Crystal and Molecular Structure of Thiacetazone

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The crystal and molecular structure at −116 °C of the title compound has been determined by X-ray methods using 3355 reflections. The crystals are monoclinic, space group $P2_1/a$ with unit cell dimensions a=13.036(3), b=6.337(1), c=14.444 (2)Å and β=111.76(1)°. The structure was refined to a conventional R-factor of 0.043. A slight elongation of the S–C bond relative to earlier reports is explained through hydrogen bonding.

Dedicated to Professor Olav Foss on his 70th birthday

The antimicrobial activity of thiosemicarbazones and related compounds has been described by Domaqk *et. al.*[1] Through the study of structure-activity relationships it was suggested that 4-acetylaminobenzaldehyde thiosemicarbazone was the most promising compound for therapeutic trials. Lowe *et al.*[2] discovered that this compound also showed activity against *Mycobacterium leprae*.[7,8] Although thiosemicarbazones show significant adverse effects when administered,[3–6] these disadvantages are considered to be outweighed when adequate precautions are taken during administration. Side-effects such as gastrointestinal disorders, agranulocytosis, liver damage, skin rashes and vertigo are most frequently reported. A closer study of structure-activity relationships for this class of drugs would be valuable and may prove important in developing new medicines for tropical diseases. As existing thiocarbazone drugs also depress bone-marrow function there is an acute need for safer drugs.[9,10] In an effort to arrive at better and safer drugs as well as improve drug specificity we have initiated a study of structure-activity relationships for anti-malaria active compounds. The present structure is the first in this series.

Experimental

Thiacetazone was recrystallized from warm ethanol, giving small yellow crystals. Crystal and ex-

Table 1. Crystal and experimental data for thiacetazone.

Compound	$C_{10}H_{12}N_4OS$
Diffractometer	Nicolet *P3/F*
Crystal size/mm	0.15×0.3×0.3
Radiation	Mo*K*α
Wave length/Å	0.71069
Crystal system	Monoclinic
a/Å	13.036(3)
b/Å	6.337(1)
c/Å	14.444(2)
β/°	111.76(1)
V/Å^3	1108.2(3)
Temp./°C	−116
Space group	$P2_1/a$
M	236.29
Z	4
F(000)	496
D_x/g cm^{-3}	1.416
μ (Mo*K*α)/cm^{-1}	2.7
Scan mode	θ/2θ
Scan speed (2θ)/° min^{-1}	3.0
Scan range (2θ)/°	1.9
Maximum sinθ/λ/Å^{-1}	0.81
No. of indep. meas.	3638
No. with $I>3.0\sigma(I)$	3355
Correction for absorption	Empirical[a]
Min. abs. corr. fact.	0.70
Max. abs. corr. fact.	1.14
Method to solve structure	MITHRIL[b]
$R=\Sigma\|F_o-F_c\|/\Sigma F_o$	0.043
$R_w=[\Sigma w(F_o-F_c)^2/\Sigma wF_o^2]^{1/2}$ [c]	0.041
$S=[\Sigma w(F_o-F_c)^2/(n-m)]^{1/2}$	1.58

[a]Ref. 12. [b]Ref. 11. [c]w is the inverse of the variance of the observed structure factors.

Table 2. Fractional coordinates of thiacetazone. Estimated standard deviations in parentheses.

Atom	*x*	*y*	*z*	U_{eq}[a]/Å^2
S1	.52787(3)	.28916(6)	.07933(2)	.022
O1	.56485(10)	−.58148(19)	.74311(8)	.026
N1	.52246(14)	−.09893(23)	.15161(9)	.029
N2	.55796(10)	.17714(19)	.26204(8)	.020
N3	.57937(10)	.03616(19)	.33928(8)	.019
N4	.70819(11)	−.34911(22)	.78220(9)	.023
C1	.53444(11)	.10628(23)	.16833(9)	.020
C2	.61873(11)	.12060(21)	.42643(9)	.019
C3	.64169(11)	−.00743(22)	.51614(9)	.018
C4	.70106(12)	.08314(22)	.60931(10)	.021
C5	.71997(12)	−.03153(24)	.69625(9)	.021
C6	.68117(11)	−.23773(23)	.69139(9)	.019
C7	.62287(11)	−.33077(22)	.59830(9)	.020
C8	.60382(11)	−.21476(23)	.51161(8)	.019
C9	.65367(12)	−.51397(24)	.80223(10)	.023
C10	.71052(14)	−.60885(29)	.90493(11)	.029
H2	.633(2)	.264(5)	.435(2)	.024
HN2	.560(2)	.304(4)	.272(2)	.016
H4	.725(2)	.211(5)	.612(2)	.019
HN4	.771(2)	−.301(4)	.833(2)	.020
H5	.759(3)	.022(5)	.757(2)	.025
H7	.597(2)	−.453(5)	.595(2)	.019
H8	.566(2)	−.273(5)	.451(2)	.024
HN11	.514(3)	−.186(5)	.192(2)	.030
HN12	.509(2)	−.145(5)	.092(2)	.021
H101	.781(5)	−.576(8)	.937(4)	.055
H102	.711(5)	−.741(11)	.902(4)	.059
H103	.669(4)	−.568(7)	.944(3)	.049

