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Structures of *anti,Z*-4,4-dimethyl-3-thiosemicarbazide, *syn,E,Z*-2,4-dimethyl-3-thiosemicarbazide and *syn,E*-1-cyclopentano-3-thiosemicarbazone

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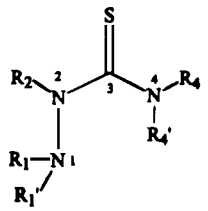
The structures of three alkyl derivatives of thiosemicarbazide are described: *anti,Z*-4,4-dimethyl-3-thiosemicarbazide (**1**), *syn,E,Z*-2,4-dimethyl-3-thiosemicarbazide (**2**), and *syn,E*-1-cyclopentano-3-thiosemicarbazone (**3**). Crystal data: for **1**: triclinic, *P*-1 (#2), a = 5.802(1)Å, b = 6.935(1)Å, c = 8.104(2)Å, α = 78.35(1)°, β = 82.13(1)°, γ = 70.71(1)°, and Z = 2; for **2**: orthorhombic, *Pbca* (#61), a = 9.417(3)Å, b = 8.624(2)Å, c = 15.169(3)Å, and Z = 8; for **3**: triclinic, *P*-1 (#2), a = 6.068(3)Å, b = 8.145(4)Å, c = 8.666(5)Å, α = 83.75(4)°, β = 86.16(5)°, γ = 74.07(4)°, and Z = 2. In general, molecules are linked by N−H···S hydrogen bonds with sulfurs accepting two or three hydrogen bonds. Structures **2** and **3**, which adopt the *syn* conformation, form N−H···N intramolecular hydrogen bonds. The solid-state structures are consistent with their infrared and proton nuclear magnetic resonance spectra.

KEY WORDS: Structure; thiosemicarbazide; infrared; nmr; hydrogen bonding.

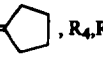
Introduction

Thiosemicarbazides and thiosemicarbazones have interesting chemical and biological properties. Thiosemicarbazide derivatives have been the subject of studies of their pharmacological, antibacterial and fungicidal properties,[1-3] their ligating properties and as intermediates in organic syntheses.[4-6] They are among the several groups of agents associated with induction of connective tissue lesions or osteolathyrism,[7] which disease results from a failure in proper connective tissue fibre polymerization.[8] Thiosemicarbazone derivatives have been investigated for a wide spectrum of biological properties, including activity against mycobacterial,[9,10] malarial,[11] bacterial[12] and viral infections.[13]



1 $R_4 = R_4 = CH_3$, $R_1,R_1' = R_2 = H$

2 $R_2 = R_4' = CH_3$, $R_1,R_1' = R_4 = H$

3 $R_1, R_1' =$  , $R_4,R_4' = R_2 = H$

They have also been shown to be potent inhibitors of DNA synthesis in mammalian cells, a property which has led to their classification among neoplastic agents.[14] The osteolathrysm of thiosemicarbazides and the antineoplastic activity of thiosemicarbazones have distinct structure-activity relationships among their substituted derivatives.[15-17] While there is insufficient grounds for understanding these biological actions at present, the structural similarity of these to biologically active thiopurines, thioamides, and thioureas makes them interesting subjects for continued study.

In the present communication, we describe the structures of two thiosemicarbazides, 4,4-dimethyl-3-

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thiosemicarbazide (**1**) and 2,4-dimethyl-3-thiosemicarbazide (**2**), and a thiosemicarbazone, 1-cyclopentano-3-thiosemicarbazone (**3**), in solution by nuclear magnetic resonance and in the solid state by infrared and x-ray crystallographic methods. These will be briefly compared to similar results previously described for 4-methyl-3-thiosemicarbazide.[18]

Experimental

Materials used were of highest available purity. Samples of **1** and **2** were obtained commercially from Aldrich Chemical Company and recrystallized from ethanol. Infrared spectra were recorded on a Perkin Elmer 16PC FT-IR spectrometer; estimated intensities: s-strong, m-medium, w-weak, sh-shoulder. Proton nuclear magnetic resonance spectra were recorded on a GE GN-300 (300MHz) wide-bore Fourier transform NMR spectrometer operating at 7.05T, reference tetramethylsilane.

