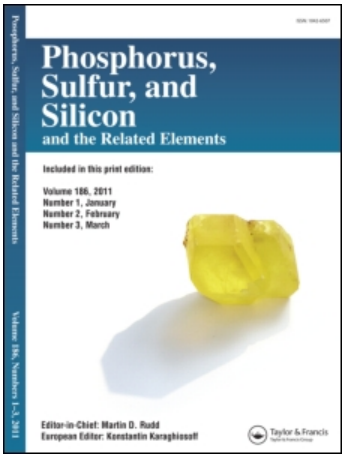


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

1,3,4-THIADIAZOLES FROM THIOSEMICARBAZIDES

John P. Scovill[a]; Daniel L. Klayman[a]; Judith L. Flippen-anderson[b]; Richard Gilardi[b]
[a] Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC [b] Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC

To cite this Article Scovill, John P. , Klayman, Daniel L. , Flippen-anderson, Judith L. and Gilardi, Richard(1991) '1,3,4-THIADIAZOLES FROM THIOSEMICARBAZIDES', Phosphorus, Sulfur, and Silicon and the Related Elements, 63: 3, 273 — 281
To link to this Article: DOI: 10.1080/10426509108036830
URL: http://dx.doi.org/10.1080/10426509108036830

Phosphorus, Sulfur, and Silicon, 1991, Vol. 63, pp. 273–281
Reprints available directly from the publisher
Photocopying permitted by license only

1,3,4-THIADIAZOLES FROM THIOSEMICARBAZIDES

JOHN P. SCOVILL and DANIEL L. KLAYMAN
Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307

and

JUDITH L. FLIPPEN-ANDERSON and RICHARD GILARDI
Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375

(Received April 24, 1991; in final form July 23, 1991)

A new method for the synthesis of 1,3,4-thiadiazoles is described. Thus condensation of 4-methyl-4-phenyl-3-thiosemicarbazide with an aldehyde or ketone affords 1,1-disubstituted-6-[1-(arylethylidine)-amino]-2,5-dithiobiureas, rather than the anticipated 4,4-disubstituted-3-thiosemicarbazones. Refluxing the 2,5-dithiobiureas in ethanol containing acetic acid as catalyst gave the corresponding 1,3,4-thiadiazol-2-yl hydrazones. Furthermore, refluxing a solution of a 4,4-disubstituted-3-thiosemicarbazone in acetonitrile containing acetic acid as catalyst also afforded 1,3,4-thiadiazol-2-yl hydrazones in excellent yield. Arylethylideneamino-2,5-dithiobiurets are thought to be intermediates in the latter reaction.

Key words: 4,4-dialkyl-3-thiosemicarbazides; 4,4-dialkyl-3-thiosemicarbazones; 1,1-dialkyl-6-[1-(arylethylidene) amino]-2,5-dithiobiureas; (5-dialkylamino-1,3,4-thiadiazol-2-yl) hydrazones; acid catalyzed cyclization.

INTRODUCTION

The instability of 4,4-disubstituted-3-thiosemicarbazides (**1**) was first noted by Jensen.[1] The decomposition of 4,4-dialkyl-3-thiosemicarbazides was studied by Larsen and Binderup, who showed that 4,4-dimethyl-3-thiosemicarbazide (**1a**) afforded 2-dimethylamino-5-mercapto-1,3,4-thiazole (**2**) upon standing at room temperature, whereas pyrolysis of **1a** gave the dimethylammonium salt of 1-amino-2,5-dimercapto-1,3,4-triazole (**3**) in addition to the above mentioned thiadiazole.[2] Pyrolysis of 4,4-diethyl-3-thiosemicarbazide (**1b**) or 4,4-dipropyl-3-thiosemicarbazide (**1c**) gave the corresponding 1-amino-6,6-dialkyl-2,5-dithiobiureas **4b**, and **4c**, respectively.[2] Formation of heterocycles **2** and **3** was thought to result from different cyclization modes of intermediate aminobiureas **4a**.[2]

In preliminary publications, we have reported on the isolation of 1,3,4-thiadiazole-2-yl hydrazones during the attempted preparation of α-*N*-heterocyclic ketone thiosemicarbazones.[3,4] In this communication we describe the application of the synthesis of 1,1-disubstituted-6-[1-(arylethylidene)amino]-2,5-dithiobiureas (**5**) to the preparation of 1,3,4-thiadiazole-2-yl hydrazones, **10**.