[a] $U_{eq} = (U_{11} + U_{22} + U_{33})/3$.

perimental data are given in Table 1. Three test reflections were measured periodically at intervals of 135 reflections during the intensity data collection; no loss of intensity was found. Corrections were made for Lorentz, polarization and absorption effects. Unit cell dimensions were determined from diffractometer setting angles for 25 reflections. The coordinates of all non-hydro-

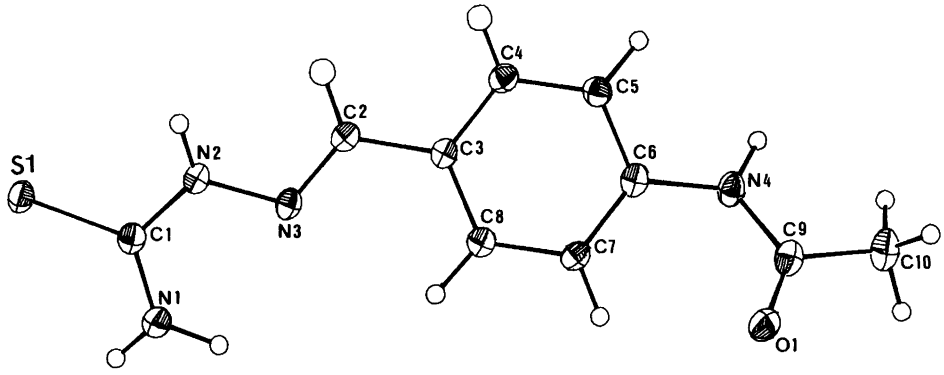

Fig. 1. The thiacetazone molecule.

Table 3. Bond lengths (Å) and angles (°) in thiacetazone. Estimated standard deviations in parentheses. The C–H distances are all between 0.85 and 1.01 Å.

S1–C1	1.709(1)	O1–C9	1.233(2)
N1–C1	1.321(2)	N2–N3	1.375(2)
N2–C1	1.349(2)	N3–C2	1.287(2)
N4–C6	1.414(2)	N4–C9	1.354(2)
C2–C3	1.463(2)	C3–C4	1.403(2)
C3–C8	1.397(2)	C4–C5	1.391(2)
C5–C6	1.394(2)	C6–C7	1.406(2)
C7–C8	1.393(2)	C9–C10	1.515(2)
N3–N2–C1	120.0(1)	N2–N3–C2	114.3(1)
C6–N4–C9	127.8(1)	S1–C1–N1	124.1(1)
S1–C1–N2	117.3(1)	N1–C1–N2	118.6(1)
N3–C2–C3	120.8(1)	C2–C3–C4	118.8(1)
C2–C3–C8	121.8(1)	C4–C3–C8	119.3(1)
C3–C4–C5	120.2(1)	C4–C5–C6	120.3(1)
N4–C6–C5	117.4(1)	N4–C6–C7	122.6(1)
C5–C6–C7	119.9(1)	C6–C7–C8	119.4(1)
C3–C8–C7	120.8(1)	O1–C9–N4	123.5(1)
O1–C9–C10	122.2(1)	N4–C9–C10	114.2(1)

gen atoms were determined by direct methods.[11] Refinements were performed by least-squares calculations; hydrogen atom positions were calculated and included in the refinements. An empirical absorption correction was applied using the program DIFABS.[12] Minimum and maximum values for the factor with which the observed structure factors are corrected are given in Table 1. The least-squares calculations proceeded with anisotropic temperature factors for the heavier atoms and isotropic temperature factors for hydrogen atoms. In order to minimize the influence of the bonding electrons on the bond lengths, the last refinement cycles included only reflections with $\sin\theta/\lambda$ greater than 0.4 $Å^{-1}$ and only the parameters of the non-hydrogen atoms were refined. Computer programs employed are described in Refs. 13 and 14. Final figures of merit are included in Table 1. Positional parameters are given in Table 2, and lists of anisotropic thermal parameters and structure factors may be obtained from the authors on request.

