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Studies of Thioacids and Their Derivatives

IX. Thiosemicarbazides

KAI ARNE JENSEN, UFFE ANTHONI, BRUNO KÄGI, CHARLES LARSEN and CARL TH. PEDERSEN*

Chemical Laboratory II (General and Organic Chemistry), University of Copenhagen. The H. C. Ørsted Institute, Copenhagen, Denmark

Methods for preparing all possible isomers of thiosemicarbazides have been developed and various methods have been compared. Special attention has been paid to the factors which determine whether a 1-alkyl- or a 2-alkylthiosemicarbazide is formed. Generally, most methods give the 2-alkylthiosemicarbazide as the primary product, but when the alkyl group is tertiary the 2-alkyl derivative is rearranged with extreme ease into the 1-isomer. Thiosemicarbazides with a secondary alkyl group, an aralkyl group or an aryl group in the 2-position may be transformed on heating into the 1-isomers with more or less ease, depending on substituents in the 4-position. Thiosemicarbazides with a primary alkyl group in the 2-position cannot normally be rearranged.

The preparation of 1-methylthiosemicarbazides (substituted or unsubstituted in the 4-position) met with unusual difficulties. They were only obtained after a great number of unsuccessful approaches, which, however, have given other results of some interest. It should be mentioned especially that methylhydrazine substituted with a protecting group in the 1-position may react with an isothiocyanate or a dialkylthiocarbamoyl chloride in such a way that the protecting group is *replaced* and a 2-methylthiosemicarbazide is formed. Attempts to remove the protecting group after a thiosemicarbazide had been formed frequently resulted in ring closure with the formation of thiadiazoles or triazoles.

During this investigation, some 300 new thiosemicarbazides and related compounds have been prepared (*cf.* Tables 1–4 and the experimental part) and some earlier assignments of the structure of known thiosemicarbazides have been changed.

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While thiosemicarbazides derived from phenylhydrazine and other aromatic hydrazines have been studied very extensively, surprisingly little is known about thiosemicarbazides derived from aliphatic hydrazines. In an earlier investigation, the senior author of this paper prepared several new 4-alkyl, 2,4-dialkyl, 1,1,4-trialkyl, and 1,2,4-trialkylthiosemicarbazides. Only the data of the 4,4-dialkylthiosemicarbazides, which represented a new type, were published.[1] Some of the 4-alkylthiosemicarbazides and 2,4-dialkylthiosemicarbazides have since been described by other workers in this field,[2,3] but the trialkylthiosemicarbazides prepared have still not been mentioned in the literature (apart from the announcement of the R_F value of 1,2,4-trimethylthiosemicarbazide in a publication from this laboratory [4]). In connection with our studies of thiohydrazides,[5–7] it was found desirable to use and extend this old material and compare the complex-forming and bacteriostatic activities of thiohydrazides and thiosemicarbazides (papers Nos. X and XI of this series; to be published). During this work, however, our interest centered more and more around purely organic chemical aspects of the problem and the main

Table 1. Monosubstituted

Thiosemicarbazide	Recryst. from	Method of preparation	M.p., °C	Formula		Analyses: C	H	N	S
1-Methyl	a	8, 3d	157–158	$C_2H_7N_3S$	Calc.:	22.85	6.71	39.98	30.45
					Found:	22.74	6.52	39.44	30.09
2-Methyl [2]	a	1, 3c, 3d, 6a, 6b, 6c	173–174 [j]	»	»	22.79	6.56	39.82	
4-Methyl [60]	b	3a, 5b, 6a, 6b	137–138	»	»			39.93	
1-Ethyl	a	1, 2a	137–138	$C_3H_9N_3S$	Calc.:	30.24	7.62	35.28	
					Found:	30.25	7.68	35.35	
2-Ethyl	a	1	110–111	»	»	29.92	7.50	35.24	
4-Ethyl [61]	b	3a	83–84	»	»			34.90	
1-Allyl	g	8	104–105	$C_4H_9N_3S$	Calc:	36.63	6.92	32.05	
					Found:	36.43	6.70	31.86	
2-Allyl [62,i]	a	1, 3c	124–125	»	»			32.08	
4-Allyl [60]	f	3a	98–99	»	»	36.65	6.83		
1-Propyl	c	1, 2a	108–109	$C_4H_{11}N_3S$	Calc.:	36.08	8.33	31.56	
					Found:	36.10	8.29	31.80	
2-Propyl	a, g	1, 3c	114–115	»	»	35.95	8.27	31.64	
4-Propyl	h	3a	61– 62	»	»			31.60	
1-Isopropyl	c	1, 2a	136–137	»	»	36.05	8.30	31.72	
2-Isopropyl	a	7	134–135	»	»	36.20	8.52	31.37	
4-Isopropyl [3]	d, h	3a, 6c	97– 98	»	»	36.30	8.11	31.60	
4-Ethoxycarbonylmethyl [107]	b	3a	183–184 [k] (decomp.)	$C_5H_{11}N_3O_2S$	Calc.:	33.90	6.26	23.72	
					Found:	34.17	6.47	23.93	
1-Butyl	c	2a, 3a	95–96	$C_5H_{13}N_3S$	Calc.:	40.80	8.90	28.55	21.74
					Found:	41.00	8.80	28.66	
2-Butyl	a, g	1, 3c, 7	95–96	»	»	40.95	8.86	28.38	
4-Butyl [3]	h	3a, 4c	70– 71	»	»	40.96	8.79	28.83	
1-Isobutyl	a	2a	100–101	»	»	41.00	9.01	28.93	21.97
2-Isobutyl	b	3c, 7	133.5–134	»	»	40.60	8.67	28.25	
4-Isobutyl [3]	f	3a	77–78 [l]	»	»	40.65	8.91		
1-*sec*-Butyl	c	2a	103–104	»	»	41.00	8.90	28.35	

topics of this paper are 1) a study of methods of preparation of all possible types of alkyl thiosemicarbazides; 2) a study of the factors which determine whether a 1-alkyl or the isomeric 2-alkylthiosemicarbazide is formed. A study of the infrared spectra of the thiosemicarbazides will be published in another paper.

Incidentally, it should be mentioned that in naming the thiosemicarbazides the traditional numbering has been used: $H_2\overset{4}{N}-\overset{3}{C}S-\overset{2}{N}H-\overset{1}{N}H_2$. In the paper on thiohydrazides,[7] we followed the proposal of Holmberg to use the terms N^1- and N^2-alkylthiohydrazides. It is important, then, to remember that a 1-alkylthiosemicarbazide corresponds to an N^2-alkylthiohydrazide and *vice versa*.

METHODS OF PREPARATION OF THIOSEMICARBAZIDES

A very large number of structurally isomeric thiosemicarbazides are, of course, possible. There will be three monoalkyl derivatives and — with identical

hiosemicarbazides.

Thiosemicarbazide	Recryst. from	Method of preparation	M.p., °C	Formula		Analyses: C	H	N	S
4-*sec*-Butyl [3]	f	3a	58–59 [m]	$C_5H_{13}N_3S$	Found:	40.80	9.02		
1-*tert*-Butyl	c	1, 5a, 7	193–194	»	»	41.10	8.98	28.60	21.38
2-*tert*-Butyl	rearr.	7	rearr.	»	»				
4-*tert*-Butyl [63]	b	3a, 6c	137–138	»	»	41.10	9.01		21.84
1-Cyclopentyl	c	2a	130–131	$C_6H_{13}N_3S$	Calc.:	45.27	8.23	26.40	
					Found:	45.50	8.16	26.65	
1-Cyclohexyl	c	1, 2a	144–145	$C_7H_{15}N_3S$	Calc.:	48.54	8.73	24.26	
					Found:	48.45	8.60	24.40	
2-Cyclohexyl	a, e	3c, 7	183–184	»	»	48.80	8.96	24.33	
4-Cyclohexyl [64]	b	3a	146–147	»	»	48.50	8.81		
1-Benzyl [3]	c	1, 2a	153–154	$C_8H_{11}N_3S$	Calc.:	53.03	6.12	23.19	
					Found:			23.40	
2-Benzyl [2,3]	c	1, 3c, 5b	170–171	»	»			23.26	
4-Benzyl [3,30]	c	3a	128–129	»	»			23.11	
1-α-Methylbenzyl [3]	c	1, 2b, 7	156–157	$C_9H_{13}N_3S$	Calc.:	55.37	6.71	21.53	
					Found:	55.45	6.53	21.31	
2-α-Methylbenzyl	rearr.	7	rearr.	»	»				
4-α-Methylbenzyl [30,65]	b	3a	89–90 [n]	»	»	55.20	6.42		
1-Phenethyl	c	2a	146–147	»	»	55.65	6.55	21.26	
2-Phenethyl [66]	a, g	1, 7	135–136	»	»	55.40	6.68	21.44	
4-Phenethyl	b	3a	114–115	»	»	55.20	6.71		
1-Benzhydryl	c	2b	185–186	$C_{14}H_{15}N_3S$	Calc.:	65.35	5.88	16.33	
					Found:	65.45	5.77	16.30	
4-Benzhydryl [67,68]	c	3a	145–146°	»	»	65.20	5.92	16.22	
4-Triphenylmethyl	c	3a	165–166 (decomp.)	$C_{20}H_{19}N_3S$	Calc.:	72.05	5.74	12.61	
					Found:	72.35	6.26	12.20	

Solvents used for recrystallization: a) water; b) ethanol-water; c) ethanol; d) ethanol-ether; e) benzene-thanol; f) ether; g) benzene; h) benzene-petroleum ether. i) Formulated by Gabriel [62] as 1-allylthiosemicarbazide.) The melting point given in Ref. 2 (183–184°C) could not be confirmed. k) Lit.[107] 171°C. l) Lit.[3] 68°C. m) Lit.[3] 2°C. n) Lit.[30,65] 84 and 80°C. o) Lit.[67,68] 144°C and 151–152°C (decomp.).

Table 2. Disubstituted thiosemicarbazides.

Thiosemicarbazide	Recryst. from	Method of preparation	M.p., °C	Formula		Analyses: C	H	N	S
1,1-Dimethyl [69,70]	a	1, 3c, 3e, 5a, 5b, 7	184–185 [1]	$C_3H_9N_3S$	Calc.:	30.24	7.62	35.28	26.92
					Found:	30.28	7.53	35.26	
1,2-Dimethyl	a, b	1, 3c, 3d, 7	131–132	»	»	30.20	7.42	35.06	
1,4-Dimethyl	a, g	8	135–136	»	»	30.38	7.62		26.88
2,4-Dimethyl [71]	a, e	3a, 6a, 6b	136–137	»	»	30.56	7.48		
4,4-Dimethyl [1]	c	4b, 6a, 6c	156–157	»	»	30.10	7.66	35.35	
1-Ethyl-1-methyl	a	7	134.5–135	$C_4H_{11}N_3S$	Calc.:	36.08	8.33	31.56	24.03
					Found:	36.28	8.33	31.28	
1-Ethyl-2-methyl	a	2c	115–116	»	»	36.11	8.12	31.30	
1-Ethyl-4-methyl	a	2a	113–114	»	»	36 20	8.62	31.46	
2-Ethyl-1-methyl	a	8	80–81	»	»	36.33	8.29	31.33	
2-Ethyl-4-methyl	a	3a	118–119	»	»	36.01	8.14	31.10	24.08
4-Ethyl-1-methyl	j	8	88–89	»	»	36.22	8.45	31.57	
4-Ethyl-2-methyl [71]	e	3a	86–87	»	»	36.23	8.37		
4-Ethyl-4-methyl	a	6c	88–89	»	»	36.28	8.28	31.28	
2-Allyl-4-methyl	i	3a	72–73	$C_5H_{11}N_3S$	Calc.:	41.37	7.64	28.95	
					Found:	41.40	7.65	28.75	
2-Methyl-4-propyl	c	3a	102–103	$C_5H_{13}N_3S$	Calc.:	40.80	8.90	28.55	21.74
					Found:	40.80	8.86		
4-Methyl-2-propyl	i	3a	73–74	»	»	40.85	8.88	28.33	21.70
4-Methyl-4-propyl	a	6c	96–97	»	»			27.88	
1-Isopropyl-4-methyl	c	2a	96–97	»	»	40.85	8.98	28.70	
2-Isopropyl-4-methyl	c, d	3a, 6b	124–125	»	»	41.00	8.74	28.54	
4-Isopropyl-2-methyl [3]	c	3a, 6c	108–109	»	»	40.96	8.75	28.54	
1,1-Diethyl [1]	a	1, 3c, 7	151–152	»	»	40.65	8.94	28.42	
2,4-Diethyl	a	3a	59–60	»	»	41.00	8.73	28.21	
4,4-Diethyl	a	4b, 6c	84–85	»	»	40.90	8.80	28.71	
N-(4-Morpholylthiocarbonyl) hydrazine	a	6c	165–166	$C_5H_{13}N_3OS$	Calc.:			26.10	
					Found:			26.20	
N-(1-Piperidylthiocarbonyl)hydrazine [37]	a	6c	92.5–93	$C_6H_{13}N_3S$	Calc.:			26.40	
					Found:			26.62	
2-Butyl-4-methyl	i	3a, 6b	82–83	$C_6H_{15}N_3S$	Calc.:	44.70	9.38	26.07	19.85
					Found:			25.78	19.56
4-Butyl-2-methyl [3]	f	3a, 4c	50–51	»	»	44.60	9.55		
2-*sec*-Butyl-4-methyl	i	3a	85–85.5	»	»	44.50	9.38		
2-Isobutyl-4-methyl	i, e	3a, 6b	107–108	»	»	44.75	9.20	25.87	20.12
1-*tert*-Butyl-4-methyl	f, e	3a, 6b	151–152	»	»	44.70	9.41	26.08	
2-*tert*-Butyl-4-methyl	rearr.	3a	114–115	»					
4-*tert*-Butyl-1-methyl	a	8	102–103	»	»	44.38	9.27		
4-*tert*-Butyl-2-methyl	f	3a, 6c	158–159	»	»	44.90	9.24	25.92	
2,4-Dipropyl	h	3a	40–41	$C_7H_{17}N_3S$	Calc.:	47.98	9.78	23.98	
					Found:			23.52	
4,4-Dipropyl	c	6c	98.5–99.5	»	»	48.52	9.75	23.44	
2,4-Diisopropyl	e	3a	101–102	»	»	47.71	9.56	23.81	
4,4-Diisopropyl	a	4b, 6c	123–124	»	»	47.63	9.83	24.14	
1-Methyl-1-phenyl [72]	c	3c, 7	187–188	$C_8H_{11}N_3S$	Calc.:	53.00	6.08	23.20	
					Found:	53.10	6.34	23.16	
1-Methyl-2-phenyl	c	8	145–146	»	»	52.68	6.24	23.14	
1-Methyl-4-phenyl	k	8	99–100	»	»	52.90	5.89	23.14	
2-Methyl-1-phenyl	c	1, 3c	205–206	»	»	52.95	6.21		
2-Methyl-4-phenyl [26]	c	3a	146–147	»	»	52.80	5.99		

Table 2. Continued.

