[Chem. Pharm. Bull. 18(2) 235—242 (1970)]

UDC 547.496.3.04

S-Alkylthioisothioureas. I

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(Received June 24, 1969)

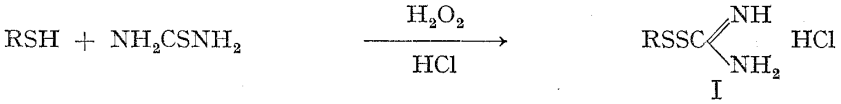
S-Alkylthioisothioureas (I) have been synthesized by the reaction of thiols, thiourea and hydrogen peroxide in aqueous solutions at low temperatures. Unsymmetrical disulfides could be obtained by the reaction of I with various thiols.

The growing biochemical and pharmacological interest in compounds containing a sulfur–sulfur bond has prompted us to look for a useful method for the synthesis of unsymmetrical disulfides. To date several methods for the synthesis of unsymmetrical disulfides have been reported; these include the reaction of thiols with Bunte salts ($RSSO_3Na$,[2]) sulfenyl chlorides (RSCl),[3] sulfenyl thiocyanates (RSSCN)[4] and thiosulfinates (RSOSR).[5] Among these the procedure using Bunte salts seems to be central to the synthesis.

The present paper deals with a novel and versatile synthesis of unsymmetrical disulfides from the corresponding thiols and S-alkylthioisothioureas, the latter compounds being obtained easily by the reaction of thiols with thiourea and hydrogen peroxide.

Only a few papers described the properties and preparations of S-alkylthioisothioureas. Toennies (1937)[6] have first shown that S-alkylthioisothiourea, S-(guanylthio)-L-cysteine, could be synthesized by the reaction of dithioformamidine dihydrochloride and cystine. In 1964, Kopylova, *et al.*[7] prepared the picrate of S-*n*-butylthioisothiourea, but they did not describe the chemical properties of this compound in any detail.

We found that, when a mixture of a thiol and thiourea was treated with 30% H_2O_2 in EtOH solution containing aqueous hydrochloric acid at low temperatures, S-alkylthioisothiourea could be easily isolated as crystals of the hydrochloride (Chart 1).



$$\mathrm{RSH} + \mathrm{NH_2CSNH_2} \xrightarrow[\mathrm{HCl}]{\mathrm{H_2O_2}} \mathrm{RSSC}\begin{array}{l}\diagup\mathrm{NH}\\ \diagdown\mathrm{NH_2}\end{array}\ \mathrm{HCl}$$

I

Chart 1

Usually a small amount of symmetrical disulfides and dithioformamidine dihydrochloride is formed in this reaction but these by-products can be easily removed from the desired S-alkylthioisothiourea. Thiols of various types, *e.g.*, *prim*-, *sec*- and *tert*-alkanethiols, aryl or pyridyl substituted alkanethiols have been found to be useful in this reaction, but phenylthioisothiourea could not be obtained from thiophenol by this method (Table I). These S-alkylthioisothiourea hydrochlorides (I) are stable in an air at room temperature or in acidic solution, but are unstable in an alkaline solution.

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[1] Location: *Juso-nishino-cho, Higashiyodogawa-ku, Osaka.*
[2] H. Dister, *Angew. Chem. Intern. Ed. Engl.*, **6**, 544 (1967).
[3] C.G. Moore and M. Porter, *J. Chem. Soc.*, **1958**, 2890.
[4] R.G. Hiskey, F.I. Carroll, R.M. Babb, J.O. Bledsoe, R.T. Puckett, and B.W. Roberts, *J. Org. Chem.*, **26**, 1152 (1961).
[5] T. Matsukawa and H. Kawasaki, *Yakugaku Zasshi*, **73**, 216 (1953).
[6] G. Toennies, *J. Chem. Soc.*, **1937**, 297.
[7] B.V. Kopylova and R.Kh. Freidlina, *C.A.*, **62**, 3934 (1965).

In order to investigate the mechanism of the formation of the S-alkylthioisothioureas we have carried out the following experiments: Thus mixtures of dithioformamidine dihydrochloride and toluene-α-thiol, of dithioformamidine dihydrochloride and dibenzyl disulfide and of dibenzyl disulfide and thiourea were allowed to react under the conditions where the present synthesis of S-alkylthioisothiourea hydrochlorides proceeds, but no appreciable amount of S-benzylthioisothiourea hydrochloride was produced.