4,4-Dimethyl-3-thiosemicarbazide, 1

Yellow prisms, mp 153°C(dec.); ir (KBr, cm^{-1}): 3293 m, 3236 m, 2921 w, 1611 m, 1530 s, 1458 w, 1383 m(sh), 1356 s, 1292 w, 1267 m, 1160 m, 1132 m, 1065 m, 982 s, 669 m, 625 w, 562 w. ^{1}H-nmr (d_6-DMSO, 32°C): δ3.108, s, 6H, methyls; δ4.644, s(broad), 2H, H_2N; δ 8.732, s(broad), 1H, *H*N.

2,4-Dimethyl-3-thiosemicarbazide, 2

Yellow prisms, mp 135–138°C; ir (KBr, cm^{-1}): 3287 s, 3182 w, 2930 m, 1632 m, 1541 s, 1458 m, 1412 w, 1356 m, 1327 s, 1176 m, 1087 m, 1033 s, 988 m, 878 s, 716 m, 662 m, 542 w, 474 w. ^{1}H-nmr (d_6-DMSO, 32°C): δ2.857, d (J = 3.91Hz), 3H, CH_3NH; δ3.426, s, 3H, CH_3N; δ4.807, s(broad), 2H, NNH_2; δ8.134, q(broad, J = 3.9Hz), *H*NCH$_3$.

1-Cyclopentano-3-thiosemicarbazone, 3

To a stirred, hot 30 mL solution of 4.12 g (49 mmol) cyclopentanone in ethanol:water (1:1) was added 6.4g (70 mmol) thiosemicarbazide in 70 mL of the same solvent and 2 mL of concentrated HCl. After refluxing for 30 m, cooling resulted in precipitation of a light yellow solid. After filtration, **3** was recrystallized from ethanol; yield 5.77 g (75%), mp 150–152°C (dec). Yellow prisms, ir (KBr, cm^{-1}): 3383 s, 3239 s, 3186 s, 3144 s, 2993 w, 2957 m, 2911 w, 2820 w, 1662 m, 1589 s, 1510 s, 1458 w, 1411 m, 1301 w, 1276 w, 1078 s, 1035 w, 961 w, 868 s, 846 w, 826 w, 750 m, 629 w, 583 m, 534 m. ^{1}H-nmr (d_6-DMSO, 32°C): δ9.843, s, 1H, N*H*; δ7.986, s, 1H, N−H_{cis}; δ7.423, s, 1H, N−H_{trans}; δ2.289, m (complex), 4H, N=C−CH_2; δ1.664, m (complex), 4H, CH_2.

Crystallography

Table 1 contains a summary of the crystal data and data collection parameters. Data were collected on a Siemens R3m/v automated diffractometer with graphite monochromatized Mo*K*α radiation (λ = 0.71073Å) using omega scans of width 2.0°. Three standards were monitored periodically (every 97 reflections). Reflection data were corrected for Lorentz, polarization, and deterioration effects but not for absorption. Positions and anisotropic vibrational parameters were refined for all non-H-atoms by full-matrix least-squares minimizing differences in F^2. Hydrogens atoms, with the exceptions of those on N, were assigned calculated positions and allowed to ride on their attached atoms with isotropic vibrational factors equal to 120% of the equivalent isotropic vibrational factor of the attached atom. Positions of the N−*H* hydrogens were refined with isotropic vibrational factors as for the other hydrogens. Methyl hydrogen on C(5) and C(6) in **1** and on C(5) in **2** were disordered over alternate threefold positions; an occupancy factor was refined to assess the distribution over these assigned locations. Positions of the nonhydrogen atoms and isotropic equivalent vibrational factors are given in Tables 2–4. Atomic scattering factors were from the *International Tables for X-Ray Crystallography*;[19] programs used were SHELXS-86[20] and SHELXL-93.[21]

Discussion

Substituted thiosemicarbazides may adopt a range of conformations. These can be distinguished by the orientation of the lone pair of electrons on N1 *(syn, anti)*, the orientation of hydrazide group *(Z, E)* and (where applicable) the relative conformations of the substituents on N4 *(Z, E)* each with respect to the