1,1-Disubstituted-6-[1-(Arylethylidene)Amino]-2,5-Dithiobiureas (**5**)

Reaction of 4-methyl-4-phenyl-3-thiosemicarbazide **1d** or related aromatic thiosemicarbazides with a variety of aromatic and heteroaromatic methyl ketones leads

1

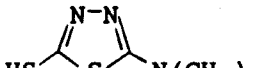
1a, $R^1=R^2=CH_3$

1b, $R^1=R^2=CH_2CH_3$

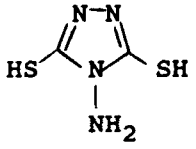
1c, $R^1=R^2=CH_2CH_2CH_3$

1d, $R^1=CH_3$, $R^2=C_6H_5$

1e, $NR^1R^2 = N(CH_2)_6$



2



3

4

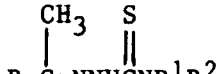
4a, $R^1=R_2=CH_3$

4b, $R^1=R^2=CH_2CH_3$

4c, $R^1-R^2=CH_2CH_2CH_3$

to the formation of 1,1-disubstituted-6-[1-(arylethylidene)amino]-2,5-dithiobiureas, **5**, rather than the anticipated 4,4-disubstituted-3-thiosemicarbazones, **6**.[5,6] This reaction indicates the ability of the *N*-alkylanilino moiety of **1d** towards nucleophilic displacement.

5

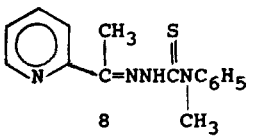


6

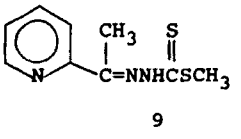
1,3,4-Thiadiazol-2-yl Hydrazones (**10**)

When it became evident that reaction of 2-acetylpyridine with 4-methylphenyl-3-thiosemicarbazide (**1d**) could not be used to obtain 2-acetylpyridine 4-methyl-4-phenyl-3-thiosemicarbazone (**8**), the preparation of **8** by the condensation of methyl 3-[1-(2-pyridinyl)ethylidene]hydrazinecarbodithioate (**9**) with *N*-methylaniline was investigated. Carbodithioate **9** has been employed by us previously to prepare a large series of 4-aryl-3-thiosemicarbazones of 2-acetylpyridine.[7] The hoped for **8** was not obtained by this reaction, but rather a product which could be formulated as either 1,3,4-thiadiazole **10a** or 1,3,4-triazole **11**. The structure of the product was established as **10a** by a single-crystal X-ray study. Compound **10a** could also be obtained by refluxing a solution in ethanol of **5a**.

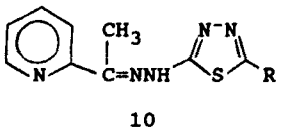
The formation of **10a** might be rationalized as follows: reaction of **9** with *N*-methylaniline leads initially to the formation of thiosemicarbazone **8**, which undergoes hydrolysis to afford thiosemicarbazide **1d** and 2-acetylpyridine; reaction of **1d** with either **8** or **9** results in formation of aminobiurea **5a**; elimination of H_2S from **5a** proceeds to give the cyclized product, **10a**, resulting from the attack of one of the sulfur atoms, in thiol tautometric form, upon the remaining thiocarbonyl group



8



9

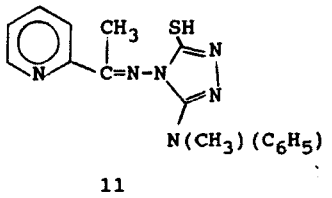


10

10a, R= $N(CH_3)C_6H_5$

10b, R= NH_2

10c, R= SCH_3



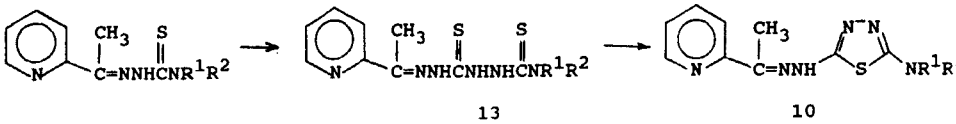
11

(cf. Scheme I). Attack of the N^1-nitrogen atom upon the C^5-thiocarbonyl group would have led, alternatively, to triazole **11** (cf. Scheme II).