Description and discussion

The thiacetazone molecule is depicted in Fig. 1, together with the numbering of the atoms. Bond lengths and angles are given in Table 3. The molecule adopts an almost planar conformation. However, as the distance between O1 and H7 would be rather short in an absolutely planar conformation, the rotation about the C6–N4 bond is −27.16°. The O1–H7 distance is then 2.47Å. Furthermore, the torsion angle C6–N4–C9–O1 is found to be −5.7°, thus bringing the O1 atom 0.974Å above the benzene ring plane, as seen in Fig. 1. The angle between the planar group N4–C9–C10–O1 and the benzene ring plane is 29.75°. For similar reasons the torsion angle N3–C2–C3–C8 is found to be 12.0°, the N3–H8 distance 2.58Å and the atom N3 to lie 0.122Å above the aromatic ring plane. The torsion angles C1–N2–N3–C2 and N1–C1–N2–N3 are 11.2° and 6.2°, respectively. Finally, the S1,C1,N1,N2 group is nearly planar since the C1 atom is only 0.021Å out of the plane of the other three atoms. This plane forms an angle of 19.8° with the benzene ring plane. The molecular conformation is thus in the range found for the thiosemicarbazones of benzamide and 4-formylpyridine.[15] The bond lengths conform well with those reported for 4-formylpyridine thiosemicarbazone except for the S1–C1 bond, which in the present structure is found to be somewhat longer [1.709 (1)Å, as compared to 1.678(3)Å]. There are also some differences in the side-chain bond angles, since both C2–N3–N2 and N2–C1–S1 are about 2° smaller, and C3–C2–N3 and N3–N2–C1 are

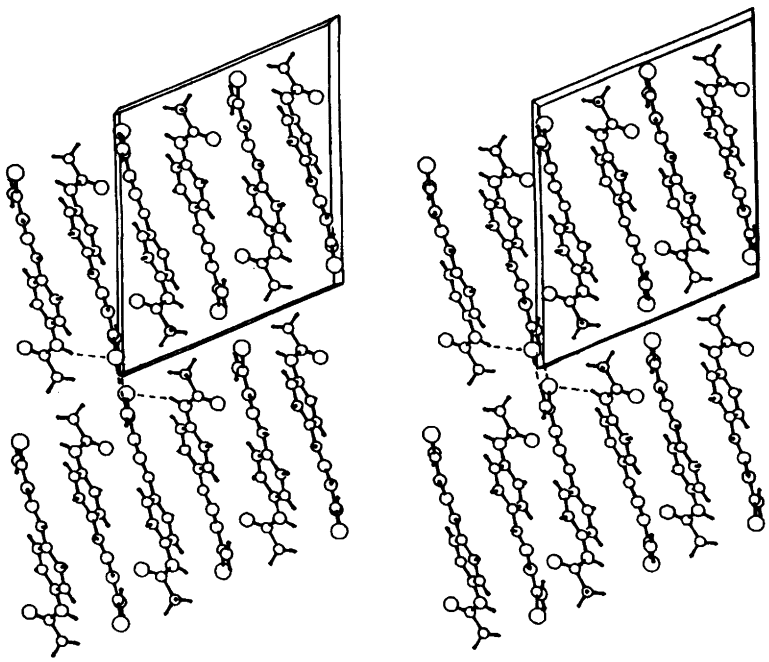

Fig. 2. Stereoscopic drawing of the packing of thiacetazone molecules in the crystals. Hydrogen bonding indicated.

about 1.5° larger, than in the 4-formylpyridine derivative (three times the combined standard deviations in the angles in the two structures is 0.7°). These differences may be due to the small variations in torsion angles between the two compounds. As in the 4-formyl derivative there are hydrogen bonds between S–C–NH_2 groups related by a centre of symmetry, as may be seen from Fig. 2. There also seems to be a hydrogen bond between S1 and N4 in a molecule related to the first by 3/2-*x*, 1/2+*y*, 1-*z*. Thus, each molecule is hydrogen-bonded to two different molecules. The fact that the sulfur atom is involved in two hydrogen bonds may explain the slight elongation of the S1–C1 bond found in the present compound as compared to similar compounds.[15] The geometry of the hydrogen bonds is described in Table 4. There are two additional molecular contacts that may be considered as hydrogen bonds, viz. those between the potential donors N1 and N2 and the acceptor O1. These contacts are also included in Table 4. In this way all possible hydrogen bonds are engaged in the crystal packing. Contacts which may be interpreted as π–π interactions occur between centrosymmetrically related molecules, the C2–C7, C2–C8 and C3–C8 distances being 3.315, 3.391 and 3.382Å, respectively. Between molecules related by a

Table 4. Hydrogen bonds in thiacetazone.

A	D	A–D	A–H	∠C,A,H	∠A,H,D
S1	N1 (1-*x*,-*y*,-*z*)	3.375	2.506	115.6	178.0
S1	N4 (3/2-*x*, 1/2+*y*, 1-*z*)	3.392	2.517	73.6	157.1
O1	N1 (1-*x*,-1-*y*, 1-*z*)	2.999	2.188	114.0	160.4
O1	N2 (1-*x*,-*y*, 1-*z*)	3.008	2.351	104.1	138.4

screw axis the shortest contacts are 3.315Å (N2–C5) and 3.258Å (N2–C6).

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