Table 1. Crystallographic data for thiosemicarbazide derivatives **1–3**

Compound	1	2	3
Formula weight	119.19	119.19	157.24
Specimen dimensions (mm)	0.4 × 0.3 × 0.2	0.4 × 0.3 × 0.1	0.4 × 0.3 × 0.3
Crystal system	Triclinic	Orthorhombic	Triclinic
Space group	*P*-1 (#2)	*Pbca* (#61)	*P*-1 (#2)
Temperature (°C)	295(2)	294(2)	293(2)
Cell constants			
a(Å)	5.802(1)	9.417(3)	6.068(3)
b(Å)	6.935(1)	8.624(2)	8.145(4)
c(Å)	8.104(2)	15.169(3)	8.666(5)
α(°)	78.35(1)	90	83.75(4)
β(°)	82.13(1)	90	86.16(5)
γ(°)	70.71(1)	90	74.07(4)
Cell volume (Å^3)	300.6(1)	1232.0(5)	409.1(4)
Formula units/cell	2	8	2
ρ_{calc} (mg m^{-3})	1.137	1.285	1.277
μ (cm^{-1})	0.042	0.041	0.033
Decomposition	−0.3(15)	0.0(10)	−6.0(20)
2θ range (°)	5.1–75.0	5.4–65.0	4.7–55.0
Index ranges *(h,k,l)*	+9, ±11, ±13	+14, +13, +22	+7, ±10, ±11
Reflections measured	3395	2653	3329
R_{merge}	0.026	0.055	0.046
Unique reflections	3155	2227	1887
Observed refl. ($I > 2\sigma_I$)	1265	848	1147
No. parameters, restraints	73, 0	73, 2	92, 0
Extinction coefficient	—	0.0040(7)	0.06(2)
Weights	$1/\sigma^2(F_o^2) + (aP)^2 + bP$, where $P = \max(F_o^2, 0) + 2F_o^2/3$		
a	0.0966	0.0355	0.1362
b	—	—	0.034
Final *R* (all data)	0.119	0.079	0.090
R (observed data)	0.055	0.028	0.066
Rw (all data)	0.173	0.069	0.242
S (goodness-of-fit)	0.820	0.628	1.133
Final difference features (e$^-$ Å^{-3})	+0.41, −0.44	+0.20, −0.10	+0.35, −0.36

Table 2. Coordinates and isotropic equivalent vibrational terms for 4,4-dimethyl-3-thiosemicarbazide (**1**)

Atom	*x*	*y*	*z*	$U_{(eq)}$[a]
S	1866(1)	7031(1)	7776(1)	53(1)
N(1)	−3105(3)	7745(2)	9717(2)	49(1)
N(2)	−2484(3)	9465(2)	8767(2)	45(1)
N(4)	1(3)	11165(2)	7139(2)	44(1)
C(3)	−305(3)	9353(2)	7897(2)	37(1)
C(5)	−1984(4)	13121(3)	7176(3)	56(1)
C(6)	2219(4)	11272(4)	6118(3)	58(1)

[a] $U_{(eq)}$ is one-third of the trace of the U^{ij} tensor.

Table 3. Coordinates and isotropic equivalent vibrational terms for 2,4-dimethyl-3-thiosemicarbazide (**2**)

Atom	*x*	*y*	*z*	$U_{(eq)}$[a]
S	32(1)	2266(1)	3898(1)	57(1)
N(1)	2233(1)	4546(2)	2100(1)	60(1)
N(2)	1241(1)	3498(1)	2472(1)	50(1)
N(4)	2036(1)	4405(1)	3789(1)	50(1)
C(3)	368(1)	2575(2)	1885(1)	62(1)
C(5)	1168(1)	3458(1)	3356(1)	43(1)
C(6)	2160(2)	4494(2)	4737(1)	66(1)

[a] $U_{(eq)}$ is one-third of the trace of the U^{ij} tensor.

Table 4. Coordinates and isotropic equivalent vibrational terms for 1-cyclopentano-3-thiosemicarbazone (**3**)

Atom	*x*	*y*	*z*	$U_{(eq)}$[a]
S	1027(2)	2314(1)	5282(1)	67(1)
N(1)	−4868(4)	4467(3)	7313(3)	52(1)
N(2)	−2704(4)	4239(3)	6589(3)	54(1)
N(4)	−2823(5)	1533(3)	6276(3)	62(1)
C(3)	−1644(5)	2709(4)	6082(4)	48(1)
C(5)	−5799(5)	5888(4)	7849(4)	50(1)
C(6)	−5008(6)	7469(4)	7828(5)	63(1)
C(7)	−6604(7)	8535(5)	8987(6)	85(1)
C(8)	−8766(7)	7954(6)	9110(6)	89(2)
C(9)	−8107(6)	6150(5)	8705(5)	69(1)

[a] $U_{(eq)}$ is one-third of the trace of the U^{ij} tensor.