4-Methyl-1-phenyl [72]	c	3b	169—170	$C_8H_{11}N_3S$	Found:	53.05	6.26	23.15	
4-Methyl-2-phenyl [24-27]	c	3a, 6b	90—91	»	»	53.35	6.32		
4-Methyl-4-phenyl [73]	c	6c	124—125	»	»	52.95	6.14	23.23	
1-Cyclohexyl-4-methyl	k	3b	115—117	$C_8H_{17}N_3S$	Calc.:	51.31	9.15	22.44	17.09
					Found:	51.80	8.70		
2-Cyclohexyl-4-methyl	i	3a, 6b	175—176	»	»	51.20	9.14	22.35	16.60
4-Cyclohexyl-1-methyl	e	8	112—113	»	»	51.20	9.03	22.54	
4-Cyclohexyl-2-methyl	e	3a	136—137	»	»	51.20	9.10		
2-Allyl-4-*tert*-butyl	e	3a	74—75	»	»	51.40	9.23	22.23	
2-Hexyl-4-methyl	i	3a	80—81	$C_8H_{19}N_3S$	Calc.:	50.77	10.12	22.20	16.91
					Found:	50.93	10.11	22.11	17.12
1-*tert*-Butyl-4-isopropyl	e	3b	121—122	»	»	50.80	10.05	22.13	
4-*tert*-Butyl-1-isopropyl	c	3b	123—124	»	»	50.95	10.08	22.03	16.95
4-*tert*-Butyl-2-isopropyl	c	3a, 6c	142—143	»	»	50.85	9.92	22.18	
4-*tert*-Butyl-2-propyl	e	3a	94—95	»	»	50.70	10.18	22.03	
1-Benzyl-1-methyl	c	3c	119—120	$C_9H_{13}N_3S$	Calc.:	55.37	6.71	21.53	16.39
					Found:	55.10	6.62		
2-Benzyl-4-methyl	i	3a	127—128	»	»	55.25	6.56	21.62	16.68
4-Benzyl-2-methyl	e	3a	150—151	»	»	55.54	7.00		
2-Ethyl-1-phenyl	c	1	146—147	»	»	55.60	6.89	21.29	
1-Ethyl-2-phenyl	c	2c	180—181	»	»	55.30	7.04	21.91	
2-Methyl-4-*p*-methoxyphenyl	e	3a	160—161	$C_9H_{13}N_3OS$	Calc.:	51.17	6.20		
					Found:	51.40	6.35		
2-Butyl-4-*tert*-butyl	g	3a	107—108	$C_9H_{21}N_3S$	Calc.:	53.17	10.41	20.67	
					Found:	53.30	10.38	20.66	
4-*tert*-Butyl-1-isobutyl	g	3b	111—112	»	»	53.00	10.59	20.78	
4-*tert*-Butyl-2-isobutyl	g	3a	112—113	»	»	53.18	10.59	20.72	
1,4-Di-*tert*-butyl	d	3a, 6c	138—139	»	»	53.39	10.40	20.80	
2-Methyl-4-(3′-diethylaminopropyl)	b	3a	69—70	$C_9H_{22}N_4S$	Calc.:	49.51	10.16		
					Found:	49.65	10.00		
1-Allyl-4-phenyl	e	8	78—79	$C_{10}H_{13}N_3S$	Calc.:	57.75	6.25		
					Found:	58.00	6.42		
2-Allyl-4-phenyl [62,m]	c	3a	122—123	»	»	57.50	6.36		
2-Methyl-4-α-methylbenzyl	f	3a	95—96	$C_{10}H_{15}N_3S$	Calc.:	57.40	7.23	20.08	15.29
					Found:	57.40	7.16	20.18	
4-Methyl-2-α-methylbenzyl	c	3a	112—113	»	»	57.60	7.54	19.96	
2-Methyl-4-phenethyl	e	3a	120—121	»	»	57.40	6.98		
4-Methyl-2-phenethyl	i	3a	123—124	»	»	57.30	7.10	20.00	15.08
1-Isopropyl-4-phenyl	c	3b	111—112	»	»	57.30	7.08	19.88	
2-Isopropyl-4-phenyl [72,n]	c	3a	144—145	»	»	57.62	7.18	20.26	
4-Methyl-2-γ-phenylpropyl	i	3a	100—101	$C_{11}H_{17}N_3S$	Calc.:	59.17	7.68	18.82	14.36
					Found:	59.30	7.65	18.76	14.52
4-*tert*-Butyl-1-cyclohexyl	a	3b	149—150	$C_{11}H_{23}N_3S$	Calc.:	57.60	10.04	18.35	
					Found:	57.40	10.03	18.33	
4-*tert*-Butyl-2-cyclohexyl	a	3a	147—148	»	»	57.45	10.02	17.68	
1-Isopropyl-4-α-methylbenzyl	k	3b	103—104	$C_{12}H_{19}N_3S$	Calc.:	60.73	8.07	17.71	
					Found:	60.50	7.94	17.56	
2-Isopropyl-4-α-methylbenzyl	b	3a	143—144	»	»	60.80	7.84	17.83	
2-Benzyl-4-*tert*-butyl	e	3a	130—131	»	»	60.20	8.10		
4,2-Diphenyl	e	4d, 5a	182—183	$C_{13}H_{13}N_3S$	Calc.:	64.18	5.36	17.29	
					Found:	64.05	5.50	17.15	
4,4-Diphenyl	c	4a, 6c	154—155	»	»	64.25	5.60	17.37	
2-Cyclohexyl-4-phenyl [75]	c	3a	163—164 °	$C_{13}H_{19}N_3S$	Calc.:	62.62	7.68	16.85	
					Found:	62.85	7.50	16.98	

Table 2. Continued.

4-*tert*-Butyl-1-α-methylbenzyl	b	3b	137–138	$C_{13}H_{21}N_3S$	Calc.:	62.12	8.42	16.72	
					Found:	62.35	8.32		
4-*tert*-Butyl-2-α-methylbenzyl	b	3a	104–105	»	»	62.20	8.30	16.55	
4-*tert*-Butyl-1-phenethyl	e	3b	115–116	»	»	62.40	8.34		
4-*tert*-Butyl-2-phenethyl	e	3a	168–169	»	»	62.15	8.42	16.65	
4,4-Dibenzyl	c	4b	134–135	$C_{15}H_{17}N_3S$	Calc.:	66.38	6.32	15.50	11.81
					Found:	66.35	6.49	15.50	11.83
1,4-Di-α-methylbenzyl	j	3a	147–148	$C_{17}H_{21}N_3S$	Calc.:	68.20	7.07	14.04	
					Found:	68.00	7.04	14.26	
2-Methyl-4-triphenylmethyl	c	3a	161–162	$C_{21}H_{21}N_3S$	Calc.:	72.60	6.09	12.10	
					Found:	72.40	6.09	12.24	

Solvents used for recrystallisation: a) water; b) methanol; c) ethanol; d) methanol-water; e) ethanol-water; f) diethyl ether; g) ethanol-diethyl ether; h) petroleum ether; i) ethanol-petroleum ether; j) benzene-petroleum ether; k) cyclohexane. l) The melting point given in Ref. 69 is 163–164°C, but repetition of the preparation has confirmed our value (private communication from Dr. J. Sandström). m) Formulated by Gabriel [62] as 1,4-derivative. n) Formulated by Lochte *et al.*[74] as 1,4-derivative. o) The melting point given in Ref. 75 (144°C) could not be confirmed.

alkyls — five dialkylthiosemicarbazides, five trialkylthiosemicarbazides, three tetraalkylthiosemicarbazides, and one pentaalkylthiosemicarbazide. We have prepared the seventeen methylsubstituted thiosemicarbazides of which only four were known. Further, we have, *inter alia*, prepared the eight possible isomeric ethylmethylthiosemicarbazides of which only one was known. Of necessity, however, we had to limit the number of preparations of thiosemicarbazides with higher alkyls and with different alkyls to some representative examples. These have been chosen with a view to the following purposes: 1) To elucidate the steric influence of alkyl groups on the formation of a 1-alkyl or a 2-alkylthiosemicarbazide. 2) To work out methods for the preparation of any type of thiosemicarbazide. While some types are easily accessible, the preparation of certain types presented extraordinary difficulties. 3) To prepare crystalline derivatives suitable for identification of the alkyl- and dialkylhydrazines.

All the thiosemicarbazides prepared (except acyl derivatives, for which see Experimental Part and Table 7) are listed in Tables 1–4. Some of the compounds were (or are now) known but have been included in the tables for comparison of melting points and methods of preparation. The methods referred to in the tables are described in detail in the experimental part. To obtain a general view of these methods, it is convenient to distinguish between thiosemicarbazides which are unsubstituted, monosubstituted and disubstituted in the 4-position (Sections 1–3). The preparations of 1-methylthiosemicarbazides and thiosemicarbazides substituted both in the 1- and the 2-position present special features * and have been treated separately (Sections 4–5).

* It was also envisaged that the reaction of *N*-isothiocyanatoamines with ammonia or amines might be a general method for the preparation of 1,1-dialkylthiosemicarbazides. Since, however, isothiocyanatoamines were unknown at the beginning of this work the study of these compounds has been the subject of separate investigations.[8]

Table 3. Trisubstituted thiosemicarbazides.

Thiosemicarbazide	Recryst. from	Method of preparation	M.p., °C	Formula		Analyses: C	H	N	S
1,1,2-Trimethyl (hydrochloride)	d	1, 3c, 3e	176—178	$C_4H_{11}N_3S$·HCl	Calc.:	28.33	7.10	24.74	Cl: 20.92
					Found:	28.27	7.06	24.52	21.04
1,1,4-Trimethyl	d	3a, 6b	155—156	$C_4H_{11}N_3S$	Calc.:	36.08	8.33	31.56	
					Found:	36.25	8.26		
1,2,4-Trimethyl	c	3a	49.5—50.5	»	»	35.95	8.08		
1,4,4-Trimethyl	e	8	71—72	»	»	36.01	8.48	31.40	
2,4,4-Trimethyl	c	4a, 4b, 6c	63—64	»	»	36.50	8.20		
4-Ethyl-1,1-dimethyl	c	3a	88—89	$C_5H_{13}N_3S$	Calc.:	40.80	8.90	28.55	
					Found:	40.66	8.64	27.58	
1-Ethyl-1,4-dimethyl	b	3a	119—120	»	»	40.88	8.85	28.38	
2-Ethyl-1,4-dimethyl (hydrochloride)	d	8	148—149	$C_5H_{13}N_3S$·HCl	Calc.:	32.68	7.70	22.88	
					Found:	32.50	7.40	22.83	
4-Allyl-1,1-dimethyl	c	3a	80—81	$C_6H_{13}N_3S$	Calc.:	45.27	8.23		
					Found:	45.20	8.26		
1,1-Diethyl-4-methyl	b	3a	91—92	$C_6H_{15}N_3S$	Calc.:	44.70	9.38	26.07	
					Found:	44.85	9.35	25.57	
1,2-Diethyl-4-methyl	b	3a	76—77	»	»	44.55	9.25	25.82	
4,4-Diethyl-2-methyl	e	4a	37—38	»	»	44.50	9.23	25.44	
1,1-Dimethyl-4-propyl	c	3a	91—92	»	»	44.66	9.31	26.25	
1,4-Dimethyl-1-propyl	b	3a	69—70	»	»	44.60	9.08		
4-Isopropyl-1,1-dimethyl	c	3a	131—132	»	»	44.65	9.47	25.80	
1-Isopropyl-1,4-dimethyl	b	3a	128—129	»	»	44.45	9.20		
4-Butyl-1,1-dimethyl	c	3a	56—57	$C_7H_{17}N_3S$	Calc.:	47.98	9.78	23.98	18.26
					Found:	47.75	9.47	23.76	
1-Butyl-1,4-dimethyl	b	3a	54—55	»	»	48.10	9.50		
4-Isobutyl-1,1-dimethyl	c	3a	100—101	»	»	47.80	9.40		
4-*sec*-Butyl-1,1-dimethyl	c	3a	105—106	»	»	48.20	9.61		
4-*tert*-Butyl-1,1-dimethyl	b	3a	153—154	»	»	47.85	9.70		18.07
4-*tert*-Butyl-1,2-dimethyl	b	3a	75—76	»	»	48.02	9.71	23.32	
1,1,4-Triethyl (hydrochloride)	h	3a	162—164	$C_7H_{17}N_3S$·HCl	Calc.:	39.71	8.58	19.86	
					Found:			19.40	
1,2,4-Triethyl (hydrochloride)	h	3a	102—104	»	»	39.20	8.76	19.65	
4-Methyl-1,2-dipropyl	b	3a	48—49	$C_8H_{19}N_3S$	Calc.:	50.77	10.12	22.20	16.91
					Found:	50.55	10.14	22.24	
1,1-Diisopropyl-4-methyl	b	3a	121—122	»	»	51.00	10.08	21.63	
1,2-Diisopropyl-4-methyl	g	3a	114—115	»	»	50.85	10.09	22.28	16.94
1,1-Diethyl-4-isopropyl	b	3a	72—73	»	»	50.76	9.96	21.90	
4-*tert*-Butyl-1-ethyl-2-methyl	b	2c	95—96	»	»	50.75	10.33	22.37	
1,1-Dimethyl-4-phenyl [76]	d	3a	180—181	$C_9H_{13}N_3S$	Calc.:	55.37	6.71	21.53	
					Found:	55.30	6.63	21.38	
1,2-Dimethyl-4-phenyl [77]	a	3a	114—115	»	»	55.25	6.66		
1,4-Dimethyl-2-phenyl	d	2c	104—105	»	»	55.35	6.65	21.50	
4,4-Dimethyl-1-phenyl	a	4a	131—132	»	»	55.37	6.62	21.34	
4,4-Dimethyl-2-phenyl (hydrochloride)	j	4a	196—197	$C_9H_{13}N_3S$·HCl	Calc.:	46.66	6.11		Cl: 15.30
					Found:	46.50	6.17		15.57
1-Cyclohexyl-1,4-dimethyl	b	3a	112—113	$C_9H_{19}N_3S$	Calc.:	53.70	9.52		
					Found:	53.99	9.36		
4-Cyclohexyl-1,1-dimethyl	b	3a	150—151	»	»	53.40	9.42		
4-Cyclohexyl-1,2-dimethyl	c	3a	74—75	»	»	54.00	9.33		
4-*tert*-Butyl-1,1-diethyl	a	3a	115—116	$C_9H_{21}N_3S$	Calc.:	53.17	10.41		
					Found:	52.90	10.02		

Table 3. Continued.