In our view the mechanism for the present reaction is as follows: A thiol is first oxidized to a sulfenic acid and then the sulfenic acid reacts with thiourea to give a S-alkylthioisothiourea as shown in Chart 2.

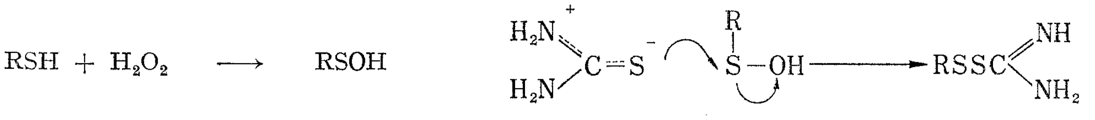
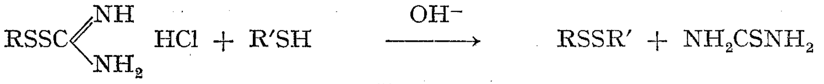


Chart 2

It has been reported that the acid hydrolysis of sodium benzyl thiosulfate (Bunte salt) yields the toluene-α-thiol.[8] But Milligan, *et al.*[9] demonstrated some years ago that the principal product of the reaction was dibenzyl disulfide under similar conditions when thiourea was present, and they considered that in acid solution sodium benzyl thiosulfate first reacts with thiourea to give S-benzylthioisothiourea, which subsequently reacts with toluene-α-thiol or sodium benzyl thiosulfate to yield benzyl disulfide. With the aim of obtaining S-benzylthioisothiourea under appropriate conditions we carried out the reaction of sodium benzylthiosulfate with thiourea in dilute hydrochloric acid solution at room temperature and obtained S-benzylthioisothiourea hydrochloride as pure crystals.

Then it was found that S-alkylthioisothioureas react very smoothly with various thiols in alkaline solutions to give unsymmetrical disulfides in good yields at room temperature (Chart 3). All the compounds prepared by this method are summarized in Table II and III.



$$\mathrm{RSSC}\begin{cases}\mathrm{NH}\\\mathrm{NH_2}\end{cases}\mathrm{HCl} + \mathrm{R'SH} \xrightarrow{\mathrm{OH^-}} \mathrm{RSSR'} + \mathrm{NH_2CSNH_2}$$

Chart 3

This procedure was further extended to the synthesis of unsymmetrical disulfides that are considered to be difficult to obtain by the known methods. It has been well known that certain thiols, in which a thiol group is attached to a carbon atom next to a nitrogen atom in N-containing heterocyclic compounds are scarcely led to unsymmetrical disulfides. Up to date, some examples of such disulfides have been known; *e.g.*, ethyl 2-benzothiazolyl disulfide[10] was prepared by the reaction of Et_2S_2 and benzothiazolyl disulfide in the presence of $Na_2S \cdot 9H_2O$, similarly 2-benzothiazolyl cyclopentyl disulfide was obtained from the corresponding disulfides,[11] and 2-benzothiazolyl 1,3-dimethyl-2-butenyl disulfide[12] was obtained by the reaction of sodium 1,3-dimethyl-2-butenyl thiosulfate (Bunte salt) with sodium 2-benzothiazolylsulfide in the presence of formaldehyde. Also, reactions of 6-mercaptopurine with methyl-, ethyl- and phenyl sulfenyl chlorides have been reported to afford the corresponding unsymmetrical disulfides,[13] respectively.

We have found that unsymmetrical disulfides in the heterocyclic series could be easily obtained by the use of S-alkylthioisothiourea; *e.g.*, a solution of 2-mercaptobenzothiazole

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[8] B. Milligan and J.M. Swan, *Rev. Pure Appl. Chem.*, **12**, 72 (1962).
[9] B. Milligan and J.M. Swan, *J. Chem. Soc.*, **1962**, 2172.
[10] M. Kleiman, *C.A.*, **45**, 606 (1951).
[11] M. Kleiman, *C.A.*, **44**, 653 (1950).
[12] A.A. Watson, *J. Chem. Soc.*, **1964**, 2100.
[13] F.J. Stiefel, B.J. Ludwig, and F.M. Berger, *C.A.*, **63**, 8381 (1965).