thioureide center. For example, an *ab initio* study of 4-methyl-3-thiosemicarbazide[18] probed the energies of all eight potential conformers and showed that the *syn,E,Z* form is the lowest energy conformer. This conformation is the molecular form found in the crystal. Structures **1–3** are additional examples among thiosemicarbazides with substitutions at one or more of each of the three nitrogen atoms. The ir and proton nmr spectra are consistent with the molecular structures assigned. Plots of the molecular structures, including some intermolecular interactions, are given in Figs. 1–3. The conformations found in the structures and represented here are are *anti,Z* for **1**, *syn,E,Z* for **2**, and *syn,E* for **3**. Selected molecular metrics for the structures are given in Table 5. In the discussion of the metrics of hydrogen bonding which follow, N−H bond lengths have been normalized to 1.01Å.

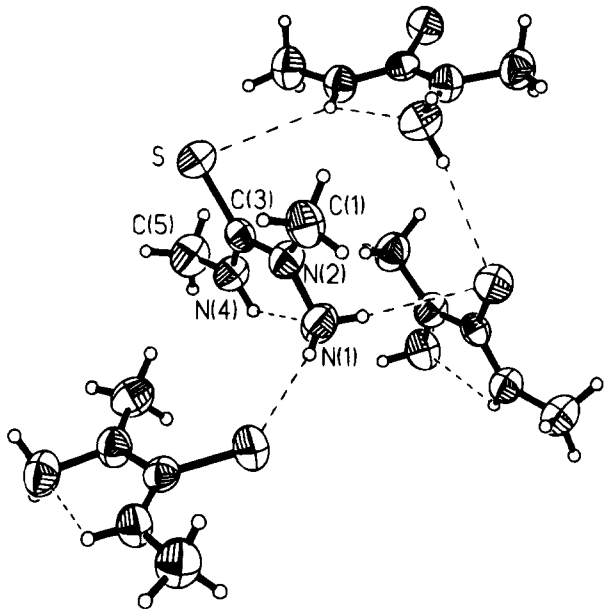

Fig. 2. Plot of the structure of 2,4-dimethyl-3-thiosemicarbazide (**2**) and intermolecular interactions.

Thiosemicarbazide **1** is found in the *anti,Z* conformation, and its nonhydrogen atoms nearly describe a plane. From *ab initio* calculations on the similar compound, 4-methyl-3-thiosemicarbazide,[18] the *anti,Z* form was found in the isolated case to be about 2 kcal/mole above the minimum energy *syn,E* conformation. As there is less than 0.1 kcal/mole difference in energy

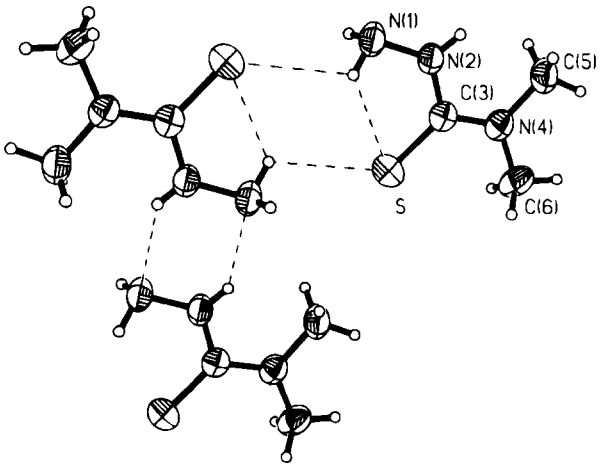

Fig. 1. Thermal ellipsoid plot (50% probability boundaries) of the molecular structure of 4,4-dimethyl-3-thiosemicarbazide (**1**) and intermolecular interactions.

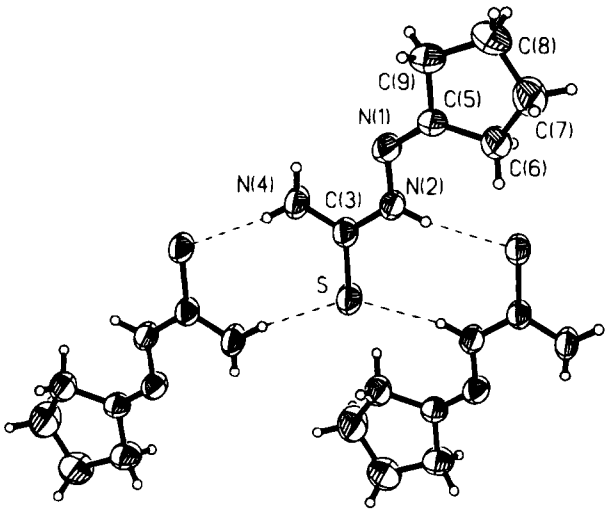

Fig. 3. Plot of the structure of 1-cyclopentano-3-thiosemicarbazone (**3**) and intermolecular interactions.