4-*tert*-Butyl-1,2-diethyl	a	3a	47–48	$C_9H_{21}N_3S$	Found:	53.15	10.25	
1-Benzyl-1,4-dimethyl	b	3a	78–79	$C_{10}H_{15}N_3S$	Calc.:	57.40	7.23	20.08
					Found:	57.60	7.14	
1-Benzyl-2,4-dimethyl	i	2b	83–84	»	»	57.15	7.11	20.06
1-Benzyl-4,4-dimethyl	a	2a	102–103	»	»	56.80	6.89	20.00
2-Benzyl-1,4-dimethyl	b	8	95–96	»	»	57.40	7.29	19.95
2-Benzyl-4,4-dimethyl (hydrochloride)	j	4a	158–160	$C_{10}H_{15}N_3S$·HCl	Calc.:	48.86	6.56	17.09
					Found:	47.76	6.34	17.06
4-Benzyl-1,1-dimethyl	a	3a	167–168	$C_{10}H_{15}N_3S$	»	57.60	7.02	20.06
1,1-Dimethyl-4-*o*-tolyl	a	3a	189–190	»	»	57.30	7.31	20.11
1,1-Dimethyl-4-*m*-tolyl	a	3a	134–135	»	»	57.55	7.34	20.31
2-Ethyl-4-methyl-1-phenyl	b	3a	111–112	»	»	57.45	7.34	20.30
1,1-Dimethyl-4-*o*-methoxyphenyl	a	3a	147–148	$C_{10}H_{15}N_3OS$	Calc.:	53.32	6.71	
					Found:	53.40	6.82	
1,1-Dimethyl-4-*p*-methoxyphenyl	a	3a	131–132	»	»	53.30	6.70	
1,1-Diisobutyl-4-methyl	b	3a	82–83	$C_{10}H_{23}N_3S$	Calc.:	55.27	10.67	19.33
					Found:	55.02	10.37	
1,2,4-Triisopropyl	h	3a	52.5–53	»	»	55.15	10.62	19.34
1,2-Dibutyl-4-methyl (hydrochloride)	h	3a	146–148	$C_{10}H_{23}N_3S$·HCl	Calc.:	47.31	9.53	16.56
					Found:	47.30	8.45	16.81
1,2,4-Tripropyl (hydrochloride)	h	3a	95–97	»	»			16.55
1,1-Dimethyl-4-α-methylbenzyl	a	3a	128–130	$C_{11}H_{17}N_3S$	Calc.:	59.17	7.68	18.81
					Found:	59.00	7.67	
1,1-Dimethyl-4-phenethyl	a	3a	107–108	»	»	58.90	7.53	
1,2-Dimethyl-4-phenethyl	c	3a	76–77	»	»	59.05	7.52	
1,1-Diethyl-4-phenyl	a	3a	129–130	»	»	59.05	7.68	18.76
4-*tert*-Butyl-1,2-diisopropyl	a	3a	92–93	$C_{11}H_{25}N_3S$	Calc.:	57.11	10.89	
					Found:	57.32	10.79	
4-Benzyl-1,1-diethyl	d	3a	111–112	$C_{12}H_{19}N_3S$	Calc.:	60.73	8.07	17.71
					Found:	60.40	7.57	
1,1-Diethyl-4-*o*-tolyl	a	3a	134–135	»	»			17.77
1,1-Diethyl-4-*m*-tolyl	a	3a	93–94	»	»	60.60	7.85	
4-*tert*-Butyl-1-methyl-1-phenyl	b	3a	144–145	»	»	60.52	7.83	
4-*tert*-Butyl-2-methyl-1-phenyl	b	3a	151–152	»	»	60.75	7.94	17.77
1-Benzyl-1-methyl-4-*tert*-butyl	a	3a	97–98	$C_{13}H_{21}N_3S$	Calc.:	62.12	8.42	
					Found:	62.00	8.36	
4-Methyl-1,2-diphenyl	a	3a	174–175	$C_{14}H_{15}N_3S$	Calc.:	65.33	5.89	16.33
					Found:	64.80	5.58	16.20
1,2-Dicyclohexyl-4-methyl	a	3a	164–165	$C_{14}H_{27}N_3S$	Calc.:			15.73 11.99
					Found:			15.72 11.88
1,2-Dicyclohexyl-4-phenyl	a	3a	130–131	$C_{19}H_{29}N_3S$	Calc.:	68.85	8.82	12.68
					Found:	68.50	8.77	12.87
4-Benzyl-1,2-diphenyl	a	3a	173–174	$C_{20}H_{19}N_3S$	Calc.:	72.03	5.76	12.60
					Found:	72.15	5.82	12.69

Solvents used for recrystallization: a) ethanol; b) ethanol-water; c) diethyl ether; d) ethanol-diethyl ether; e) diethyl ether-petroleum ether; f) ethanol-petroleum ether; g) benzene-petroleum ether; h) ethyl acetate; i) cyclohexane; j) ethyl acetate-ethanol.

Table 4. Tetra- and pentasubstituted thiosemicarbazides.

Thiosemicarbazide	Method of preparation	M.p. or b.p. °C	Formula		Analyses C	H	N
1,1,2,4-Tetramethyl (hydrochloride)	3a	123—125 [a]	$C_5H_{13}N_3S$·HCl	Calc.:	32.70	7.69	22.90
				Found:	32.50	7.57	22.82
1,1,4,4-Tetramethyl (hydrochloride)	4a	162—164 [a]	»	»			22.66
1,2,4,4-Tetramethyl (hydrochloride)	4a	193—195 [a]	»	»			22.99
1,1,4,4-Tetramethyl	4a	91—92 [b]	$C_5H_{13}N_3S$	Calc.:	40.80	8.90	
				Found:	40.62	8.62	
1,2,4,4-Tetramethyl	4a	b.p. 85—87 (2 mm Hg)	»	»	41.26	8.98	
1,1,2,4,4-Pentamethyl	4a	b.p. 83—85 (2 mm Hg)	$C_6H_{15}N_3S$	Calc.:	44.70	9.38	
				Found:	45.15	9.08	
1,1,2-Trimethyl-4-*tert*-butyl	3a	114—115 [c]	$C_8H_{19}N_3S$	Calc.:	50.77	10.12	22.20
				Found:	50.65	10.37	22.44
1,1,4,4-Tetraethyl (hydrochloride)	4a	152—153 [d]	$C_9H_{21}N_3S$·HCl	Calc.:	45.06	9.25	
				Found:	45.09	9.45	
2,4,4-Trimethyl-1-phenyl	4a	90.5—91.5 [e]	$C_{10}H_{15}N_3S$	Calc.:	57.40	7.23	20.08
				Found:	57.30	7.24	19.93

Solvents used for recrystallization: a) ethyl acetate; b) ether; c) water; d) ethyl acetate-ethanol; e) pentane, after layer chromatography on silica gel. Melting points of the hydrochlorides were determined in sealed capillary tubes.

1. Thiosemicarbazides unsubstituted in the 4-position

a. Rearrangement of hydrazinium thiocyanates (Method 1). As is well known 1-phenylthiosemicarbazide is formed by rearrangement of phenylhydrazinium thiocyanate. Cattelain [2] found that methyl- and benzylhydrazine react in a similar way with thiocyanic acid, but in these cases the 2-substituted thiosemicarbazides were formed. We have found that thiosemicarbazides unsubstituted in the 4-position may in general be prepared by heating the thiocyanate of a hydrazine at 150—160°C; the reaction proceeds not only with monoalkylhydrazines but also with 1,1-dialkyl- and 1,2-dialkylhydrazines and with trimethylhydrazine.

As a rule, however, the yields are very low; often only 10—20 % of a pure compound could be obtained. This is, in part, due to the fact that the transformation of the hydrazinium thiocyanates into thiosemicarbazides is incomplete. The reaction products always contain large amounts of unchanged hydrazinium thiocyanate. Another reason for the low yields is that a mixture of the two isomers, the 1- and 2-alkylthiosemicarbazide, is formed. As already noted by Hoggarth [3] when repeating the preparation of 2-benzylthiosemicarbazide according to Cattelain,[2] the crude product melts over a wide range and is difficult to purify by recrystallization. This is a general property of the crude products. An attempt was therefore made to separate the isomers by

preparative thin-layer chromatography. While this method confirmed that a mixture of the two isomers was formed, it was found unsuited for the preparation of 1-alkylthiosemicarbazides because these may be oxidized to thiosemicarbazones during the prolonged exposure to air. The chromatographic separation further showed that no compounds other than the two isomeric alkylthiosemicarbazides are formed to any appreciable extent.

In general, repeated recrystallizations yield only one isomer. This is normally the 2-alkylthiosemicarbazide when the alkyl group is primary. However, with increasing size of the alkyl group the 1-alkylthiosemicarbazide is formed in larger amount and the product isolated after several recrystallizations may be the 1-alkylthiosemicarbazide. From ethylhydrazine we have in some experiments isolated 2-ethylthiosemicarbazide and in others 1-ethylthiosemicarbazide.

Alkylhydrazines with a secondary alkyl, such as isopropylhydrazine, cyclohexylhydrazine, α-methylbenzylhydrazine, and *tert*-butylhydrazine yield only the 1-alkylthiosemicarbazide and accordingly behaves like aromatic hydrazines. Probably the 2-isomer is formed first in all cases but is rearranged to the 1-isomer more easily when the alkyl is secondary or tertiary than when it is primary (*cf.* Sect. 2); therefore the 2-isomer will predominate with alkylhydrazines with a primary alkyl group and the 1-isomer with hydrazines with a secondary or tertiary alkyl group. The formation of 1-ethylthiosemicarbazide in some of the experiments may have been caused by the application of a higher temperature during the reaction.

It is not possible to carry out these preparations under very well defined conditions. The unsubstituted thiosemicarbazide has been prepared by heating hydrazinium thiocyanate to 100°C,[9] but usually no rearrangement of the hydrazinium thiocyanates took place until the temperature reached 150—160°C, when we have to do with the decomposition of a molten salt. It was found that better yields of 2-methylthiosemicarbazide may be obtained by carrying out the reaction with the thiocyanate suspended in a high boiling solvent, but when this method was applied to prepare 2-ethyl- and 2-propylthiosemicarbazide mixtures of the 1- and 2-isomers again resulted so it was not explored further.

Accordingly, the rearrangement of hydrazinium thiocyanates is not a satisfactory method for preparing 1- or 2-monoalkylthiosemicarbazides.

b. Reduction of thiosemicarbazones (Method 2). The 1-monoalkylthiosemicarbazides (except 1-methylthiosemicarbazides, see Sect. 4) could be obtained in good yields by reduction of thiosemicarbazones. Hoggarth [3] reduced some thiosemicarbazones of aromatic aldehydes and ketones with sodium amalgam and *inter alia* obtained 1-benzylthiosemicarbazide in this way. We have found that thiosemicarbazones of aliphatic aldehydes and ketones also could be reduced to thiosemicarbazides but found it preferable generally to use sodium borohydride as the reducing agent. In this way 1-ethylthiosemicarbazide and several other 1-alkylthiosemicarbazides were prepared (Table 1). This method could not be used directly to prepare thiosemicarbazides substituted in both the 1- and 2-positions (see Sect. 5).

The reduction with sodium borohydride failed in certain cases. In the case of the thiosemicarbazone of glyoxylic acid, reduction resulted in cleavage of

the C=N bond with the formation of thiosemicarbazide. The same was found when the reduction was carried out with sodium amalgam or with hydrazine and hydrogen peroxide.[10] The thiosemicarbazones of glyoxal and benzophenone were unaffected by sodium borohydride, but benzophenone thiosemicarbazone could be reduced to 1-benzhydrylthiosemicarbazide with sodium amalgam.

The method further failed when attempts were made to prepare 1-methylthiosemicarbazide and 1-allylthiosemicarbazide because the reaction of thiosemicarbazide with formaldehyde or acrolein gives polymeric substances. The preparation of 1-methylthiosemicarbazide will be discussed in Section 4. The methods described there can also be applied to prepare 1-allylthiosemicarbazide and probably in similar cases where the reduction of thiosemicarbazones is not applicable.

c. Addition of hydrogen sulfide to cyanohydrazines (Method 7). The 2-alkylthiosemicarbazides, unsubstituted in the 4-position, were obtained in good yields from cyanohydrazines and hydrogen sulfide (*cf.* the preparation of 2-phenylthiosemicarbazide[11]). The reaction of cyanogen bromide with monoalkylhydrazines resulted in all cases in cyanohydrazines with the CN group attached to the same nitrogen atom as the alkyl group. On addition of hydrogen sulfide to these cyanohydrazines 2-alkylthiosemicarbazides were obtained, except in the case of the *tert*-butyl and α-methylbenzyl derivatives where 1-*tert*-butylthiosemicarbazide and 1-α-methylbenzylthiosemicarbazide resulted, possibly because the 2-derivatives rearranged (*cf.* 2-*tert*-butyl-4-methylthiosemicarbazide, Sect. 2).

1,1-Dimethylhydrazine and 1,2-dimethylhydrazine could also be transformed into thiosemicarbazides *via* a cyanohydrazine. Although trimethylhydrazine reacts with cyanogen bromide to form trimethylcyanohydrazine,[12] the latter could not be induced to add hydrogen sulfide. 1,1,2-Trimethylthiosemicarbazide has, however, been prepared in other ways. 1-Cyano-1-methyl-2-phenylhydrazine was similarly unaffected by hydrogen sulfide.

d. Ammonolysis of monothio- and dithiocarbazates (Method 5). In a German patent[13] it has been claimed that 1-benzylthiosemicarbazide may be obtained from the corresponding dithiocarbazate and ammonia. While it was confirmed that thiosemicarbazides may be obtained from dithiocarbazates and ammonia, it was found that the benzylthiosemicarbazide in question is not 1-benzylthiosemicarbazide but 2-benzylthiosemicarbazide. It was found that alkylhydrazines normally react with carbon disulfide to give exclusively the dithiocarbazate isomer in which the dithiocarboxylic group is bound to the same nitrogen atom as the alkyl group, the only exception being *tert*-butylhydrazine which yielded the other isomer.

Although 2-benzylthiosemicarbazide could be obtained in good yield by ammonolysis of the dithiocarbazate obtained from benzylhydrazine, $CH_3S-CS-N(CH_2C_6H_5)-NH_2$, the ammonolysis of dithiocarbazates is not generally a good method for preparing thiosemicarbazides. The esters resist treatment with hot concentrated aqueous ammonia in an autoclave for a very long time when the temperature is kept at 100°C. When the temperature is raised above 120°C decomposition sets in and, in most cases, no thiosemicarbazide could be isolated.

Monothiocarbazates ("xanthogenhydrazides") of the type

$RO-CS-NR'-NH_2$ did not react with ammonia to form thiosemicarbazides. From $CH_3O-CS-NH-N(CH_3)_2$ and aqueous ammonia a slight yield of 1,1-dimethylthiosemicarbazide was obtained and $C_2H_5O-CS-NH-NHBu^t$ yielded 1-*tert*-butylthiosemicarbazide.

e. Hydrazinolysis of monothio- and dithiocarbamates (Method 6). As a method of preparing 2-alkylthiosemicarbazides, the reaction between hydrazine and *O*-alkyl thiocarbamates (thiourethans, xanthamides), $H_2N-CS-OR$, or alkyl dithiocarbamates (dithiourethans), $H_2N-CS-SR$, was explored.