(IIa) and I in MeOH was treated with aqueous sodium bicarbonate at room temperature to give the corresponding alkyl 2-benzothiazolyl disulfides (IIIa). Also, alkyl 2-benzimidazolyl disulfides (IIIb) could be prepared from 2-mercaptobenzimidazole (IIb) in a similar way. These reactions are shown in Chart 4 (Tables IV and V). It should be noted that none of alkyl 2-benzimidazolyl disulfides have thus far been obtained by the reaction of 2-mercaptobenzimidazole with Bunte salts.

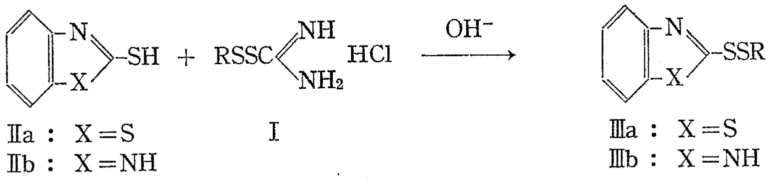

Chart 4

S-Benzylthioisothiourea hydrochloride (IV) reacted with sodium benzoate or sodium cinnamate to give crystalline S-benzylthioisothiourea benzoate (Va) and cinnamate (Vb), respectively, in good yields. The reaction of IV with sodium cyanide in an aqueous solution afforded benzyl thiocyanate[14] (VI), however, the reaction product of IV and potassium thiocyanate was not S-benzylthio thiocyanate ($C_6H_5CH_2SSCN$) but S-benzylthioisothiourea hydrogen thiocyanate (VII). Furthermore, acetyl benzyl disulfide[15] (VIII) could be easily obtained by the reaction of IV with potassium thioacetate at room temperature. These reactions are summarized as follows (Chart 5).

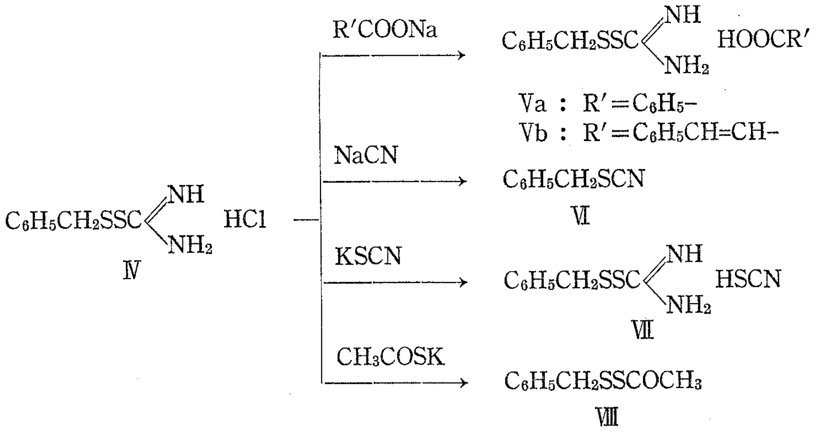

Chart 5

In alkaline solution S-alkylthioisothioureas are unstable, and free bases could not be isolated. For example, on the treatment of I with dimethylamine, symmetrical trisulfides were easily obtained in satisfactory yields (Table VI). The reaction probably proceeds according to the following equations (Chart 6).

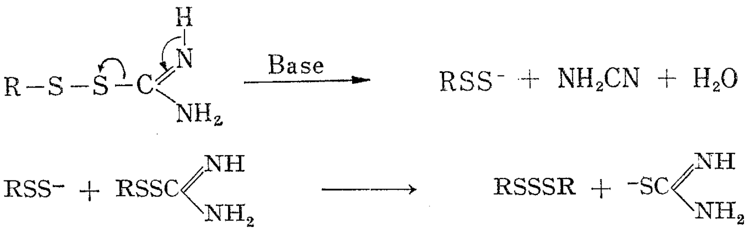

Chart 6

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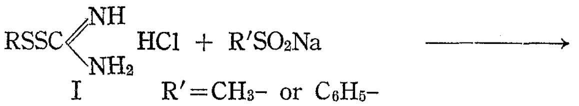
[14] H.B. Footner and S. Smiles, *J. Chem. Soc.*, **1925**, 2887.
[15] B. Milligan, B. Saville, and J.M. Swan, *J. Chem. Soc.*, **1961**, 4850.

Furthermore, I reacts with sodium methane- or benzene-sulfinate to give the corresponding S-alkylthiosulfonates (Chart 7).