In support of the mechanism of Scheme I, we observed that a variety of conditions may be employed to prepare 1,3,4-thiadiazol-2-yl hydrazones (**10**). In Method A, a solution of a thiosemicarbazone in propionitrile containing a trace of acetic acid is heated at reflux. In Method B, a thiosemicarbazide is allowed to react with carbodithioate **9**. In Method C, a thiosemicarbazone is condensed with a thiosemicarbazide. In each case, an aminobiurea is a likely intermediate.

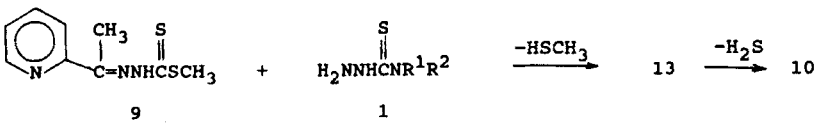
The yields and properties of the various 1,3,4-thiadiazoles obtained by the above mentioned methods are summarized in Table I.

Method A



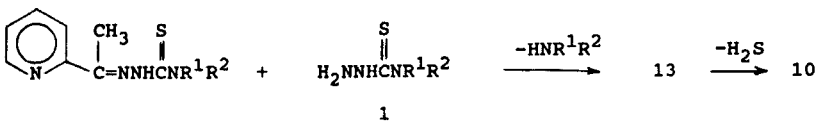
13 10

Method B

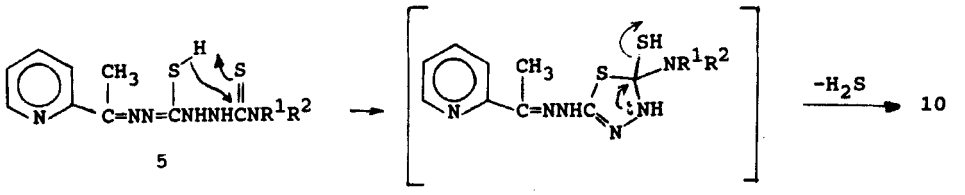


9 1 13 10

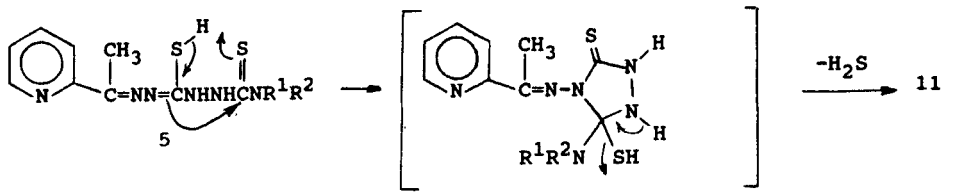
Method C



1 13 10



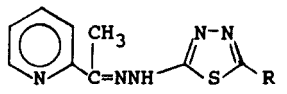
SCHEME I



SCHEME II

TABLE I

Methyl 2-pyridinyl ketone [2-(*N*-dialkylamino)-1,3,4-thiadiazol-5-yl]hydrazones



Cmpd. No.	R	mp, °C	Formula	recryst. solvent	yield, % A	B	C
10a	$N(CH_3)(C_6H_5)$	217-218	$C_{16}H_{16}N_6S$	MeCN	55	60	65
10d	$N(CH_3)_2$	230-232	$C_{11}H_{14}N_6S$	DMF	32	69	59
10e	$N(CH_2)_4$	237-338	$C_{13}H_{16}N_6S$	DMF	51	36	60
10f	$N(CH_2)_6$	217-218	$C_{15}H_{20}N_6S$	DMF	66		63
10g	$N(CH_2)_{12}$	216-218	$C_{21}H_{32}N_6S$	MeCN	50		
10h		236-238	$C_{17}H_{22}N_6S$	DMF	44		