According to a German patent [14] (*cf.* also Mameli *et al.*[15]) *O*-ethyl thiocarbamate reacts with hydrazine or methylhydrazine to form thiosemicarbazide and 2-methylthiosemicarbazide, respectively, and this was found to be the case although the yield are rather unsatisfactory. In the patent the methylthiosemicarbazide formed has been described as 1-methylthiosemicarbazide, but it is actually 2-methylthiosemicarbazide. Better yields could be obtained from *O*-methyl or *O*-phenyl thiocarbamate and hydrazine or methylhydrazine, but the reaction is slow and no thiosemicarbazides could be obtained from higher alkylhydrazines, or from di- or trialkylhydrazines.

From *S*-methyl dithiocarbamate, $H_2N-CS-SCH_3$, a 75 % yield of thiosemicarbazide or 2-methylthiosemicarbazide could be obtained but, here again, no other substituted thiosemicarbazides could be obtained although the dithiocarbamate reacted rapidly with the hydrazines with evolution of methanethiol. It was found that the hydrazines induce a base-catalysed decomposition of the dithiocarbamate into methanethiol and thiocyanic acid, so that actually hydrazinium thiocyanates are formed. The positive results with hydrazine or methylhydrazine may be due to the fact that their thiocyanates rearrange into thiosemicarbazides more easily than the thiocyanates of higher hydrazines. Similar results were obtained with carboxymethyl dithiocarbamate, $H_2N-CS-SCH_2COOH$.

f. Elimination of a substituent from the 4-position (Method 3c). It was found that 4-*tert*-butylthiosemicarbazide is converted almost quantitatively into thiosemicarbazide on boiling with concentrated hydrochloric acid whereas 1-*tert*-butylthiosemicarbazides were unaffected by such treatment. This reaction appeared to show some promise for the preparation of 1- and 2-alkylthiosemicarbazides since 2-alkyl-4-*tert*-butylthiosemicarbazides are formed in very good yields from hydrazines and *tert*-butyl isothiocyanate and in some cases can be rearranged to 1-alkyl-4-*tert*-butylthiosemicarbazides. When these thiosemicarbazides were heated with concentrated hydrochloric acid, elimination of the *tert*-butyl group took place very easily and, in most cases, the corresponding thiosemicarbazides unsubstituted in the 4-position — identified by mixed melting points and infrared spectra — could be isolated. Usually, however, the yields were low since the thiosemicarbazide was degraded to the hydrazine. In a few cases (*e.g.* 2-methyl-1-phenylthiosemicarbazide) very good yields were obtained and the method could also be used with advantage to prepare 1-methylthiosemicarbazide (see Sect. 4).

4-Triphenylmethylthiosemicarbazide hydrolysed in hot water to thiosemicarbazide but was decomposed by hydrochloric acid; 2-methyl-4-triphenylmethylthiosemicarbazide was decomposed even with hot water. Moreover, it was found that triphenylmethyl isothiocyanate did not form a thiosemi-

carbazide with many hydrazines but acted as a tritylating agent with the formation of hydrazinium thiocyanates.

Trimethylsilyl isothiocyanate reacts in much the same way as triphenylmethyl isothiocyanate. With methylhydrazine, it directly formed 2-methylthiosemicarbazide, the trimethylsilyl group being transferred to another hydrazine molecule (*cf.* Jensen *et al.*[16]):

$$(CH_3)_3SiNCS + 2\ CH_3NH-NH_2 \rightleftharpoons H_2N-CS-N(CH_3)NH_2 + (CH_3)_3SiN(CH_3)NH_2$$

1,2-Dialkylhydrazines reacted in a similar way, but 1,1-dimethylhydrazine and 1,1,2-trimethylhydrazine yielded only hydrazinium thiocyanates. Hydrazobenzene and trimethylsilyl isothiocyanate slowly formed benzidinium thiocyanate.

1,1,2-Trimethylthiosemicarbazide was first obtained by treating trimethylhydrazine with acetyl isothiocyanate and hydrolysing the 4-acetylthiosemicarbazide formed. The reaction of hydrazines with acyl isothiocyanates, however, has no general applicability for the preparation of thiosemicarbazides unsubstituted in the 4-position. With 1,1-dimethylhydrazine, acetyl isothiocyanate behaved as an acetylating agent and yielded the hydrazinium thiocyanate, but benzoyl isothiocyanate and 1,1-dimethylhydrazine formed 4-benzoyl-1,1-dimethylthiosemicarbazide which could be hydrolysed to 1,1-dimethylthiosemicarbazide. With 1,2-dialkylhydrazines or monoalkylhydrazines, acyl isothiocyanates form 4-acylthiosemicarbazides, but these very easily undergo ring-closure to triazole or thiadiazole derivatives, either spontaneously or under hydrolytic conditions (*cf.* Sugii,[17] Hoggarth,[18] and results from this laboratory,[55] to be published). This difficulty could not be circumvented by reacting 1-acyl-1-alkylthiosemicarbazides with acyl isothiocyanates, because the 1,4-diacylthiosemicarbazides will also undergo ring-closure spontaneously or on attempts at hydrolysis.

The question was explored whether a benzyloxycarbonyl group in the 4-position could be removed without ring-closure by hydrogenolysis. By treatment of hydrazobenzene with benzyloxycarbonyl isothiocyanate, a 4-benzyloxycarbonylthiosemicarbazide was obtained. Like other 4-acylthiosemicarbazides with a hydrogen atom in the 1-position, it underwent ring-closure on attempts at hydrolysis and also hydrogenolysis by means of triethylsilane and palladium or platinum resulted in the formation of a triazolone which resisted all attempts at ring-opening. A benzyl group directly bound to nitrogen could not be removed in this way: 4-benzyl-1,2-diphenylthiosemicarbazide and 1-benzyl-1-methylthiosemicarbazide were unaffected on treatment with triethylsilane and palladium.

g. Reactions with reactive derivatives of thiocarbamic acid. The acid chloride of thiocarbamic acid,[19] $H_2N-CS-Cl$, and some mixed anhydrides, *viz.* *S*-acetyl dithiocarbamate,[20] $H_2N-CS-SCOCH_3$, and *S*-ethoxycarbonyl dithiocarbamate,[21] $H_2N-CS-S-COOEt$, are known and their reactions with hydrazines were tested. Thiocarbamoyl chloride was split instantaneously by hydrazines into HCl and HSCN so that no thiosemicarbazides could be obtained directly in this way. A similar reaction took place with *S*-ethoxycarbonyl dithiocarbamate which reacted violently with aliphatic hydrazines yielding

carbonyl sulfide and a hydrazinium thiocyanate. Aromatic hydrazines (as examples, phenylhydrazine and 1-methyl-2-phenylhydrazine were tested) reacted more slowly and again first gave the hydrazinium thiocyanate. On further heating, this was converted into the thiosemicarbazide in excellent yields. Although this reaction is identical with the reaction discussed under a) the application of *S*-ethoxycarbonyl dithiocarbamate seems to offer certain advantages, probably because a well-defined dose of thiocyanic acid can be added to the hydrazine in this way without traces of strong mineral acids which may be very deleterious to the rearrangement of the thiocyanate. By heating 1-methyl-2-phenylhydrazine with potassium thiocyanate to which an equivalent amount of hydrochloric acid had been added, we obtained only dark polymeric substances. On the other hand, when the hydrazine was heated with *S*-ethoxycarbonyl dithiocarbamate a 90 % yield of 2-methyl-1-phenylthiosemicarbazide was at once obtained.

In view of these experiences, it was somewhat surprising to find that 1-*tert*-butoxycarbonyl-1-methylhydrazine on heating with *S*-ethoxycarbonyl dithiocarbamate in benzene solution slowly formed 1-*tert*-butoxycarbonyl-1-methylthiosemicarbazide without the intermediate formation of a thiocyanate. This can probably be explained by the fact that the decomposition of *S*-ethoxycarbonyl dithiocarbamate into thiocyanic acid, carbonyl sulfide, and ethanol is subject to base catalysis, and an acylated hydrazine is too weak a base to catalyse this reaction. Battegay and Hégazy [19] found that thiocarbamoyl chloride reacts with alcohols to form thiocarbamates but is decomposed into thiocyanic acid and hydrochloric acid by amines. No reaction took place between *S*-ethoxycarbonyl dithiocarbamate and acetyl- or trifluoroacetylhydrazines.

S-Acetyl dithiocarbamate was found to function as an acetylating agent; thus it converted 1-methyl-2-phenylhydrazine almost quantitatively into 1-acetyl-1-methyl-2-phenylhydrazine.

Hydrazobenzene also decomposed *S*-ethoxycarbonyl dithiocarbamate with the formation of thiocyanic acid but at the same time, a benzidine rearrangement took place so that the resulting product was benzidinium thiocyanate (benzidine was identified by its infrared spectrum). 1,2-Diphenylthiosemicarbazide could not be obtained in this way.*

h. Other methods studied. Attempts were made to obtain thiosemicarbazides by heating hydrazinium dithiocarbamates, $H_2NNRH_2^+$ H_2NCSS^-, or ammonium dithiocarbazates, NH_4^+ $H_2NNRCSS^-$, alone or with lead carbonate, but without success. When unsubstituted hydrazine was used as starting material thiocarbohydrazide could be isolated as a main product; from alkylhydrazines no well defined products were obtained. In this respect the aliphatic dithiocarbazates differ from ammonium phenyldithiocarbazate which gives a fair yield of 1-phenylthiosemicarbazide.[22]

* At a late stage of this investigation 1,1'-thiocarbonyldi(1,2,4-triazole) was introduced as a reactive thiocarbonyl compound and used for the preparation of 1,2-diphenylthiosemicarbazide. The scope of this reaction for the preparation of other thiosemicarbazides is being investigated.

2. Thiosemicarbazides monosubstituted in the 4-position

a. From hydrazines and isothiocyanates (Method 3). The general method for the preparation of these derivatives is the reaction between alkyl isothiocyanates and hydrazine or substituted hydrazines. The reaction proceeds very rapidly with monoalkylhydrazines, irrespective of the substituent in the hydrazine, and the yields are very satisfactory (often almost quantitative). Dialkylhydrazines, acylhydrazines, and trimethylhydrazine react more slowly but usually also give thiosemicarbazides in good yields. Unlike the reaction between carboxymethyl dithioates and hydrazines (see paper No. V of this series [7]), the reaction between isothiocyanates and hydrazines is very little influenced by steric factors. The radical *R* of the isothiocyanate seems to be almost without influence on the course of the reaction; even *tert*-butyl isothiocyanate yields the 2-isomer with most alkylhydrazines, but when the 2-radical is secondary or tertiary the products rearrange with particular ease to 1-derivatives (see below).

Normally the 2-isomer is obtained as the only product. A consequence of this is that the crude alkylthiosemicarbazides, in contrast to the crude *N*-alkylthiohydrazides,[7] generally are crystalline. A further consequence is that isothiocyanates, in contrast to carboxymethyl dithioates, react with 1,2-dialkylhydrazines with secondary alkyl groups. 1,2-Diisopropylhydrazine and 1,2-dicyclohexylhydrazine react almost as readily as 1,2-dimethylhydrazine and even hydrazobenzene reacts slowly with most isothiocyanates (1,2,4-triphenylthiosemicarbazide was prepared in this way in 1892 [23]).

In some cases the 2-alkylthiosemicarbazides can be rearranged to 1-alkylthiosemicarbazides. The ease with which this reaction occurs depends both upon the alkyl group in the 2-position and the alkyl group in the 4-position:

Thiosemicarbazides with a *tert*-butyl group in the 2-position are generally unstable. 2-*tert*-Butyl-4-methylthiosemicarbazide was prepared from *tert*-butylhydrazine and methyl isothiocyanate at −10°C but rearranged almost completely on recrystallization, even from petroleum ether. It melts sharply at 114°C but at once solidifies again and then melts at 151−152°C, the melting point of 1-*tert*-butyl-4-methylthiosemicarbazide. From *tert*-butylhydrazine and *tert*-butyl isothiocyanate, only 1,4-di-*tert*-butylthiosemicarbazide was obtained. The transient existence of 2-*tert*-butylthiosemicarbazide in the reaction between the cyanohydrazine and hydrogen sulfide could be proved by the nickel reaction (see below) but only 1-*tert*-butylthiosemicarbazide could be isolated.

Thiosemicarbazides with a secondary alkyl group in the 2-position are more stable. However, 2,4-di-α-methylbenzylthiosemicarbazide rearranged to the 1,4-derivative simply on recrystallization and thiosemicarbazides with a secondary alkyl group in the 2-position and a *tert*-butyl group in the 4-position could generally be rearranged on boiling with water for a few hours. 2-*sec*-Alkylthiosemicarbazides with other groups in the 4-position could not be rearranged in this way, but some rearranged on melting (see Experimental Part). 2-*sec*-Alkylthiosemicarbazides (*e.g.* 2-isopropyl-, 2-α-methylbenzyl, and 2-cyclohexylthiosemicarbazide) unsubstituted in the 4-position did not rearrange even on melting.

Accordingly the behaviour of 2-*sec*-alkylthiosemicarbazides is very similar to the behaviour of the 2-phenylthiosemicarbazides studied by Marckwald,[24] Busch *et al.*[25,26] and Dixon.[27]

When the radical in the 2-position is primary the thiosemicarbazides do not as a rule rearrange, even on melting. However, 2-isobutyl-4-*tert*-butylthiosemicarbazide and 2-phenethyl-4-*tert*-butylthiosemicarbazide rearranged to the 1-derivatives on heating with boiling water for 6 h. Previously Busch *et al.*[26] succeeded in rearranging 2-benzyl-4-phenylthiosemicarbazide to 1-benzyl-4-phenylthiosemicarbazide on heating to 130°C.

The differentiation of the 1- and 2-isomers can of course be made on the basis of their behaviour towards benzaldehyde since only a thiosemicarbazide unsubstituted in the 1-position can form a thiosemicarbazone. In most cases, however, a convenient qualitative reaction was used: the 2-isomers give a red or brown colour reaction with nickel chloride in alcoholic solution whereas the 1-isomers give no colour in neutral solution. The constitution of an isomer is also evident from its infrared spectrum, since only the 2,4-isomer shows an NH_2-deformation band above 1600 cm^{-1}.

In this way the structure of all new thiosemicarbazides has been established beyond doubt and some older assignments have been changed.