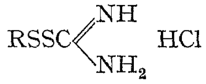
$$RSSC(=NH)NH_2\ HCl + R'SO_2Na \longrightarrow RSSO_2R'$$

I $R' = CH_3-$ or C_6H_5-

Chart 7

These reactions demonstrate that S-alkylthioisothiourea hydrochlorides (I) are useful reagents for the preparation of various types of unsymmetrical disulfides.

Table I. S-Alkylthioisothiourea Hydrochlorides



$$RSSC(=NH)NH_2\ HCl$$

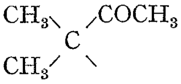
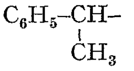
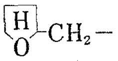
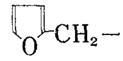
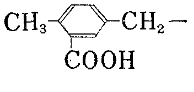
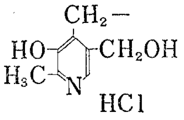
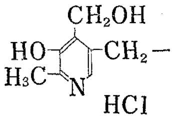
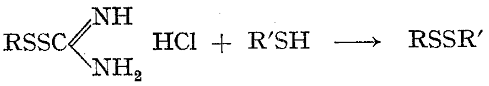
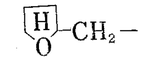
				Analysis (%)							
R	mp (°C)	Yield (%)	Formula	Calcd.				Found			
				C	H	N	S	C	H	N	S
n-C_3H_7–	122—124	70.3	$C_4H_{11}N_2S_2Cl$	25.73	5.93			25.76	5.92		
n-C_4H_9O–	120—123	53	$C_5H_{13}N_2S_2Cl$	29.91	6.52			29.74	6.48		
$CH_3(CH_2)_{11}$–	100—103	40	$C_{13}H_{29}N_2S_2Cl$	49.92	9.34		20.50	50.14	9.38		20.71
$HOCH_2CH_2$–	106.5	87.7	$C_3H_9ON_2S_2Cl$	19.09	4.81	14.85		19.42	4.84	15.05	
 $(CH_3)_2C(COCH_3)$–	150—152	53	$C_6H_{13}ON_2S_2Cl$	31.50	5.73	12.25		31.39	5.61	12.33	
	200	72	$C_{11}H_{19}N_2S_2Cl$	47.38	6.87	10.05		47.14	6.80	10.05	
$C_6H_5CH_2$–	145—148	81	$C_8H_{11}N_2S_2Cl$	40.92	4.72	11.93		40.90	4.76	12.00	
$C_6H_5CH_2CH_2$–	137	79.6	$C_9H_{13}N_2S_2Cl$	43.44	5.27	11.26		43.30	5.36	11.22	
 C_6H_5–$CH(CH_3)$–	162—164	63.5	$C_9H_{13}N_2S_2Cl$	43.44	5.27	11.26		43.50	5.30	11.27	
2-$ClC_6H_4CH_2$–	155—156	65	$C_8H_{10}N_2S_2Cl_2$	35.69	3.74	10.41		35.88	3.68	10.28	
4-$ClC_6H_4CH_2$–	150—152	60	$C_8H_{10}N_2S_2Cl_2$	35.69	3.74	10.41	23.82	35.80	3.83	10.50	23.90
3-$ClC_6H_4CH_2$–	142—143	52	$C_8H_{10}N_2S_2Cl_2$	35.69	3.74	10.41		35.62	3.65	10.44	
2,6-di$ClC_6H_3CH_2$–	151—152	77	$C_8H_9N_2S_2Cl_3$	31.64	2.98	9.22	21.11	31.74	2.95	9.16	20.68
4-$(CH_3)_2CHC_6H_4CH_2$–	154—155	70	$C_{11}H_{17}N_2S_2Cl$	47.72	6.19	10.12		47.71	6.08	9.97	
$(CH_3)_3C$–$C_6H_4CH_2$–	165—167	69.8	$C_{12}H_{19}N_2S_2Cl$	49.55	6.58	9.63		49.44	6.52	9.64	
2-$FC_6H_4CH_2$–	132—134	73	$C_8H_{10}N_2S_2ClF$			11.08	25.37			10.97	25.82
4-CH_3O-$C_6H_4CH_2$–	153—155	59	$C_9H_{13}ON_2S_2Cl$	40.82	4.95	10.58		40.58	4.87	11.07	
	123—125	74	$C_6H_{13}ON_2S_2Cl$	31.50	5.72	12.24		31.61	5.53	12.17	
	137—139	53	$C_6H_9ON_2S_2Cl$	32.06	4.04	12.46		32.05	3.94	12.46	
$(CH_3)_3C$–	166—168	81.6	$C_5H_{13}N_2S_2Cl$	29.91	6.52	13.96		29.84	6.28	13.88	
	185 (decomp.)	81	$C_{10}H_{13}O_2N_2S_2Cl$	41.02	4.48	9.57		41.00	4.63	9.32	
	159—161 (decomp.)	40	$C_9H_{15}O_2N_3$- S_2Cl_2	32.53	4.55	12.64	19.30	32.61	4.67	12.59	18.91
	153—155 (decomp.)	33	$C_9H_{15}O_2N_3$- S_2Cl_2	32.53	4.55	12.64	19.30	32.69	4.51	12.34	18.60