The identification of 1,3,4-thiadiazole **10a** as the reaction product was made on the basis of single crystal x-ray study (cf. Figure 1). The molecule is seen to consist of two planar segments; one plane is defined by the *N*-phenyl moiety, with all the remaining non-hydrogen atoms forming the second plane. The phenyl ring is rotated approximately 45° about the *N*-phenyl bond out of the main plane. Except for the normal single bond length of the *N*-methyl bond (1.464Å), all bond lengths fall between normal single and double bond values, indicating that conjugation extends throughout the molecule. Hydrogen-bonded dimers are apparent in the crystal; the NH group and the closest N atom of the thiadiazole ring act as donor and acceptor to the same atoms in a centrosymmetrically related molecule. The hy-

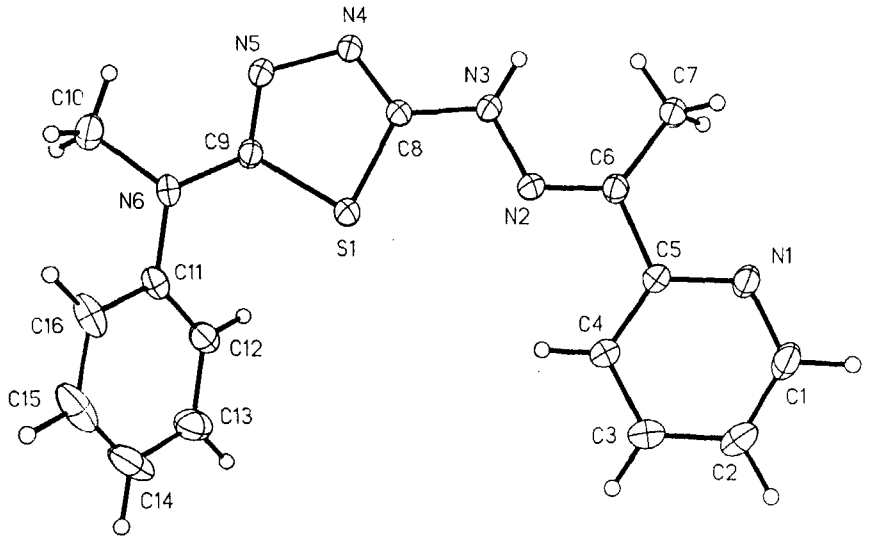


FIGURE 1 Diagram of **10a** as determined by the X-ray analysis. Thermal ellipsoids have been drawn at the 20% probability level.

TABLE II
Bond lengths (Å) for **10a**

S(1)-C(8)	1.735(2)	C(1)-C(2)	1.354(4)
S(1)-C(9)	1.749(2)	C(2)-C(3)	1.373(4)
N(1)-C(1)	1.342(3)	C(3)-C(4)	1.366(3)
N(1)-C(5)	1.337(3)	C(4)-C(5)	1.384(3)
N(2)-C(6)	1.285(2)	C(5)-C(6)	1.482(3)
N(2)-N(3)	1.368(2)	C(6)-C(7)	1.495(3)
N(3)-C(8)	1.363(2)	C(11)-C(12)	1.383(3)
N(4)-C(8)	1.299(3)	C(11)-C(16)	1.388(4)
N(4)-C(5)	1.402(2)	C(12)-C(13)	1.375(4)
N(5)-C(9)	1.295(3)	C(13)-C(14)	1.367(5)
N(6)-C(9)	1.376(3)	C(14)-C(15)	1.373(5)
N(6)-C(10)	1.464(3)	C(15)-C(16)	1.369(5)
N(6)-C(11)	1.413(3)		

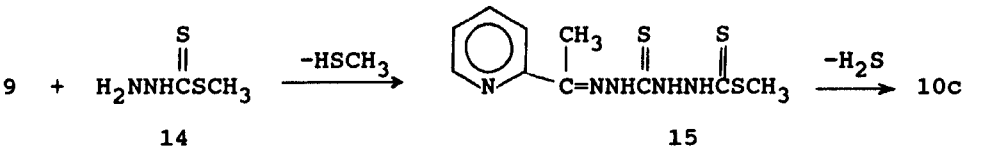
drogen-based N . . . N and N . . . H distances, 2.97 and 2.13Å respectively, are the only intermolecular approaches less than the usual van der Waals contact distances (cf. Table II). Bond angles are provided in Table III.