Since the reaction between hydrazines and isothiocyanates normally yields the 2,4-dialkylthiosemicarbazide (which only in special cases can be rearranged to the 1,4-dialkylthiosemicarbazide), another method is needed to prepare 1,4-dialkylthiosemicarbazides. With the exception of the 1-methyl derivatives to be discussed later, these are generally obtainable by reduction of 4-alkylthiosemicarbazones of aldehydes and ketones, *e.g.* 1-ethyl-4-methylthiosemicarbazide from acetaldehyde 4-methylthiosemicarbazone.

b. Hydrazinolysis of N-*alkyldithiocarbamates (Method 6).* That the steric influence is only slight in the reactions between hydrazines and isothiocyanates may be due to the circumstance that the addition takes place at the linear grouping —N=C=S. When 4-alkylthiosemicarbazides are formed from *O*-alkyl *N*-alkylthiocarbamates, RNH—CS—OR′, or alkyl *N*-alkyldithiocarbamates, RNH—CS—SR′, the steric influence might be expected to be similar to that in the formation of thiohydrazides.[7] It was, however, found that methyl *N*-methyl dithiocarbamate, $CH_3NH—CS—SCH_3$, which reacted rapidly with alkylhydrazines, always gave 2,4-dialkylthiosemicarbazides. The reason is that the hydrazines induce a base-catalysed decomposition of the alkyl dithiocarbamate into methanethiol and an isothiocyanate (*cf.* the analogous reaction of acyl dithiocarbamates [28,29]), so that the formation of the thiosemicarbazide actually proceeds through the reaction between the hydrazine and an isothiocyanate. The yields are comparable to those obtained in the reactions between hydrazines and isothiocyanates so that an *S*-alkyl *N*-alkyl dithiocarbamate can be used instead of an isothiocyanate to prepare 4-alkylthiosemicarbazides.

The same result was obtained with the [(alkylthiocarbamoyl)thio]-acetic acids, $RNH—CS—SCH_2COOH$ (R = isopropyl or *tert*-butyl). These reacted rapidly with monoalkylhydrazines giving 2,4-dialkylthiosemicarbazides. Further, *S*-acyl *N*-alkyldithiocarbamates, *e.g.* $C_4H_9NH—CS—S—CO—OC_2H_5$, which are formed as intermediates in one of the methods of preparing isothiocyanates, can be used directly to obtain 4-alkylthiosemicarbazides.

The monothiocarbamates (as examples $CH_3NH-CS-OCH_3$ and $CH_3NH-CS-OC_6H_5$ were studied), on the other hand, reacted only slowly with hydrazines and the yields of 4-alkylthiosemicarbazides were small because of side reactions.

c. Other methods studied. Some 4-alkylthiosemicarbazides were obtained by aminolysis of *S*-methyl dithiocarbazate, $CH_3S-CS-NHNH_2$, but the yields were low (10–40 %).* *N*-Alkylated dithiocarbazates, such as $CH_3S-CS-N(CH_3)NH_2$ or $CH_3S-CS-NHN(CH_3)_2$, were recovered unchanged after heating for several hours with a primary amine.

From alkoxythiocarbonylhydrazines and primary amines it has only been possible to obtain 4-alkylthiosemicarbazides in very small yields in a few cases.

No thiosemicarbazides could be obtained from alkylammonium salts of dithiocarbazic acids or from hydrazinium salts of *N*-alkyldithiocarbamic acids.

Baird *et al.*[30] and Hoggarth *et al.*[3] have prepared some 4-alkylthiosemicarbazides by aminolysis of thiosemicarbazones. This method cannot compete with the use of an isothiocyanate as starting material. Moreover, it was found that 2-alkylthiosemicarbazones did not react with a primary amine, so 2,4-dialkylthiosemicarbazides could not be prepared in this way.

Finally some attempts to prepare thiosemicarbazides by hydrazinolysis of thioureas were carried out. It is known that, *e.g.*, 1,4-diphenylthiosemicarbazide is formed from *N,N'*-diphenylthiourea and phenylhydrazine,[31-33] but attempts to prepare 4-butylthiosemicarbazide from *N,N'*-dibutylthiourea and hydrazine or 2-methyl-4-phenylthiosemicarbazide from *N,N'*-diphenylthiourea and methylhydrazine have given negative results. Hence, the method seems unsuited for the preparation of alkyl-substituted thiosemicarbazides.

3. Thiosemicarbazides disubstituted in the 4-position

a. From N,N-*dialkyl dithiocarbamates.* The first 4,4-dialkylthiosemicarbazides[1] were prepared from carboxymethyl dialkyldithiocarbamates, $R_2N-CS-SCH_2COOH$, and hydrazine in dilute aqueous solution. We have now prepared a number of other 4,4-dialkyl- and 4,4-diarylthiosemicarbazides by this method. Unlike the reaction between hydrazine and the ordinary carboxymethyl dithioates,[6] the reaction is very slow and considerable amounts of thiocarbohydrazide are formed simultaneously. In some cases none of the desired 4,4-dialkylthiosemicarbazide was obtained and no thiosemicarbazides could be prepared in this way from alkylhydrazines. However, when the carboxymethyl dialkyldithiocarbamate was dissolved in undiluted hydrazine the 4,4-disubstituted thiosemicarbazides could be obtained in all cases and in much better yields. 2,4,4-Trimethylthiosemicarbazide was obtained in a similar way from methylhydrazine but in slight yield and no thiosemicarbazide could be obtained from 1,1-dimethylhydrazine and carboxymethyl dimethyldithiocarbamate, so the method is not applicable to the preparation of trialkyl- and tetraalkylthiosemicarbazides.

The carboxymethyl esters are as usual more reactive than simple esters. *S*-Methyl dimethyldithiocarbamate could be recovered almost quantitatively after treatment for 72 h with a boiling ethanolic solution of hydrazine (Nachmias [35] claims to have prepared

* After the completion of this paper the reaction between dithiocarbazates and amines has been studied in detail by McElhinney [34] and some of the by-products which account for the low yields of thiosemicarbazides have been identified.

4,4-dimethylthiosemicarbazide by this reaction, but conditions and yields are not given). *S*-Phenyl dimethyldithiocarbamate (and other *S*-aryl dimethyldithiocarbamates, *cf.* Kulka [36]) is decomposed on prolonged treatment with hydrazine with the formation of dimethylamine, hydrogen sulfide, and thiocarbohydrazide. Lieber and Orlowski [37] obtained (1-piperidylthiocarbonyl)hydrazine, $C_5H_{10}N-CS-NHNH_2$, by hydrazinolysis of *S*-methyl 1-piperidinedithiocarboxylate, but only in 4 % yield, whereas we have obtained this compound in 30 % yield from the corresponding carboxymethyl ester.

From *O*-methyl dimethylthiocarbamate, $(CH_3)_2N-CS-OCH_3$, and hydrazine, a very small yield of 4,4-dimethylthiosemicarbazide has been obtained but in most experiments only thiocarbohydrazide could be isolated. The phenyl ester, $(CH_3)_2N-CS-OC_6H_5$, reacted with hydrazine to give a fair yield of 4,4-dimethylthiosemicarbazide, but here again no thiosemicarbazides could be obtained from the reaction with alkylhydrazines.

b. From thiocarbamoyl chlorides or thiuram monosulfides. Dialkylthiocarbamoyl chlorides and hydrazine react to form 4,4-dialkylthiosemicarbazides (*cf.* Jensen,[1] Lawyer [38]), although in rather low yields because of the formation of side-products such as tetraalkylthiuram monosulfides or *N*,*N'*-diacylhydrazines (*cf.* Ried *et al.*[39]). Alkylhydrazines react similarly. Although the reactions with dialkyl and trialkylhydrazines are rather slow, tetraalkyl- and pentaalkylthiosemicarbazides have also been prepared in this way. Thus, 2,4,4-trimethylthiosemicarbazide, 1,1,4,4-tetramethylthiosemicarbazide, 1,2,4,4-tetramethylthiosemicarbazide, and 1,1,2,4,4-pentamethylthiosemicarbazide were obtained from dimethylthiocarbamoyl chloride and methylhydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, and trimethylhydrazine, respectively. Other thiocarbamoyl chlorides react in a similar way. With monoalkylhydrazines dialkylthiocarbamoyl chlorides seem generally to give 2,4,4-trialkylthiosemicarbazides; thus, benzylhydrazine and dimethylthiocarbamoyl chloride gave 2-benzyl-4,4-dimethylthiosemicarbazide. The isomeric 1-benzyl-4,4-dimethylthiosemicarbazide could be prepared by reduction of benzaldehyde 4,4-dimethylthiosemicarbazone. Phenylhydrazine and dimethylthiocarbamoyl chloride gave, as expected, 1-phenyl-4,4-dimethylthiosemicarbazide. The isomeric 2-phenyl-4,4-dimethylthiosemicarbazide was obtained from the reaction product of dimethylthiocarbamoyl chloride and benzaldehyde phenylhydrazone.

We had difficulties in preparing the hitherto unknown diphenylthiocarbamoyl chloride and did not obtain it in a pure state, but the crude product from thiophosgene and diphenylamine reacted well with hydrazine to give 4,4-diphenylthiosemicarbazide (Ried *et al.*[40] have reported unsuccessful attempts to prepare this compound). It was also prepared from carboxymethyl 4,4-diphenyldithiocarbamate and hydrazine. Some attempts were made to prepare the unknown tri-, tetra- and pentaphenylthiosemicarbazides from the crude diphenylthiocarbamoyl chloride and phenylhydrazine, hydrazobenzene, 1,1-diphenylhydrazine or triphenylhydrazine, but no pure compounds could be obtained.

Tetraalkylthiuram monosulfides, $R_2N-CS-S-CS-NR_2$, which are in fact thioanhydrides of dialkyldithiocarbamic acids, react in a similar way as the acid chlorides. Thus, 4,4-dimethylthiosemicarbazide, 4,4-diethylthiosemicarbazide and 4,4-diisopropylthiosemicarbazide were obtained from the corresponding thiuram monosulfides and hydrazine. We also obtained 2,4,4-trimethylthiosemicarbazide from tetramethylthiuram monosulfide and methyl-

hydrazine. However, the thiuram monosulfides are less reactive than the acid chlorides and as even these react slowly with di- and trialkylhydrazines it does not seem practicable to use this method for the preparation of tetra- and pentaalkylthiosemicarbazides.

It is not possible to use mixed anhydrides instead of thiocarbamoyl chlorides in these reactions: *S*-Ethoxycarbonyl *N,N*-dimethyldithiocarbamate, $(CH_3)_2N-CS-S-COOC_2H_5$, reacted with hydrazines only to form hydrazinium dimethyldithiocarbamates.

c. Other methods studied. As found by Kazakov and Postovskiĭ,[41] the acetophenone hydrazone of *S*-methyl dithiocarbazate reacts with sufficiently basic secondary amines (aliphatic and non-aromatic heterocyclic amines) to form acetophenone thiosemicarbazones, but in our experiments the hydrolysis of these thiosemicarbazones did not take place as smoothly as described by the Russian authors so this method is not a satisfactory one. Moreover, acetone or acetophenone hydrazones of the type $CH_3S-CS-NR-N=CR_2$ were unaffected on boiling with a secondary amine such as piperidine or dibutylamine.

Alkoxythiocarbonylhydrazines (monothiocarbazates, "xanthogenhydrazides") react in a complicated way with secondary amines. An intense red colour indicates the formation of a tetrazine and no thiosemicarbazides could be isolated. Here again no reaction took place between acetophenone hydrazones of alkoxythiocarbonylhydrazines and secondary amines.

As mentioned, acetone thiosemicarbazone or acetophenone thiosemicarbazone react with primary amines to form 4-alkylthiosemicarbazones, but no thiosemicarbazides could be isolated from the reaction with secondary amines (piperidine, dibutylamine).

From dimethylammonium dithiocarbazates, or from hydrazinium or alkylhydrazinium *N,N*-dimethyldithiocarbamates, no thiosemicarbazides could be obtained on heating or treatment with lead carbonate. This again (*cf.* Sect. 1h) contrasts with the behaviour of phenyldithiocarbazic acid which readily forms 1-phenyl-4,4-dialkylthiosemicarbazides on treatment with secondary amines.[42]

4. Preparation of 1-methylthiosemicarbazides

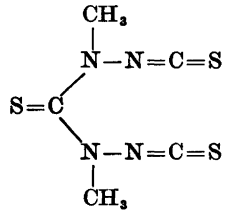
The preparation of thiosemicarbazides, substituted with only one methyl group in the 1-position, met with extraordinary difficulties. The general method for the preparation of 1-alkylthiosemicarbazides — which in this case would be tantamount to reducing a formaldehyde thiosemicarbazone — could not be applied because the reaction of thiosemicarbazide or 4-substituted thiosemicarbazides with formaldehyde results in polymeric substances (*cf.* Chabrier and Cattelain [43]). Other attempts (see below) to introduce the methyl group by reduction or methylation reactions were equally unsuccessful.

Several attempts were carried out where the starting substance was a derivative of methylhydrazine in which the methyl-bearing nitrogen was protected. Numerous methods for protecting an amino group are, of course, known from peptide chemistry but their application to thiosemicarbazides met with difficulties for the following reasons: 1) The thiosemicarbazides are rather sensitive both to reduction, oxidation, and hydrolysis and may decompose with the formation of hydrogen sulfide or sulfur. 2) The usual methods of hydrogenation or hydrogenolysis cannot be applied because the thiosemicarbazides poison the catalysts used. 3) Attempts to remove the protecting group often result in ring-closure with the formation of 1,3,4-thiadiazoles or 1,2,4-triazoles. 4) The protecting group may be *replaced* in the reaction with an isothiocyanate or thiocarbamoyl chloride. Thus it was found that 1-methyl-

1,2-bis(trimethylsilyl)hydrazine yielded 2-methylthiosemicarbazides and not 1-methylthiosemicarbazides.[16] 5) Finally, the attachment of the protecting group to the right nitrogen atom may, in itself, present difficulties.

1-Methylthiosemicarbazide was first obtained in a rather special way but later both 1-methylthiosemicarbazide, 1,4-dimethylthiosemicarbazide and 1,4,4-trimethylthiosemicarbazide were obtained from 1-methyl-1-acylhydrazines. The method introduced by Carpino [44] to use *tert*-butoxycarbonyl as the protecting group, proved especially valuable because this group can be removed with particular ease. Other acyl groups have, however, also been used as protecting groups. The method is also applicable to the preparation of other 1-alkylthiosemicarbazides if the necessary *tert*-butoxycarbonylhydrazine can be prepared.

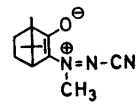
It should be emphasized that references in the literature to 1-methylthiosemicarbazides unsubstituted in the 2-position are all erroneous. Thus, the compound referred to in a German patent [14] as 1-methylthiosemicarbazide is 2-methylthiosemicarbazide, and a compound listed by Reid [45] as 1-methylthiosemicarbazide is 1-(*p*-carboxyphenyl)-4-methylthiosemicarbazide. Beckett and Dyson [46] prepared a compound from methylhydrazine and thiophosgene which they formulated as:



and on the reaction of this compound with aniline they obatined *sym*-diphenylthiourea and a methylphenylthiosemicarbazide which was formulated as 1-methyl-4-phenylthiosemicarbazide. If the structure of the starting material were correctly formulated, the formation of a 1-methylthiosemicarbazide in this reaction seems reasonable, but repetition of the preparation has shown that the reaction product is an ill-defined, polymeric substance which reacts with aniline to give *N,N'*-diphenylthiourea and some 2-methyl-4-phenylthiosemicarbazide. The melting point given by Beckett and Dyson for their methylphenylthiosemicarbazide (143°C) also agrees with that of the well known 2-methyl-4-phenylthiosemicarbazide. The hitherto unknown 1-methyl-4-phenylthiosemicarbazide was prepared by us in another way (see below) and has m.p. 99—100°C.