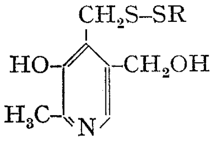
Table II. Unsymmetrical Disulfides


$$RSSC\begin{matrix}\nearrow NH\\ \searrow NH_2\end{matrix}\ HCl + R'SH \longrightarrow RSSR'$$

R	R′	mp or bp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	S	Found C	H	S
$C_6H_5CH_2$–	C_2H_5–	76—81 0.25	69	$C_9H_{12}S_2$	58.64	6.56	34.80	58.73	6.62	34.56
$C_6H_5CH_2$–	C_3H_7–	90—96 0.5	40	$C_{10}H_{14}S_2$	60.55	7.11	32.34	60.83	7.22	32.35
$C_6H_5CH_2$–		142—146 0.35	80	$C_{12}H_{16}OS_2$	59.95	6.70	26.67	60.24	7.05	26.74
$C_6H_5CH_2$–	C_6H_5–	138—141 0.25	90	$C_{13}H_{12}S_2$	67.19	5.20	27.61	67.15	5.15	28.12
	2-$ClC_6H_4CH_2$–	66—67[a]	62	$C_{17}H_{21}S_2Cl$	62.83	6.51		62.93	6.22	
4-$ClC_6H_4CH_2$–		67—68[b]	73	$C_{17}H_{21}S_2Cl$	62.83	6.51	19.73	62.54	6.57	20.03
2,6-diClC_6H_3- CH_2–		69—70[b]	78	$C_{17}H_{20}S_2Cl_2$	56.81	5.61	17.84	56.84	5.59	17.86
	2-$NH_2C_6H_4$–	75—77[c]	79.5	$C_{16}H_{21}NS_2$[d]	65.93	7.26		66.19	7.15	
$C_6H_5CH_2$–	2-$NH_2C_6H_4$–	62—65[b]	90	$C_{13}H_{13}NS_2$[e]	63.11	5.29	25.90	63.35	5.14	25.03
$C_6H_5CH_2$–	$\overset{|}{C}H$–CH_2CH_2– $\overset{|}{(C}H_2)_4CONH_2$	78—80[f]	66.5	$C_{22}H_{29}$- ONS_4[g]	56.49	6.47	28.39	58.34	6.37	28.08

a) Recryst. from MeOH–H_2O.
b) Recryst. from MeOH.
c) Recryst. from EtOH–H_2O.
d) N: Calcd., 4.80. Found: 4.66.
e) N: Calcd., 5.66. Found: 5.43.
f) Recryst. from ligroin.
g) N: Calcd., 3.10. Found: 3.04.

Table III. Pyridoxine Derivatives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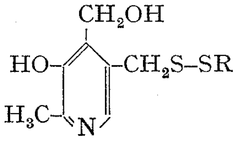
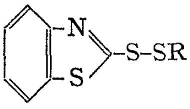

X

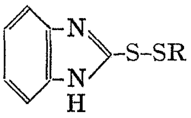
	R	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd. C	H	S	Found C	H	S
X	C_4H_9–	112—114	83	MeOH–H_2O	$C_{12}H_{19}O_2NS_2$	52.71	7.00	23.45	52.91	6.79	23.43
	$CH_3(CH_2)_{11}$–	105—107	52	EtOH–H_2O	$C_{20}H_{35}O_2NS_2$	62.29	9.14	16.62	62.31	8.88	16.34
		151—153	57	EtOH–H_2O	$C_{18}H_{25}O_2NS_2$	61.49	7.16	18.24	60.68	7.27	17.96
	$C_6H_5CH_2$–	122—124	58	MeOH–H_2O	$C_{15}H_{17}O_2NS_2$	58.60	5.57	20.85	58.44	5.52	20.28
XI	C_4H_9–	111—113	64	MeOH–H_2O	$C_{12}H_{19}O_2NS_2$	52.71	7.00	23.45	52.66	7.18	23.05
	$CH_3(CH_2)_{11}$–	109—109.5	70	MeOH–H_2O	$C_{20}H_{35}O_2NS_2$	62.29	9.14	16.62	62.89	9.17	16.46
	$C_6H_5CH_2$–	137—139	57	MeOH–H_2O	$C_{15}H_{17}O_2NS_2$	58.60	5.57	20.85	58.81	5.61	20.78