TABLE III
Bond angles (in degrees) for **10a**

C(8)-S(1)-C(9)	85.5(1)	N(1)-C(1)-C(2)	124.5(2)
C(1)-N(1)-C(5)	116.9(2)	C(1)-C(2)-C(3)	118.1(2)
N(3)-N(2)-C(6)	119.0(2)	C(2)-C(3)-C(4)	119.2(3)
N(2)-N(3)-C(8)	114.8(2)	C(3)-C(4)-C(5)	119.4(2)
N(5)-N(4)-C(8)	111.6(2)	C(4)-C(5)-N(1)	122.0(2)
N(4)-N(5)-C(9)	112.0(2)	C(4)-C(5)-C(6)	121.9(2)
C(9)-N(6)-C(10)	116.8(2)	C(6)-C(5)-N(1)	116.1(2)
C(9)-N(6)-C(11)	122.9(2)	C(5)-C(6)-N(2)	115.3(2)
C(10)-N(6)-C(11)	120.6(2)	C(5)-C(6)-C(7)	119.8(2)
		C(7)-C(6)-N(2)	124.9(2)
		N(3)-C(8)-S(1)	120.0(2)
		N(3)-C(8)-N(4)	124.3(2)
		N(4)-C(8)-S(1)	115.7(1)
		N(5)-C(9)-S(1)	115.1(1)
		N(5)-C(9)-N(6)	122.0(2)
		N(6)-C(9)-S(1)	122.8(2)
		N(6)-C(11)-C(12)	120.8(2)
		N(6)-C(11)-C(16)	120.7(2)
		C(12)-C(11)-C(16)	118.4(2)
		C(11)-C(12)-C(13)	120.7(3)
		C(12)-C(13)-C(14)	120.2(3)
		C(13)-C(14)-C(15)	119.7(3)
		C(14)-C(15)-C(16)	120.6(3)
		C(15)-C(16)-C(11)	120.4(3)

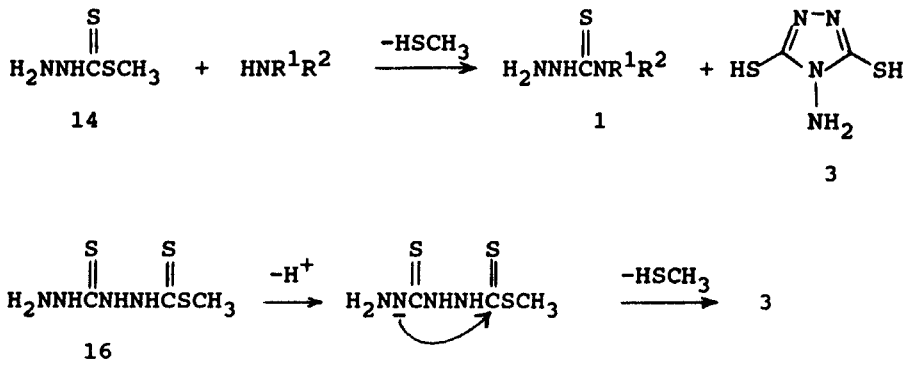
The attempted preparation of methyl 2-pyridinyl ketone (2-amino-1,3,4-thiadiazol-5-yl)hydrazone **10b** through the reaction of carbodithioate **9** and thiosemicarbazide gave methyl 2-pyridinyl ketone (5-methylthio-1,3,4-thiadiazol-2-yl)hydrazone, **10c**. The formation of **10c** is difficult to rationalize unless one assumes that hy-

drolysis of **9** affords 2-acetylpyridine and methyl hydrazinecarbodithioate (**14**). Reaction of **14** with **9** could result in the formation of carbodithioate **15**, which could undergo cyclization with loss of hydrogen sulfide, to give **10c**. In support of this mechanism, we observe that reaction of carbodithioate **9** with **14** does indeed produce 1,3,4-thiadiazole **10c**.