1-Methylthiosemicarbazide was obtained by the following methods:

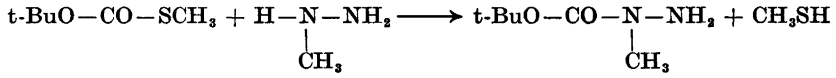
a) From the reaction of diazocamphor with potassium cyanide and then dimethyl sulfate, Forster and Saville [47] obtained a compound which was formulated as:



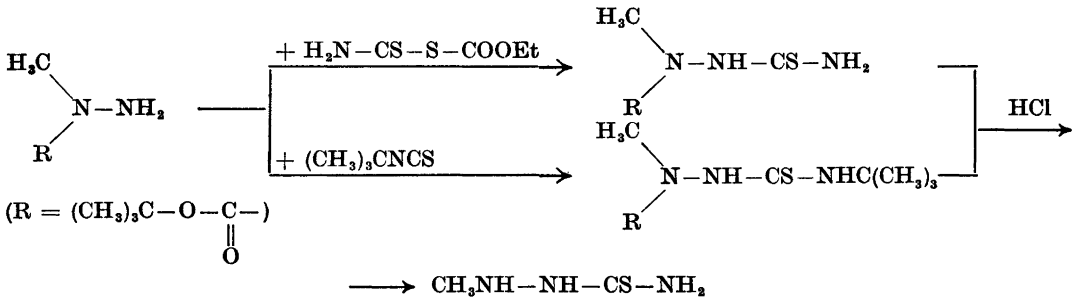
On hydrolysis this compound yielded a semicarbazide which was different from the known 2-methylsemicarbazide and was formulated as 1-methylsemi-

carbazide. Although there has been some doubt concerning the correctness of this result (*cf.* also a forthcoming paper on semicarbazides) we found that the compound of Forster and Saville on reaction with ammonium hydrogen sulfide and hydrolysis yielded a thiosemicarbazide which according to analysis, infrared spectrum and complex-forming properties was 1-methylthiosemicarbazide.

b) Methylhydrazine reacted with *O-tert*-butyl *S*-methyl thiocarbonate to give 1-methyl-1-*tert*-butyloxycarbonylhydrazine in good yield:



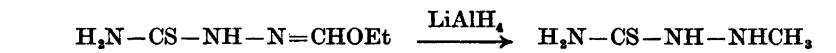
The thiocarbamoyl group could be introduced into this hydrazide directly by reaction with *S*-ethoxycarbonyl dithiocarbamate or through reaction with *tert*-butyl isothiocyanate. A *tert*-butyl group in the 4-position is removed less easily than the *tert*-butyloxycarbonyl group in the 1-position so that 1-methyl-4-*tert*-butylthiosemicarbazide may be obtained as an intermediate:



In the method of Carpino, trifluoroacetic acid is used to split off the *tert*-butyloxycarbonyl group. We have found it preferable to use concentrated hydrochloric acid which cleaves off the *tert*-butoxycarbonyl group instantaneously at room temperature. The solution is then evaporated *in vacuo* at once and the residue dissolved in a little water; on neutralisation with ammonia, the product crystallises. 1-Methylthiosemicarbazide thus obtained was found to be identical in all respects with the product of method a).

Other acyl derivatives of methylhydrazine reacted much less readily with the above-mentioned reagents than the *tert*-butyloxycarbonyl derivative. 1-Methyl-1-trifluoroacetylhydrazine reacted with *tert*-butyl isothiocyanate only on prolonged refluxing and then 2-methyl-4-*tert*-butylthiosemicarbazide was formed, *i.e.* the trifluoroacetyl group was *replaced* by the reaction with the isothiocyanate. 1-Methyl-1-trifluoroacetylhydrazine reacted slowly with acetyl isothiocyanate to form a triazole derivative.[48]

c) 1-Methylthiosemicarbazide was further prepared by reduction of 1-ethoxymethylenethiosemicarbazide [49] with lithium aluminium hydride:



This is probably the most convenient method for the preparation of larger amounts of 1-methylthiosemicarbazide. Attempts to prepare 1-methylthiosemicarbazide by reduction of 1-formylthiosemicarbazide or 1-ethoxycarbonylthiosemicarbazide with lithium aluminium hydride were unsuccessful.

1-Allylthiosemicarbazide. Allylhydrazine reacted with *O-tert*-butyl *S*-methyl thiocarbonate in a similar way as methylhydrazine to give 1-allyl-1-*tert*-butoxycarbonylhydrazine. This was transformed into 1-allylthiosemicarbazide on reaction with *S*-ethoxycarbonyl dithiocarbamate and hydrolysis of the reaction product.

1,4-Dimethylthiosemicarbazide. a) After many negative attempts this compound was obtained in several ways which all have in common that they start with a 1-acyl-1-methylhydrazine from which a 4-methylthiosemicarbazide is formed on reaction with methyl isothiocyanate. The most satisfactory method is to use 1-methyl-1-*tert*-butoxycarbonylhydrazine, for the *tert*-butoxycarbonyl group can easily be removed with hydrochloric acid. Other isothiocyanates react just as well as methyl isothiocyanate so that other 4-substituted 1-methylthiosemicarbazides, *e.g.* 1-methyl-4-ethylthiosemicarbazide or 1-methyl-4-phenylthiosemicarbazide, can be prepared in this way.

Other 1-acylthiosemicarbazides may form heterocyclic rings on attempts at hydrolysis. Thus, 1-formyl-1,4-dimethylthiosemicarbazide, formed from 1-formyl-1-methylhydrazine and methyl isothiocyanate, on hydrolysis (or only on melting or recrystallization) eliminates one molecule of water and forms a triazole derivative.[48] 1,4-Dimethyl-1-trifluoroacetylthiosemicarbazide forms the corresponding 5-trifluoromethyltriazole.

In fact, this observation which was made at the very beginning of the attempts to prepare 1,4-dimethylthiosemicarbazide delayed the work because it was thought that the formation of such heterocyclic compounds would be a common property of 1-acylthiosemicarbazides. However, it was later found that thiosemicarbazides formed from 1-acetyl-1-methylhydrazine and isothiocyanates may often be hydrolysed without ring-closure. Thus, both 1,4-dimethylthiosemicarbazide, 1-methyl-4-ethylthiosemicarbazide and 1-methyl-4-cyclohexylthiosemicarbazide were obtained from 1-acetyl-1-methylhydrazine. However, from 1-acetyl-1-methyl-4-phenylthiosemicarbazide a heterocyclic compound was again obtained.[48]

1-Ethoxycarbonyl-1-methylhydrazine reacted with methyl isothiocyanate to give the expected 1-ethoxycarbonyl-1,4-dimethylthiosemicarbazide, but this was extremely resistant towards acid hydrolysis and most of it could be recovered unchanged after heating with concentrated strong acids. Alkaline hydrolysis promoted complete decomposition.

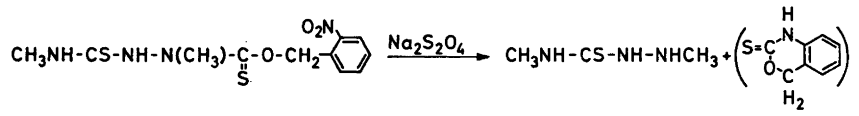
The experiences with the formyl and ethoxycarbonyl derivatives induced us to search for acyl derivatives from which the acyl group could be removed by hydrogenolysis. (Benzyloxycarbonyl)methylhydrazine, prepared from methylhydrazine and dibenzyl carbonate, and methyl isothiocyanate gave a thiosemicarbazide which on hydrogenolysis with triethylsilane yielded 2,4-dimethylthiosemicarbazide. In accordance herewith it was found that the predominant product from the reaction between dibenzyl carbonate and methylhydrazine is 1-methyl-2-benzyloxycarbonylhydrazine.[50] However, 1-(benzyloxythiocarbonyl)-1-methylhydrazine is formed in similar yield to its

isomer in the reaction between methylhydrazine and (benzyloxythiocarbonylthio)acetic acid.[51] The 4-methylthiosemicarbazide derived from this product could be reduced with triethylsilane to 1,4-dimethylthiosemicarbazide.

1,4-Dimethylthiosemicarbazide has further been obtained by acid hydrolysis of 1-isopropoxythiocarbonyl-1,4-dimethylthiosemicarbazide or 1-benzyloxythiocarbonyl-1,4-dimethylthiosemicarbazide, but generally more extensive decomposition took place on hydrolysis of this type of compound. Thus, attempts to prepare 1-methyl-4-phenylthiosemicarbazide or 1-allyl-4-methylthiosemicarbazide in this way were unsuccessful.

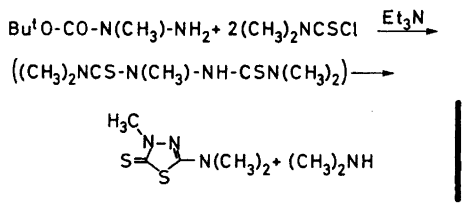
b) 1,4-Dimethylthiosemicarbazide has also been prepared by reduction of 1-ethoxymethylene-4-methylthiosemicarbazide with lithium aluminium hydride. The starting material was easily obtainable from the reaction of 4-methylthiosemicarbazide with ethyl orthoformate, so this method may compete with the preparation *via* 1-*tert*-butoxycarbonyl-1-methylhydrazine.

c) Some attempts were made to protect the methyl-bearing nitrogen of methylhydrazine with a group which might be expected to be removable by spontaneous ring-closure on reduction. 1-(*o*-Nitrobenzyloxythiocarbonyl)-1,4-dimethylthiosemicarbazide actually yielded 1,4-dimethylthiosemicarbazide on reduction with sodium dithionite, although in small yield:



1-Allylthiosemicarbazides substituted in the 4-position were prepared from 1-*tert*-butoxycarbonyl-1-allylhydrazin and isothiocyanates, analogously to the 1-methyl-4-alkylthiosemicarbazides.

1,4,4-Trimethylthiosemicarbazide. This compound has only been obtained in slight yield from the reaction between 1-*tert*-butoxycarbonyl-1-methylhydrazine and dimethylthiocarbamoyl chloride. It was isolated from the reaction mixture in the form of its slightly soluble nickel salt. The main product of the reaction was 2-dimethylamino-4-methyl-1,3,4-thiadiazol-2-ine-5-thione:



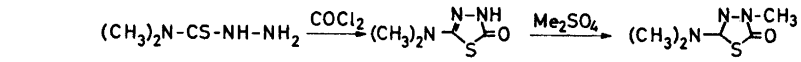
This thiadiazole derivative was also formed from other 1-alkoxythiocarbonyl-1-methylhydrazines [51] and dimethylthiocarbamoyl chloride, but no 1,4,4-trimethylthiosemicarbazide could be isolated in these cases (see Experimental Part).

The reaction between methylhydrazine (or 1-methyl-1,2-bis(trimethylsilyl)-hydrazine [16]) and dimethylthiocarbamoyl chloride afforded only 2,4,4-tri-

methylthiosemicarbazide without a trace of the isomer. No rearrangement of the 2,4,4-isomer into the 1,4,4-isomer took place on heating at 100°C (at higher temperature it decomposed).

It was further attempted to prepare 1,4,4-trimethylthiosemicarbazide in a similar manner as Busch and Limpach [52] prepared 1-methyl-2,4-diphenylthiosemicarbazide:

2-Dimethylamino-1,3,4-thiadiazol-2-in-5-one was prepared from 4,4-dimethylthiosemicarbazide and *N*-methylated with dimethyl sulfate:



No thiosemicarbazide could be obtained by hydrolysis of this compound. When 1,4,4-trimethylthiosemicarbazide had been obtained by the above mentioned method it also became evident that it would not stand the rather drastic conditions necessary for hydrolysis of the thiadiazolinone.

Some of the results obtained in the unsuccessful attempts to prepare 1-methylthiosemicarbazides may be of general interest and a brief summary of the experiments will therefore be given:

a) Since the nitrogen atom attached to the methyl group in methylhydrazine is expected to be the more basic or nucleophilic of the two nitrogen atoms the addition of a proton should result in the ion $CH_3H_2N^+-NH_2$. Methylhydrazinium salts do not, however, react with isothiocyanates at room temperature, even in the course of months. When the pH of the solution is increased above 8 a slow reaction takes place but only 2,4-dialkylthiosemicarbazides are formed, *i.e.* only the free hydrazine reacts with the isothiocyanate. On boiling an aqueous-alcoholic solution of methylhydrazinium chloride with methyl isothiocyanate substitution took place in both the 1- and the 2-position with the formation of 1-methyl-1,2-di(methylthiocarbamoyl)hydrazine, $CH_3NH-CS-N(CH_3)-NH-CS-NHCH_3$.

Addition compounds of methylhydrazine with triphenylboron, tributyl borate, or trimethoxyboroxine react readily with methyl isothiocyanate but only 2,4-dimethylthiosemicarbazide is formed. Even when tributyl borate was used as the solvent, *i.e.* in large excess, 2,4-dimethylthiosemicarbazide was formed in quantitative yield. If the methylamino group is attached to the boron compound the latter must be displaced by the isothiocyanate in these reactions.

b) Since thiosemicarbazones of formaldehyde can generally only be isolated as polymeric substances, reduction of the thiosemicarbazones (or hydroxymethylthiosemicarbazides) *in statu nascendi* was tried by adding formaldehyde and the reducing agent simultaneously to a solution of the thiosemicarbazide. 4,4-Dimethylthiosemicarbazide, formaldehyde and sodium borohydride yielded 1,1,4,4-tetramethylthiosemicarbazide (identified by analysis, melting point and infrared spectrum) whereas thiosemicarbazide or 4-methylthiosemicarbazide seems to give mixtures of methylated 2-aminothiadiazolines or 2-aminothiadiazolidines.

Some attempts were made to reduce the thiosemicarbazone of glyoxylic acid to 1-carboxymethylthiosemicarbazide with the purpose of decarboxylating the latter to 1-methylthiosemicarbazide. However, this thiosemicarbazone was unaffected by diborane and reduction with various other reducing agents resulted in cleavage of the C=N bond with the formation of thiosemicarbazide.