TABLE IV. Benzothiazole Derivatives



R	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
$(CH_3)_3C-$	82— 84	83	$MeOH-H_2O$	$C_{11}H_{13}NS_3$	51.72	5.13	5.48	51.86	4.98	5.38
	92— 94	48	$EtOH-H_2O$	$C_{17}H_{19}NS_3$	61.21	5.76	4.20	61.12	5.77	4.19
$C_6H_5CH_2-$	68	86	MeOH	$C_{14}H_{11}NS_3$	58.09	3.83	4.83	57.71	3.66	4.86
$C_6H_5CH_2CH_2-$	40— 43	92	$EtOH-H_2O$	$C_{15}H_{13}NS_3$	59.38	4.32	4.61	59.19	4.34	4.71
$4-(CH_3)_3C-C_6H_4CH_2-$	93— 95	84	$EtOH-H_2O$	$C_{18}H_{19}NS_3$	62.56	5.54	4.05	62.68	5.45	4.06
$2-ClC_6H_4CH_2-$	75— 76	62	$EtOH-H_2O$	$C_{14}H_{10}NS_3Cl$	51.91	3.11	4.32	51.34	3.20	3.62
$4-ClC_6H_4CH_2-$	101—103	78	MeOH	$C_{14}H_{10}NS_3Cl$	51.91	3.11	4.32	52.19	3.13	4.35
$2,6-diClC_6H_3CH_2-$	107—108	78	EtOH	$C_{14}H_9NS_3Cl_2$	46.92	2.53	3.91	46.95	2.61	3.72
$4-CH_3OC_6H_4CH_2-$	83— 84	94	$EtOH-H_2O$	$C_{15}H_{13}ONS_3$	56.40	4.10	4.38	56.31	4.25	4.50

TABLE V. Benzimidazole Derivatives



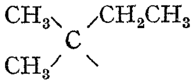
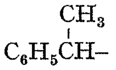
R	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
$(CH_3)_3C-$	224—227	77.5	$AcOH-H_2O$	$C_{11}H_{14}N_2S_2$	55.42	5.92	11.75	55.40	5.91	11.74
 $(CH_3)_2C(CH_2CH_3)-$	189—191.5	80	toluen–ligroin	$C_{12}H_{16}N_2S_2$	57.11	6.38	11.09	57.41	6.34	11.37
	205—207	60	AcOEt–ligroin	$C_{17}H_{20}N_2S_2$	64.52	6.37	8.85	64.73	6.42	8.94
$C_6H_5CH_2-$	143—144	59.3	$EtOH-H_2O$	$C_{14}H_{12}N_2S_2$	61.73	4.44	10.29	62.04	4.53	10.33
 $C_6H_5CH(CH_3)-$	128—130	88	$EtOH-H_2O$	$C_{15}H_{14}N_2S_2$	62.90	4.93	9.78	62.68	4.78	9.92
$C_6H_5CH_2CH_2-$	130—131	83.4	$EtOH-H_2O$	$C_{15}H_{14}N_2S_2$	62.90	4.93	9.78	62.77	4.68	9.88
$4-(CH_3)_3C-C_6H_4-CH_2-$	158—160	76.5	$EtOH-H_2O$	$C_{18}H_{20}N_2S_2$	65.81	6.14	8.53	66.00	5.98	8.27
$2,6-diClC_6H_3-CH_2-$	171—171.5	82	EtOH	$C_{14}H_{10}N_2S_2Cl_2$	49.27	2.95	8.21	49.11	2.79	7.94

