Å	C(5)···C(8^{iv})	3·32 Å
N(4)···(9^{iv})	3·31	C(5)···N(12^{iv})	3·35
N(4)···(15^{ii})	3·38	C(6)···C(7^{iv})	3·43

Symmetry code

(i) $x, \frac{3}{2}-y, \frac{1}{2}+z$	(iii) $-x, 2-y, -z$
(ii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$	(iv) $-x, 1-y, -z$

pyridine-ring N is similarly bonded to N(3) whereas in 5-HP it is bonded to the hydroxyl H. H(1)′ is weakly intermolecularly hydrogen bonded to O(15) and intramolecularly bonded to N(4) [H(1)′···N(4) = 2·34 Å; N(1)–H(1)′···N(4) = 104°]. This latter bond, which is almost identical with the hydrogen bond found in solid ammonia (2·3 Å) (Olovsson & Templeton, 1959) and close to the optimized value calculated for the ammonia dimer (2·5 Å) (Kollman & Allen, 1971), is probably the reason for the ubiquitous *cis* N(1), N(4) configuration about C(2)–N(3) found in these derivatives.

This investigation was supported by Grant Number CA-17594, awarded by the National Cancer Institute, DHEW.

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