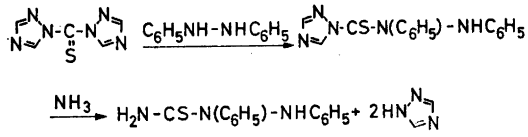
c) Holmberg [53] obtained N^2-methylthiobenzhydrazide (1-methyl-2-thiobenzoylhydrazine) by the reaction of arabinose thiobenzhydrazone with formaldehyde and we therefore tried to prepare 1-methylthiosemicarbazide in a similar manner from arabinose thiosemicarbazone but without success.

d) Methylhydrazine forms a nitroso derivative, which is a 1-substituted product, $H_2N-N(NO)CH_3$, since it forms a benzylidene derivative.[50,54] Several attempts were made to combine this hydrazine with methyl isothiocyanate, but no reaction took place (even on heating the molten components and adding various catalysts). On treatment of the nitroso compound with cyanogen bromide or dimethylthiocarbamoyl chloride a slow decomposition with the formation of NO took place.

5. Thiosemicarbazides substituted both in the 1- and the 2-position

The preparation of 1,2-dialkylthiosemicarbazides, derived from symmetrical dialkylhydrazines, offers no difficulties. The hydrazines may be converted to the corresponding thiosemicarbazides by methods 1 (rearrangement of thiocyanates) or 6 (*via* cyanohydrazines), and in some cases also by elimination of the *tert*-butyl group from 4-*tert*-butyl-1,2-dialkylthiosemicarbazides.

Neither of these methods can be used to prepare thiosemicarbazides from symmetrical diarylhydrazines. Hydrazobenzene rearranges to benzidine on heating with thiocyanic acid (or with ethoxycarbonyl dithiocarbamate; see Sect. 1g), it is unaffected or oxidized by cyanogen bromide (depending on the solvent) and it does not react with *tert*-butyl isothiocyanate. Further, several attempts to obtain 1,2-diphenylthiosemicarbazide from the reaction products of hydrazobenzene with acyl isothiocyanates [55] or by dehydrogenation of cyclohexanone 2-phenylthiosemicarbazone were unsuccessful. However, this thiosemicarbazide was obtained by ammonolysis of phenoxythiocarbonyl-1,2-diphenylhydrazine (prepared from hydrazobenzene and $C_6H_5O-CS-Cl$ [51]) at elevated temperature, or by the reaction of thiocarbonyl-di(1,2,4-triazole) with hydrazobenzene followed by ammonia:



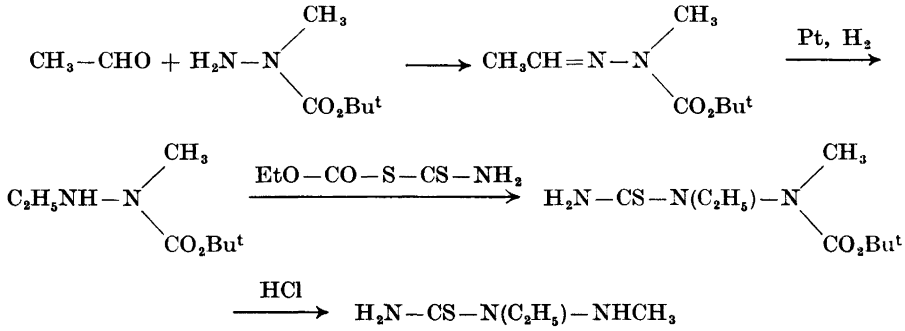
Since 4,4-diphenylthiosemicarbazide also was prepared in this work (see Sect. 3b), all five isomeric diphenylthiosemicarbazides are now known (1,4- and 2,4-diphenylthiosemicarbazide have been studied extensively and 1,1-diphenylthiosemicarbazide has been prepared from 2-cyano-1,1-diphenylhydrazine [56]).

With certain exceptions (*e.g.* hydrazobenzene and *tert*-butyl isothiocyanate) both 1,2-dialkyl- and 1,2-diarylhydrazines react with alkyl or aryl isothiocyanates to form 1,2,4-trisubstituted thiosemicarbazides * (Sect. 2a).

The preparation of thiosemicarbazides substituted with two different alkyl groups in the 1- and 2-position presented some difficulty. It was expected that such compounds could be prepared simply by application of method 2,

* The statement by Otterbacher and Whitmore [59] that hydrazobenzene and phenylhydrazine react with two moles of phenyl isothiocyanate is incorrect. The melting points of their products correspond to the expected 1,2,4-triphenylthiosemicarbazide and 1,4-diphenylthiosemicarbazide.

e.g. 1-propyl-2-butylthiosemicarbazide from propionaldehyde 2-butylthiosemicarbazone and the isomeric 1-butyl-2-propylthiosemicarbazide from butyraldehyde 2-propylthiosemicarbazone. However, these thiosemicarbazones could not be reduced with sodium borohydride and were decomposed on attempts to reduce them with sodium amalgam. It was then found that such thiosemicarbazones could be reduced with diborane. In this way 1-ethyl-2-methylthiosemicarbazide was obtained from acetaldehyde 2-methylthiosemicarbazone. The isomeric 1-methyl-2-ethylthiosemicarbazide was obtained through the following reactions:



The preparation of the other six isomeric ethylmethylthiosemicarbazides offered no difficulties, so that all eight possible isomers are now known.

Similarly, 1-benzyl-2,4-dimethylthiosemicarbazide was prepared by reduction of 1-benzylidene-2,4-dimethylthiosemicarbazide with diborane and the isomeric 2-benzyl-1,4-dimethylthiosemicarbazide *via* 2-benzylidene-1-*tert*-butoxycarbonyl-1-methylhydrazine.

The preparation of thiosemicarbazides from 1-alkyl-2-arylhydrazines offers a new problem. 1-Methyl-2-phenylhydrazine or 1-ethyl-2-phenylhydrazine react with alkyl isothiocyanates or ethoxycarbonyl dithiocarbamate to give 1-phenyl-2-alkylthiosemicarbazides. The isomers with the phenyl group in the 2-position could be prepared by reduction of 2-phenylthiosemicarbazones with diborane. This method is applicable in this case also to the preparation of 1-methylthiosemicarbazides since it was found that 2-phenylthiosemicarbazide and 2-phenyl-4-methylthiosemicarbazide form well-defined, monomeric thiosemicarbazones with formaldehyde.

Other attempts to prepare 1-methyl-2-phenylthiosemicarbazides were unsuccessful. The methyl-bearing nitrogen of 1-methyl-2-phenylhydrazine could not be protected with the *tert*-butoxycarbonyl group since no reaction took place with $Bu^tO—CO—SCH_3$. The acetyl derivative, 1-acetyl-1-methyl-2-phenylhydrazine did not react with methyl isothiocyanate or ethoxycarbonyl dithiocarbamate (with acetyl isothiocyanate it formed a triazole derivative [55]).

The interesting method used by Busch and Limpach [52] to prepare 1-methyl-2,4-diphenylthiosemicarbazide, *viz.* methylation of 3-phenyl-2-phenylimino-1,3,4-thiadiazolidin-5-one and hydrolysis of the 4-methyl derivative formed, could not be used to obtain 1,4-dimethyl-2-phenylthiosemicarbazide since 4-methyl-2-phenylthiosemicarbazide in contrast to 2,4-diphenylthiosemicarbazide reacts with phosgene to give a triazolidone instead of a thiadiazolidone. Attempts to obtain 1-methyl-2-phenylthiosemicarbazides

from thiadiazole or triazole derivatives prepared directly from 1-methyl-2-phenylhydrazine have been unsuccessful because the heterocyclic compounds have resisted all attempts at ring-opening.

2,4,4-Trimethyl-1-phenylthiosemicarbazide was obtained from 1-methyl-2-phenylhydrazine and dimethylthiocarbamoyl chloride.

Thiosemicarbazides with two different aryl groups in the 1- and 2-position have not been investigated. The only way to prepare such compounds seems to be to let the hydrazo compound react with an isothiocyanate and separate the mixture of the two isomeric thiosemicarbazides by recrystallization or chromatography.

6. Properties of thiosemicarbazides

In contrast to thiocarboxylic hydrazides,[6,7] many of which are liquid at room temperature, all mono- and dialkylthiosemicarbazides of Tables 1 and 2 are crystalline substances. Some of the higher alkylated thiosemicarbazides (Tables 3 and 4) are liquid and were isolated as hydrochlorides or distilled *in vacuo*.

Thiosemicarbazides have so weak basic or acidic character that they cannot be titrated in aqueous solution. The isomeric 1- and 2-alkyl derivatives cannot, therefore, as in the case of thiohydrazides [7] or alkoxythiocarbonylhydrazines,[51] be separated by treatment of the mixture with dilute sodium hydroxide.

Thiosemicarbazides are generally much more stable than thiohydrazides. Most of the new thiosemicarbazides do not differ essentially from the known thiosemicarbazides, the chemical properties of which are well known. The 4,4-dialkylthiosemicarbazides are, however, exceptional, because they may decompose rapidly on standing.[1] A study of this decomposition has been published in another paper.[57]

Several thiosemicarbazones (Table 6) were prepared as starting materials for 1-alkyl thiosemicarbazides and some 5-aminothiadiazolines were prepared from 1-alkylthiosemicarbazides and aldehydes. In this connection it was investigated whether thiadiazolines were formed from methyl isothiocyanate and the crude reaction product of an aldehyde and methylhydrazine. The latter is known to form methylhydrazones,[58] but in view of the fact that isothiocyanates, carbon disulfide, and cyanogen bromide add exclusively to the methyl-bearing nitrogen it seemed possible that methylhydrazine would react with aldehydes also to form compounds of the type $RCHOH-N(CH_3)-NH_2$. The latter should give a thiadiazoline with methyl isothiocyanate, but only 2,4-dimethylthiosemicarbazones, identical with those formed directly from 2,4-dimethylthiosemicarbazide, could be isolated.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Büchi melting point apparatus. Elemental analyses were performed in the analytical department of this laboratory (chief analyst Mr. Preben Hansen).

Hydrazines and acylhydrazines

In addition to the hydrazines used in the earlier work [7] the following hydrazines were prepared: 1,2-diethylhydrazine, 1,1,2-trimethylhydrazine, 1-methyl-2-phenylhydrazine, and 1-ethyl-2-phenylhydrazine. The first three mentioned were prepared

according to the literature,[80-82] the last was obtained by reduction of acetaldehyde phenylhydrazone with diborane since difficulties were encountered in carrying out the reduction catalytically.[83]

1-Acetyl-1-methylhydrazine, free from the 2-isomer, was prepared according to Hinman and Fulton.[64] The preparation of 1-formyl-1-methylhydrazine, 1-methyl-1-trifluoroacetylhydrazine, 1-ethoxycarbonyl-1-methylhydrazine and the two isomers of mono(benzyloxycarbonyl)methylhydrazine has been described by Pedersen.[50] The diacylated derivative was prepared in the following manner:

1,2-Bis-(benzyloxycarbonyl)-1-methylhydrazine. To a well-stirred and cooled solution of 2.3 g of methylhydrazine in 5 ml of water were added simultaneoulsy from two dropping funnels 17 g of benzyl chloroformate and a solution of 4 g of sodium hydroxide in 12 ml of water. The temperature was kept below 20°C and the stirring was continued after all had been added (*ca.* ½ h). After 1½ h the oily layer, which had separated, suddenly solidified. It was filtered, washed with water and dried. Yield 14.8 g (95 %). Colourless crystals with m.p. 67—68°C after recrystallization from ethanol. (Found: C 64.85; H 5.74; N 9.09. Calc. for $C_{17}H_{18}N_2O_4$: C 64.95; H 5.78; N 8.91).

This compound has been mentioned in the literature,[85] but without information about properties and method of preparation.

When 1-methyl-2-phenylhydrazine, dissolved in tetrahydrofuran, was treated in a similar manner with one mole of benzyloxycarbonyl chloride an oily reaction product resulted which was purified by extraction with ether, drying with sodium sulfate and removal of the ether *in vacuo*. Analyses of this product agreed with a benzyloxycarbonyl derivative of 1-methyl-2-phenylhydrazine, but it may have contained both possible isomers, although without doubt it was predominantly 1-benzyloxycarbonyl-1-methyl-2-phenylhydrazine. It was prepared as a possible starting material for the preparation of 1-methyl-2-phenylthiosemicarbazides but did not react with methyl isothiocyanate, benzyloxycarbonyl isothiocyanate or dimethylthiocarbamoyl chloride and therefore was not investigated further.

Alkoxythiocarbonylhydrazines and (alkylthio)thiocarbonylhydrazines will be described in a following paper.[61]

Other acylhydrazines used in this work were 1-acetyl-1-methyl-2-phenylhydrazine, 1-acetyl-2-phenylhydrazine and the following new compounds:

Benzaldehyde 1-acetyl-1-methylhydrazone. To a solution of 1-acetyl-1-methylhydrazine (8.8 g) in methanol (20 ml) were added one drop of concentrated hydrochloric acid and then, slowly with cooling 10.6 g of benzaldehyde. The solution was heated under reflux for 12 h in a stream of nitrogen and then distilled. The fraction with b.p. 105—107°C at 0.1 mm Hg (6.2 g) became crystalline and was recrystallized from methanol-water. M.p. 81—82°C. (Found: C 68.10; H 7.20; N 16.10. Calc. for $C_{10}H_{12}N_2O$: C 68.15; H 6.88. N 15.90). The brownish, crystalline residue from the distillation (6.4 g) yielded colourless; crystals of the same substance after recrystallization from methanol-water and benzene-petroleum ether.

1-Acetyl-2-benzyl-1-methylhydrazine. The foregoing compound (5 g) dissolved in methanol (30 ml) was hydrogenated with Raney nickel (2 g) at 100°C and 100 atm. pressure. The filtered solution yielded on evaporation a colourless, crystalline substance (3.7 g) which was recrystallized from benzene-petroleum ether. M.p. 60—61°C. (Found: C 67.30; H 7.81; N 15.88. Calc. for $C_{10}H_{14}N_2O$: C 67.37; H 7.93; N 15.72).

1-tert-Butoxycarbonyl-1-methylhydrazine. A mixture of equivalent amounts of *O-tert*-butyl *S*-methyl monothiocarbonate [44] and methylhydrazine was heated with reflux and stirring at 100°C for 24 h and fractionated *in vacuo*. A 50—70 % yield of a colourless liquid distilling at 65—67°C (10 mm Hg) has been obtained in various preparations. The product was gas-chromatographically pure. (Found: C 49.21; H 9.66. Calc. for $C_6H_{14}N_2O_2$: C 49.30; H 9.67). Although it is easily decomposed by hydrochloric acid, a crystalline hydrochloride could be isolated by addition of an ethereal solution of hydrogen chloride to an ethereal solution of the hydrazine. M.p. 124—125°C after recrystallization from ether-methylene chloride. (Found: C 39.40; H 8.28; N 15.73. Calc. for $C_6H_{15}ClN_2O_2$: C 39.40; H 8.28; N 15.38).