Table 5. Bond lengths, selected interbond and torsion angles between non-H-atoms in **1–3**

Compound	1	2	3
C=S	1.697(2)	1.697(1)	1.679(3)
N1–N2	1.408(2)	1.417(2)	1.391(3)
N2–C3	1.347(2)	1.343(2)	1.342(4)
C3–N4	1.339(2)	1.329(2)	1.336(4)
N2–C		1.450(2)	
N4–C; =C	1.447(2)Z	1.445(2)	1.262(4)
	1.464(2)E		
N1–N2–C3	124.3(1)	116.6(1)	118.8(2)
N2–C3–S3	120.9(1)	122.2(1)	121.3(2)
N2–C3–N4	115.9(1)	116.5(1)	116.0(3)
N1–N2–C3–N4	−176.7(2)	−0.1(2)	2.2(5)

calculated between the 4*Z* and 4*E* methyl conformations in *anti,Z*-4-methyl-3-thiosemicarbazide, the orientation of the methyls in the nearly planar methylthioamide moiety are virtually isoergic where the hydrazide conformation is *Z* and the lone pair on N1 is *anti* to the C–N2 bond. Compound **1**, which has 4,4-dimethyl substitution, is unable to form the intramolecular N4–H···N1 hydrogen bond which stabilizes the *syn,E* conformation, providing a reasonably supportive mechanism for adoption of and an argument for a lower conformational energy of the *anti,Z* form. There are two weak hydrogen bonds in the molecular plane between one hydrogen on N1, and two sulfurs; one intramolecular with H···S 2.60Å, and angle at H 105°, and one intermolecular with H···S 2.83Å, and angle at H 118°.

The principle intermolecular hydrogen bonding donors and acceptors in **1** are between the hydrazide groups. In the solid, molecules form hydrogen bonded dimers in the mean molecular plane across a crystallographic center of symmetry (Fig. 1). The thioamide N2 donates a hydrogen bond to the terminal amino N1 of an inversion relative with H···N 2.080Å, and angle at H 138.9°. This interaction is facilitated by the *anti* conformation of the N1 nonbonded pair. Terminal amino hydrogens are also engaged in hydrogen bonding. In addition to the three-center in-plane interactions described above, the other hydrogen on N1 forms a longer distance interaction with sulfurs on adjacent molecules out of the mean molecular plane with H···S distances of 2.93Å, and an angle at H of 135°. Combined with the hydrazide hydrogen bonding, the intermolecular associations in the molecular plane link the semicarbazide molecules in a continuous ribbon along the crystallographic *c* axis. Longer distance associations between ribbons occur through out-of-plane N–H···S contacts. Sulfurs therefore make two intermolecular contacts with N1 hydrogens with angles at sulfur (H···S=C) greater than 90° (122.3°, 109.7°), a geometry that is usual for hydrogen bonding in (thio)carbonyl groups. The H···S···H angle is 97.6°, and the sum of angles at S (329.6°) consistent with the observation that a component of the hydrogen bonding occurs somewhat out of the mean molecular plane. In the ir spectrum, the higher energy ν(C–N) is for C–N4. In **1**, this relatively strong band is observed at 1529 cm^{-1}, or about 12 cm^{-1} lower in energy than the comparable band in **2**. This is consistent with the disubstitution of N4 in **1** compared to the monosubstitution in **2**.

Nonhydrogen atoms in **2** also lie nearly in a plane. The compound displays the *syn,E,Z* conformation in which both methyl substituents are oriented away from the CN_3 core chain. As in 4-methyl-3-thiosemicarbazide,[18] this conformation brings into favorable contact the thioamide N–H donor and N1 acceptor lone pair for formation of an intramolecular hydrogen bond. In the infrared spectrum of **2**, the δNH_2 mode is observed at 1632 cm^{-1}, or nearly 20 cm^{-1} higher energy than in **1**, which lacks this feature. Since δNH_2 involves

Table 6. N–H···S hydrogen bonding distances (H···S, Å) and angles at H (°) in thioureides **1–3**[a]