Table VI. Symmetrical Trisulfides

RSSSR

R	mp (°C)	Yield (%)	Formula	Analysis (%)					
				Calcd.			Found		
				C	H	S	C	H	S
$C_6H_5CH_2$–	48.5— 49.5	90	$C_{14}H_{14}S_3$	60.38	5.06	34.56	60.63	5.19	33.20
2-Cl$C_6H_4CH_2$–	75	76	$C_{14}H_{12}S_3Cl_2$	48.41	3.48		48.34	3.47	
4-Cl$C_6H_4CH_2$–	82 — 83	52	$C_{14}H_{12}S_3Cl_2$	48.41	3.48		48.26	3.45	
2,6-diCl$C_6H_3CH_2$–	171 —172.5	55	$C_{14}H_{10}S_3Cl_4$	40.39	2.39	23.11	40.21	2.31	23.42
4-CH_3O-$C_6H_4CH_2$–	60 — 62	59	$C_{16}H_{18}O_2S_3$	56.77	5.36		57.05	5.37	
4-$(CH_3)_3C$-$C_6H_4CH_2$–	89 — 91	83	$C_{22}H_{30}S_3$	67.63	7.74	24.63	67.90	7.86	23.95
	213 —214	65	$C_{20}H_{30}S_3$	65.51	8.24	26.25	65.53	8.25	26.42

Table VII. Thiosulfonates

$$RSSC\begin{matrix}\diagup NH \\ \diagdown NH_2\end{matrix} HCl + R'SO_2Na \longrightarrow RSSO_2R'$$

R	R′	mp (°C)	Yield (%)	Formula	Analysis (%)			
					Calcd.		Found	
					C	H	C	H
$C_6H_5CH_2$–	CH_3–	42—44	69	$C_8H_{10}O_2S_2$	47.49	4.98	47.49	4.95
2-Cl$C_6H_4CH_2$–	CH_3–	54—55	89	$C_8H_9O_2S_2Cl$	40.58	3.83	40.55	3.79
4-Cl$C_6H_4CH_2$–	CH_3–	71—72	85	$C_8H_9O_2S_2Cl$	40.58	3.83	40.56	3.71
2,6-diCl$C_6H_3CH_2$–	C_6H_5–	79—81	45	$C_{13}H_{10}O_2S_2Cl_2$	46.85	3.02	47.08	2.94
4-ClC_6H_4-$\underset{\vert}{CH}$-CH_3	C_6H_5–	43—45	60.8	$C_{14}H_{13}O_2S_2Cl$	53.83	4.19	53.63	4.16
2-Cl$C_6H_4CH_2$–	C_6H_5–	55—57	74	$C_{13}H_{11}O_2S_2Cl$	52.25	3.71	52.21	3.71

Experimental

Only representative examples of all the experiments carried out were described. All melting points were determined in capillary tube and uncorrected.

S-Alkylthioisothiourea Hydrochlorides(Table I)——A mixture of β-phenylethanethiol (30.5 g), thiourea (20.1 g), conc. HCl (35 ml), H_2O (35 ml) and EtOH (500 ml) was kept at 0—10°, while 30% H_2O_2 (28.0 g) was added dropwise for 1 hr. The mixture was stirred for additional 2 hr at this temperature. A small amount of precipitates, dithioformamidine dihydrochloride, was removed by filtration. The filtrate was evaporated under reduced pressure, and the residue was dissolved in a small volume of EtOH. The solution was diluted with ether and cooled overnight. The precipitates were collected, washed with ether and dried. Recrystallization from EtOH–ether yielded pure S-phenethylthioisothiourea hydrochloride as colorless needles (43.4 g), which melted at 137°.

S-Alkylthioisothiourea hydrochlorides are soluble in H_2O and in EtOH. These salts can be recrystallized from EtOH–ether mixture and generally have well-defined melting points.

Unsymmetrical Disulfides (Tables II and III)——To a solution of 1-adamantanethiol (0.5 g) and 2,6-dichlorobenzylthioisothiourea hydrochloride (1.0 g) in MeOH (15 ml) was added a solution of $NaHCO_3$ (0.4 g) in H_2O (5 ml) with stirring in an ice-bath. After stirring at 10° for 1 hr, a precipitate produced was collected by filtration and recrystallized from dilute MeOH to yield 2,6-dichlorobenzyl 1-adamantyl disulfide (0.7 g) melting at 69—70°.

Unsymmetrical Disulfides (Tables IV and V)——2-Mercaptobenzimidazole (1.4 g) and 4-*tert*-butylbenzylthioisothiourea hydrochloride (2.90 g) were dissolved in MeOH (30 ml) and to the $NaHCO_3$ (1.2 g) solution in H_2O (50 ml) was added with vigorous stirring at room temperature. After 30 min the precipitate was collected and recrystallized from EtOH to give 2-benzimidazolyl 4-*tert*-butylbenzyl disulfide (2.50 g), mp 158—160°.