CONCLUSION

In some respects, the chemistry of the 4-alkylanilino-3-thiosemicarbazides **1d** described in this communication is seen to resemble that which McElhinney has described for methyl hydrazinecarbodithioate (**14**).[7,8] This author has shown that reaction of **14** with primary or secondary amines gives reasonable yields of thiosemicarbazides,[7] **1**, as well as the corresponding amine salts of **3**.[8] 1-Amino-2,5-dithiobiureas (**4**) or methyl carbodithioate (**16**), are likely intermediates in this cyclization reaction. Under the basic conditions employed by McElhinney[8] (as well as for Larsen and Binderup[2]), the nucleophilicity of the N^6-nitrogen atom may be enhanced by deprotonation. Subsequent attack of the N^6-nitrogen atom upon the C^2-thiocarbonyl group with expulsion of the methyl mercaptan gives triazole **3**. Conversion of **4** to **3** presumably follows a similar course. However, the cyclization of the 2,5-dithiobiureas to give 1,3,4-thiadiazoles rather than 2-mercapto-1,3,4-triazoles suggests that under the acidic conditions investigated in this study, a thiocarbonyl sulfur atom acts as the intramolecular nucleophile.



EXPERIMENTAL

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on a Perkin Elmer mdl 283 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian HR 220 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Satisfactory microanalyses ($\pm 0.3\%$) were obtained for each compound.

Method A: Preparation of 1,3,4-thiadiazol-2-yl hydrazones from thiosemicarbazones. This method is exemplified by the following preparation of **10h**: A solution of 1.0 g (33 mmole) of 3-azabicyclo[3.2.2]-nonane-3-thiocarboxylic acid 2-[1-(2-pyridinyl)ethylidene]hydrazide[10] in 8 mL of EtCN was treated with a drop of glacial HOAc and heated at reflux at 48 h. The reaction mixture was chilled and the crystals which separated were collected, affording 248 mg (44%) of **10h**, mp 236–238°C: ir 1613, 1580, 1510, 1457, 1437, 1225, 1205, 970, 777 cm^{-1}.

Anal. Calcd. for $C_{17}H_{22}N_6S$: C, H, N, S.

Method B: Preparation of 1,3,4-thiadiazol-2-yl hydrazones by reaction of methyl 3-[1-(2-pyridinyl)ethylidene]hydrazinecarbodithioate[10] *(***9**) and a thiosemicarbazide. This method is exemplified in the following preparation of **10d**: A solution of 1.89 g (4.43 mmole) of **9**[10] and 1.0 g of 4,4-dimethyl-3-thiosemicarbazide[7] in 10 mL of MeCN was heated at reflux for 10 h. The reaction mixture was then chilled and the crystals which had separated were collected. This afforded 795 mg (69%) of **10d** (after recrystallization from DMF), mp 232–233°C: ir 1593, 1575, 1535, 1418, 1287, 1155, 780, 761, 742, 719, 675 cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}N_6S$: C, H, N, S.

Method C: Preparation of 1,3,4-thiadiazol-2-yl hydrazones by the reaction of a thiosemicarbazone and a thiosemicarbazide. This method is exemplified by the reaction of 1H-hexahydroazepine-1-thiocarboxylic acid 2-[1-(2-pyridinyl)ethylidene]hydrazide[10] and 1H-hexahydroazepine-1-thiocarboxylic acid hydrazide.[7,9] (**1e**): A solution of 1.55 g (8.66 mmole) of **1e** and 2.89 g (8.66 mmole) of 1H-hexahydroazepine-1-thiocarboxylic acid 2-[1-(2-pyridinyl)ethylidene]hydrazide in 5 mL of EtCN containing 2 mL of glacial HOAc was heated at reflux for 18 h. The solution was chilled and the crystals which separated were collected, affording 1.73 g (63%) of **10f**, mp 216–218°C: ir 2930, 2830, 1590, 1575, 1523, 1429, 1287, 1150, 777 cm^{-1}. nmr δ 10.64 (*br. s*, NH), 8.52 ("*d*", 1H, J = 4.5, H_6), 8.07 ("*d*", 1H, J = 8 Hz, H_3), 7.67 ("*t* of *ds*", 1H, J = 6 Hz, J = 2 Hz, H_4), 7.18 ("*t*", 1H, J = 5.5 Hz, H_5), 2.58 (*t*, 4H, J = 5.5 Hz, —CH_2NCH_2—), 2.54 (*s*, 3H, C—CH_3), 1.84 (4H), 1.61 (4H).