	Intramolecular		Intermolecular			
	NH···S		In-plane NH···S		Out-of-Plane NH···S	
	Distance	Angle at H	Distance	Angle at H	Distance	Angle at H
1	2.60	106	2.83	118	2.92	135
2			2.52	168	2.64	163
3			2.42	169		
			2.55	149		

[a] N–H distances normalized to 1.01Å; esd's for lengths <0.02Å, for angles <2°.

movement of the N (N1), the difference is consistent with the presense of an intramolecular hydrogen bond in **2** compared to **1**. The H···N distance is 2.11Å; the angle at H is 106°. Thioamide hydrogen on N4 is part of a three-center hydrogen bonding system and makes an additional longer distance interaction with the sulfur of the molecule at 1/2 − *x*, 1/2 + *y*, *z*, with H···S 2.95Å and angle at H 133°. Both hydrogens of N1 are directed away from the molecular plane, and each is engaged in intermolecular Hydrogen bonding with sulfur acceptors on neighboring molecules (Fig. 2). These two center hydrogen bonds have H···S distances of 2.52Å and 2.64Å, and angles at H of 168° and 163°, respectively. The H···S distances are suggestive of relatively weak intermolecular hydrogen bonding, and the angles made between the three donors at sulfur sum to less than 330° (129°, 89°, 78°). There are no intermolecular N−H···N interactions.

The thiosemicarbazone derivative, **3**, is substituted at N1 and has the *syn,E* conformation. With the exception of the four methylenes, the nonhydrogen atom framework is nearly planar. Thioureide moieties form two hydrogen bonds linking chains of molecules into ribbons in which the interactions occur between molecules around crystallographic centers-of-symmetry and the ribbons extend along the *c* axis. These are similar to N−H···S hydrogen bonding network found in 6-thioguanine.[22] Molecular planes between any hydrogen bonded pair are parallel but offset so as to make the ribbons pleated. Sulfur accepts hydrogen bonds from NH and NH_2 groups on neighboring molecules (Fig. 3). The N2−H···S distance is 2.42Å, and the angle at H is 169.1°; and the N4−H···S distance is 2.55Å, and the angle at hydrogen is 149°. At the sulfur, the two hydrogen bonds are on either side with C=S···H angles of 112° and 116°, and the H···S···H angle 113°. This is the usual hydrogen bonding geometry for carbonyl and thiocarbonyl groups. The sum of the sulfur interaction angles (341°) deviates from 360° indicating that the hydrogen bonding contacts at sulfur are slightly out of the mean molecular plane.

Within the 1-cyclopentano-3-thosemicarbazone molecule (**3**), the lone pair on N1 is *syn* to the thiocarbonyl and able to accept a hydrogen bond from the remaining hydrogen on the thioamide N4 which is in the mean molecular plane. This intramolecular hydrogen bond has an N4−H···N1 distance of 2.19Å, and the angle at H is 102°.

Each compound (**1–3**) has only N−H donors for hydrogen bonding and nitrogen and sulfur acceptors, and in each sulfur accepts at least two hydrogen bonds. The *E*-thiosemicarbazone **3** has both thioamide N−H's disposed to promote pairs of N−H···S interactions in the molecular plane, and hydrogen bonded ribbons of molecules form. A crystallographic center-of-symmetry or a screw axis can describe the relationship between molecules. Sulfurs in this geometry form two hydrogen bonds in a manner like that of carbonyls,[23] that is, the direction of the donors appears to be nearly in the thioamide plane and toward the lone pairs on sulfur. Adoption of the *Z*-hydrazide conformation (as in **2**), in which intramolecular N−H···S can occur, may not necessarily interfere with the two-donor in-plane thiocarbonyl hydrogen bonding scheme, but two N4 alkyl substituents may interfere with hydrogen bonding on one "side" of the sulfur. It has already been mentioned that 4,4-dialkyl substitution may effectively promote the Z-hydrazide conformation. Acceptance by sulfur in substituted thiosemicarbazides of two in-plane hydrogen bonds is influenced or perhaps determined by hydrazide conformation and substitution at N2 and N4. In those cases in which intramolecular N−H···N links can form between N1 and N4 (as in **2** and **3**), which require the *syn,E* conformation, in-plane intramolecular N−H···S links are not seen.

Acknowledgments

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Supplementary Material. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1003/5259 (for **1**), CCDC-1003/5260 (for **2**) and CCDC-1003/5261 (for **3**). Copies of available material can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2-1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.)

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