Symmetrical Trisulfides (Table VI)——To a stirred solution of 1-adamantylthioisothiourea hydrochloride (0.7 g) in MeOH (5 ml) was added 40% $(CH_3)_2NH$ (0.9 g) at room temperature. Immediately bis (1-adamantyl) trisulfide precipitated and the precipitates were collected. Recrystallization from MeOH gave colorless needles (0.3 g), mp 213—214°.

Thiosulfonates (Table VII)——To a solution of 2-chlorobenzylthioisothiourea hydrochloride (2.7 g) in 50% MeOH (20 ml) was added sodium benzenesulfinate (2.0 g) under cooling with stirring. 2-Chlorobenzyl benzenethiosulfonate separated as colorless crystals. Recrystallization from MeOH gave colorless needles (2.2 g), mp 55—57°.

Benzylthioisothiourea Benzoate (Va) and Cinnamate (Vb)——Benzoic acid (0.61 g) was dissolved in a solution of $NaHCO_3$ (0.42 g) in H_2O (20 ml) and a solution of IV (1.17 g) in MeOH (10 ml) was added to this with vigorous stirring at room temperature. The reaction mixture was stirred under cooling and the precipitate was collected. Recrystallization from 70% EtOH gave colorless plates (0.9 g), mp 135—136°. *Anal.* Calcd. for $C_{15}H_{16}O_2N_2S_2$: C, 56.22; H, 5.03; N, 8.74. Found: C, 56.21; H, 4.91; N, 8.71. Similarly benzylthioisothiourea cinnamate (VIb) was obtained as colorless crystals, mp 129—130°. *Anal.* Calcd. for $C_{17}H_{18}O_2N_2S_2$: C, 58.93; H, 5.23; N, 8.08. Found: C, 59.28; H, 5.03; N, 7.78.

Benzyl Thiocyanate (VI)——To a solution of NaCN (0.1 g) in H_2O (5 ml) was added with stirring benzylthioisothiourea hydrochloride (0.23 g) under cooling. The precipitate of benzyl thiocyanate was collected and dried, mp 39—41° (0.135 g). The identification with an authentic sample was carried out by mixed mp determination and the comparison of the IR spectra.

Benzylthioisothiourea Hydrogen Thiocyanate (VII)——A solution of KSCN (0.15 g) dissolved in H_2O (3 ml) was stirred at room temperature. To this was added IV (0.23 g) in one portion. After stirring for 1 hr the separated solid was filtered. Recrystallization from AcOEt afforded colorless prisms, mp 115—118° (0.18 g). *Anal.* Calcd. for $C_9H_{11}N_3S_3$: C, 41.99; H, 4.30; N, 16.32. Found: C, 42.26; H, 4.25; N, 16.27.

Acetyl Benzyl Disulfide (VIII)——IV (0.938 g) in H_2O (15 ml) was added to an ice-cold solution of thiolacetic acid (0.38 g) in 4% K_2CO_3 (15 ml) under vigorous stirring. After 15 min crystalline substance was collected, washed with water and dried *in vacuo*. Recrystallization from ligroin yielded colorless prisms (0.75 g) which melted at 55—57°. *Anal.* Calcd. for $C_9H_{10}OS_2$: S, 32.34. Found: S, 31.85.

Preparation of IV from Sodium Benzylthiosulfate——Thiourea (0.8 g) was dissolved in a mixture of conc. HCl (1 ml) and 50% EtOH (10 ml). To this solution was added sodium benzylthiosulfate (Bunte salt, 2.8 g) in 80% EtOH (50 ml). A current of N_2 gas was passed through the stirred mixture at room temperature for 2 hr, and then the reaction mixture was evaporated to dryness and extracted with hot EtOH. To this EtOH solution was added acetone and after standing overnight the precipitate was collected and then recrystallized from a mixture of EtOH and acetone giving 0.75 g (32%) of the product as colorless prisms, mp 143°. The identification with an authentic sample was made by the mixed mp determination and the comparison of the IR spectra.

Acknowledgement The authors are grateful to Dr. S. Tatsuoka, General Manager of the Division, and Dr. Y. Abe, Research Manager of the Chemical Research Laboratories, for the encouragement throughout this work.