Anal. Calcd. for $C_{15}H_{20}N_6S$: C, H, N, S.

*Methyl 2-pyridinyl ketone (5-methylthio-1,3,4-thiadiazol-2-yl)hydrazone (***10c**). A solution of 4.50 g (20 mmole) of carbodithioate **9** and 1.82 g (20 mmole) of thiosemicarbazide in 200 mL of EtOH was heated at reflux for 28 h. The pale yellow needles which separated were collected, affording 1.66 g (31%) of **10c**, mp 229–231°C dec. An analytical sample prepared by recrystallization from DMF had mp 234–235°C: ir 3150, 3050, 3010, 2930, 1620, 1587, 1563, 1472, 1418, 1295, 780 cm^{-1}; nmr (d_6-DMSO + $CDCl_3$) δ 8.56 ("*d*", 1H, J = Hz, H_6), 7.95 ("*d*", 1H, J = 8 Hz, J = 1 Hz, H_3), 7.80 ("*t* of ds", 1H, J = 8 Hz, J = 1.5 Hz, H_4), 7.34 ("*t*", 1H, J = 7 Hz, J = 1 Hz, H_5), 2.66 (*s*, 3H, S—CH_3), 2.39 (*s*, 3H, C—CH_3).

Anal. Calcd. for $C_{10}H_{11}N_5S_2$: C, H, N, S.

X-ray Experimental $C_{16}H_{16}N_6S$, triclinic, $P\bar{1}$, crystal size = (.5 × .7 × .15) mm, cell constants (room temp.) based on least-squares refinement of 25 reflections are a = 7.743 (10)Å, b = 8.963 (12)Å, c = 11.964 (12)Å, α = 97.38 (8)°, β = 101.61 (8)°, and γ = 91.58 (9)°, z = 2. dcalc = 1.34 g cm^{-3}, u = 2.0 cm^{-1}. Nicolet R3 diffractometer (MoKα, λ = 0.71069, graphite monochromator), θ-2θ scan technique, $2° \leq 2\theta \leq 45°$, $-h \pm k \pm 1$, 2112 reflections. Data corrected for Lorentz-polarization effects, no absorption correction or extinction correction. Solved by direct methods, refined by full-matrix least-squares (on F) with anisotropic thermal parameters for non-H atoms and isotropic thermal parameters for H atoms (267 variables). Final R = 0.038 (Rw = 0.044) for 1793 reflections with $|F_o| \geq 3\ F_o$, goodness of fit = 1.41, maximum absolute density in final difference map = .180eÅ^3. All programs from Nicolet SHELXTL program library.[11,12]

ACKNOWLEDGEMENT

The NRL authors were supported, in part, by the Office of Naval Research.

REFERENCES

1. K. A. Jensen, *J. Prakt. Chem.*, **159**, 1989 (1941).
2. C. H. Larsen and E. Binderup, *Acta Chem. Scand.*, **21**, 1984 (1967).
3. D. L. Klayman, J. P. Scovill, J. Bruce and J. F. Bartosevich, *J. Med. Chem.*, **27**, 84 (1983).

4. D. L. Klayman, J. P. Scovill, J. F. Bartosevich, J. Bruce, S. P. Massie, S. D. Grant and A. Gonzalez, *Eur. J. Med. Chem.*, **19**, 4 (1984).
5. J. P. Scovill, *Phosphorus and Sulfur*, **60**, 15 (1991).
6. J. P. Scovill, *Phosphorus and Sulfur*, **61**, 77 (1991).
7. R. S. McElhinney, *J. Chem. Soc. (C)*, 950 (1966).
8. R. S. McElhinney, *J. Chem. Soc. (C)*, 1256 (1966).
9. J. Sandstrom, *Acta. Chem. Scand.*, **15**, 1295 (1961).
10. D. L. Klayman, J. P. Scovill, J. F. Bartosevich and C. J. Mason, *J. Med. Chem.*, **22**, 1367 (1979).
11. G. M. Sheldrick, "SHELXTL, Minicomputer Programs for Structure Determination," University of Gottingen, Gottingen, West Germany (1980).
12. Tables of atomic coordinates have been deposited with the Crystallographic Data Centre, Cambridge University Chemical Laboratory, Cambridge CB2, 1EW, England.