That this compound contains the *tert*-butoxycarbonyl group at the same nitrogen as the methyl group is evident from the fact that it yields exclusively 1-methylthiosemicarbazides with isothiocyanates. With acetaldehyde or benzaldehyde in hexane solution it gave the liquid hydrazones:

Acetaldehyde 1-tert-butoxycarbonyl-1-methylhydrazone ($C_8H_{16}N_2O_2$), b.p. 90—92°C at 11 mm Hg. Yield 71 %. On hydrogenation (catalyst: PtO_2 on activated carbon) at room temperature it yielded *1-tert-butoxycarbonyl-2-ethyl-1-methylhydrazine*, b.p. 70—72°C at 11 mm Hg, yield 55 %. (Found: C 54.60; H 10.43. Calc. for $C_8H_{18}N_2O_2$: C 55.13; H 10.43).

Benzaldehyde 1-tert-butoxycarbonyl-1-methylhydrazone ($C_{13}H_{18}N_2O_2$), b.p. 120—121°C at 0.1 mm Hg. Yield 76 %. On hydrogenation (catalyst: Raney nickel) at 100°C it yielded *2-benzyl-1-tert-butoxycarbonyl-1-methylhydrazine*, b.p. 90—93°C at 0.1 mm Hg; yield 48 %. (Found: C 66.20; H 7.98. Calc. for $C_{13}H_{20}N_2O_2$: C 66.06; H 8.53).

1-Allyl-1-tert-butoxycarbonylhydrazine was prepared from allylhydrazine in a similar manner as the methyl derivative, except that a bath temperature of 150°C had to be used to obtain a reasonable yield (44 %). B.p. 82—83°C at 11 mm Hg.

Isothiocyanates

All the alkyl or aryl isothiocyanates used were known compounds. They were prepared from primary amines and thiophosgene or by other conventional methods.[86,39] For the preparation of the acyl isothiocyanates, see Ref. 55. Trimethylsilyl isothiocyanate was prepared from trimethylsilyl chloride and silver thiocyanate.[87]

(Thiocarbamoylthio)acetic acids

The *N,N*-dialkyl derivatives were prepared by the following general method:

Solutions of potassium hydroxide (0.4 mole) in water (20 ml) and the secondary amine (0.4 mole) in ethanol (60 ml) were mixed and carbon disulfide (0.4 mole) was added with ice cooling, keeping the temperature below 20°C. After 1 h a solution of chloroacetic acid (0.4 mole) in 2 N sodium hydroxide (200 ml) was added and the mixture was kept for about 12 h. The acid was liberated by addition of conc. hydrochloric acid to the filtrated solution.

This method could not be used when the secondary amine was diphenylamine, but the sodium salt of diphenyldithiocarbamic acid was prepared from diphenylamine, carbon disulfide, and sodium amide and treated with sodium chloroacetate as above. The acids prepared are listed in Table 5.

The unsubstituted carboxymethyl dithiocarbamate or (thiocarbamoylthio)acetic acid was prepared according to Holmberg.[88] In the same way the *N*-isopropyl derivative was obtained in a very small yield and the *N-tert*-butyl derivative in a fair yield (Table 5): To a solution of the primary amine (2 moles) in abs. ethanol (50 ml) a solution of carbon disulfide (1 mole) in ether (50 ml) was added, keeping the temperature below 15°C. The dithiocarbamate was filtered off, dissolved in water and treated with sodium chloroacetate as above. On addition of conc. hydrochloric acid the *tert*-butyl derivative separated as an oil which crystallized on cooling and rubbing. It was pure after washing with water and showed no tendency to ring-closure on heating. The isopropyl derivative was obtained as an oil which could not be induced to crystallize. It was extracted with ether and the ether solution was dried with sodium sulfate. On evaporation an oil was obtained from which a small amount of crystals separated in the course of some days. The crystals were filtered and washed with a little ether. They proved to be pure carboxymethyl *N*-isopropyldithiocarbamate. No more than 5 % could be obtained from the oil which probably contained the cyclic rhodanine as the main product. The compound obtained by Wieniawski *et al.*[89] and described as the rhodanine was probably not cyclized since the m.p. given does not differ much from the m.p. of our product.

The carboxymethyl *N*-alkyldithiocarbamates with an unbranched alkyl group show a very pronounced tendency to ring-closure. Yang Shih-Hsien *et al.*[90] claim to have prepared the methyl derivative, but according to the m.p. (69—71°C) and colour (yellow) of their product there can be no doubt that it was actually 3-methylrhodanine. According to Garraway and Wain [91] the open-chain compound can be obtained by immediate ether extraction on acidification of the solution, but in our experiments we were only able to isolate 3-methylrhodanine. Also from ethyl-, propyl-, and butyldithiocarbamates we have only obtained the rhodanines (3-alkyl-2-thioxo-4-thiazolidones) as oily products which could be distilled *in vacuo*.

It did not seem excluded that the rhodanines could be used instead of the dithiocarbamates for the preparation of thiosemicarbazides. In fact, Gränacher [92] reports that a good yield of 1,4-diphenylthiosemicarbazide is obtained from 3-phenylrhodanine and phenylhydrazine. In our experiments *ca.* 50 % yields of thiosemicarbazide and 4-alkylthiosemicarbazides have been obtained from rhodanines and hydrazine hydrate in ethanol (without cooling) but no thiosemicarbazides were obtained from methylhydrazine. Davidsson [93] obtained a 92 % yield of 4-(mercaptoacetyl)thiosemicarbazide from rhodanine and hydrazine hydrate in cold ethanol and from 5-alkylrhodanines thiazolidine-2,4-dione hydrazones were obtained. The reaction between rhodanines and alkylhydrazines may therefore be rather complex.

Thiosemicarbazones

The thiosemicarbazones derived from unsubstituted thiosemicarbazide were all known compounds.[43,94] With the exception of benzaldehyde 2-methylthiosemicarbazone,[2] benzaldehyde 2,4-dimethylthiosemicarbazone,[95] benzaldehyde 4,4-dimethylthiosemicarbazone,[96] and the 4-methylthiosemicarbazones of acetone [97] and acetophenone[9,8] none of the thiosemicarbazones derived from substituted thiosemicarbazides have been described earlier. They were mostly obtained in the standard manner from the components in ethanolic or aqueous-ethanolic solution, if necessary with addition of a trace of hydrochloric acid as catalyst and heating of the solution to boiling. For the preparation of the formaldehyde 2-phenylthiosemicarbazones tetrahydrofuran was used as solvent. Some of the thiosemicarbazones were also prepared by addition of the aldehyde to an aqueous solution of the hydrazine, extraction with ether and addition of methyl isothiocyanate to the ethereal solution of the hydrazone. The following examples illustrate the procedures used:

*Acetaldehyde 2-methyl-4-*tert*-butylthiosemicarbazone.* 2-Methyl-4-*tert*-butylthiosemicarbazide (4.5 g) was suspended in 50 % ethanol (100 ml) and acetaldehyde (2.7 g) was added. The mixture was slowly heated until all had dissolved and then cooled. Yield 4.8 g (92 %) of colourless crystals, m.p. 102—103°C.

Cyclohexanone 2-phenylthiosemicarbazone. 2-Phenylthiosemicarbazide (0.8 g) was dissolved in ethanol (100 ml) and cyclohexanone (1 g) and one drop of conc. hydrochloric acid were added. The solution was heated under reflux for 1 ½ h and concentrated *in vacuo*. On cooling 1.0 g (81 %) of colourless crystals with m.p. 158—159°C separated. Recrystallization from ethanol raised the m.p. to 159—160°C. (Found: C 62.90; H 7.12; N 16.76. Calc. for $C_{13}H_{17}N_3S$: C 63.11; H 6.94; N 16.99).

No thiosemicarbazone could be obtained from 2-phenylthiosemicarbazide and 2-cyclohexenone.

Formaldehyde 4-methyl-2-phenylthiosemicarbazone. 4-Methyl-2-phenylthiosemicarbazide (2.9 g) was dissolved in tetrahydrofuran (20 ml) and 40 % aqueous formaldehyde (1.5 ml) and a trace of hydrochloric acid were added. The colourless solution rapidly became brown. It was evaporated *in vacuo* and left 3.3 g of an oil in which according to thin-layer chromatography 3 compounds were present. Preparative thin-layer chromatography on silica gel PF with benzene-ethyl acetate (20:1) afforded 2.7 g of an oil which rapidly crystallized. M.p. 70—71°C after recrystallization from pentane-diethyl ether. Formaldehyde 2-phenylthiosemicarbazone was prepared in the same manner.

Butyraldehyde 2,4-dimethylthiosemicarbazone. Butyraldehyde (0.36 g) was added to a solution of 2,4-dimethylthiosemicarbazide (0.60 g) in 10 ml of hot ethanol. On cooling and addition of water the thiosemicarbazone separated as an oil which crystallized on standing in a refrigerator. M.p. 34°C after recrystallization from pentane. The same compound was obtained by addition of butyraldehyde to a cooled aqueous solution of methylhydrazine, extraction of the solution with ether and addition of methyl isothiocyanate to the dried ethereal solution.

The 2,4-dimethylthiosemicarbazones of benzaldehyde, *o*-methoxybenzaldehyde, *p*-methoxybenzaldehyde, *o*-butoxybenzaldehyde, cinnamaldehyde, and furfural, as well as the 4-methyl-2-phenethylthiosemicarbazone of benzaldehyde were similarly obtained both from the thiosemicarbazide and from the hydrazine and the aldehyde.

The analyses and melting points of the new thiosemicarbazones, prepared from aldehydes, have been listed in Table 6.

Table 5. *N*-Substituted derivatives of (thiocarbamoylthio)acetic acid.

R of R–SCH_2COOH	Name of R	Formula	Yield, %	M.p., °C	Analyses					
					Calc.			Found		
					C	H	N	C	H	N
$Pr^iNH-CS-$	*N*-Isopropylthiocarbamoyl	$C_6H_{11}NO_2S_2$	5	75–76	37.20	5.81	7.32	37.30	5.81	7.32
$Bu^tNH-CS-$	*N*-*tert*-Butylthicarbamoyl	$C_7H_{13}NO_2S_2$	55	115–16	40.58	6.32	6.76	40.45	6.43	6.84
Me_2N-CS-	*N*,*N*-Dimethylthiocarbamoyl [1]	$C_5H_9NO_2S_2$	90–95 [a]	146–47			7.81			7.85
$MeEtN-CS-$	*N*-Methyl-*N*-ethylthiocarbamoyl	$C_6H_{11}NO_2S_2$	92 [e]	127–28	37.20	5.81	7.32	37.40	5.78	7.02
Et_2N-CS-	*N*,*N*-Diethylthiocarbamoyl [1]	$C_7H_{13}NO_2S_2$	90–95 [a]	90–91			6.76			6.75
$MePrN-CS-$	*N*-Methyl-*N*-propylthiocarbamoyl	$C_7H_{13}NO_2S_2$	97 [b]	107–08	40.58	6.32	6.76	40.00	6.24	6.52
Pr_2N-CS-	*N*,*N*-Dipropylthiocarbamoyl [79]	$C_9H_{17}NO_2S_2$	98 [c]	74–75	45.95	7.28	5.96	46.15	7.28	5.85
Pr^i_2N-CS-	*N*,*N*-Diisopropylthiocarbamoyl	$C_9H_{17}NO_2S_2$	22 [b]	124–25	45.95	7.28	5.96	45.85	7.49	5.82
Bu_2N-CS-	*N*,*N*-Dibutylthiocarbamoyl [1]	$C_{11}H_{21}NO_2S_2$	95 [c]	68–69			5.32			5.34
$MePhN-CS-$	*N*-Methyl-*N*-phenylthiocarbamoyl [78]	$C_{10}H_{11}NO_2S_2$	37 [d]	197–98 (decomp.)	49.79	4.60	5.81	49.85	4.62	5.65
Ph_2N-CS-	*N*,*N*-Diphenylthiocarbamoyl	$C_{15}H_{13}NO_2S_2$	35 [d]	206–07	59.40	4.32	4.62	59.55	4.45	4.43
$O(CH_2)_4N-CS-$	Thiocarbomorpholidoyl [35]	$C_7H_{11}NO_3S_2$	97 [d]	169–70 (decomp.)	38.01	5.01	6.33	38.26	4.83	6.15
$(CH_2)_5N-CS-$	Thiocarbopiperididoyl [35]	$C_8H_{13}NO_2S_2$	89 [b]	151–52 (decomp.)	43.83	5.98	6.39	44.40	5.65	5.97

Solvents used for recrystallization: [a]) benzene; [b]) methanol/water; [c]) light petroleum; [d]) ethanol; [e]) water.

The reaction of aldehydes with 1-alkylthiosemicarbazides. This reaction usually affords a thiazoline. From 1-methylthiosemicarbazide and benzaldehyde 2-amino-4-methyl-5-phenyl-2-thiazoline was obtained as colourless crystals with m.p. 158–159°C after recrystallization from ethanol. (Found: C 55.70; H 5.84; N 21.72. Calc. for $C_9H_{11}N_3S$: C 55.95; H 5.74; N 21.75).

However, from 1,4-dimethylthiosemicarbazide no thiazolines could be obtained. The analyses of the reaction products of 1,4-dimethylthiosemicarbazide with formaldehyde (m.p. 180–181°C; recryst. from water) and benzaldehyde (m.p. 138–139°C; recryst. from ethanol) indicate that they are alkylidenedithiosemicarbazides, *viz.* 1,1′-methylenedi-1,4-dimethylthiosemicarbazide, $C_7H_{16}N_6S_2$, and 1,1′-benzylidenedi-1,4-dimethylthiosemicarbazide, $C_{13}H_{22}N_6S_2$. Whether 1,4-dialkylthiosemicarbazides will normally form this sort of product has not been investigated.

Table 6. Thiosemicarbazones, $R^3NH-CS-NR^2-N=CH-R^1$.

R^1	R^2	R^3	Formula	yield	M.p., °C	Analyses (C, H, N)			
H	Ph	H	$C_8H_9N_3S$	17	145–146 [b]	Found:	53.70;	5.21;	22.87
						Calc.:	53.60;	5.07;	23.45
H	Ph	Me	$C_9H_{11}N_3S$	85	70–71 [c]	Found:	56.01;	5.79;	21.45
						Calc.:	55.92;	5.75;	21.75
Me	Me	H	$C_4H_9N_3S$	72	142–143 [c]	Found:	36.78;	6.94	
						Calc.:	36.61;	6.93	
Me	H	Me	$C_4H_9N_3S$	80	123–124 [c]	Found:	36.58;	6.99;	32.05
						Calc.:	36.64;	6.87;	31.94
Me	Me	Bu [t]	$C_8H_{17}N_3S$	92	102–103 [c]	Found:	51.00;	9.20;	22.33
						Calc.:	51.29;	9.17;	22.44
Me	Ph	H	$C_9H_{11}N_3S$	60	144–146 [c]	Found:	55.85;	5.77;	21.49
						Calc.:	55.92;	5.75;	21.75
Pr [n]	Me	Me	$C_7H_{15}N_3S$	60	34.0–34.5 [d]	Found:	48.65;	8.59;	24.12
						Calc.:	48.54;	8.73;	24.26
Pr [n]	Pr [n]	H	$C_8H_{17}N_3S$		54–55 [c]	Found:	51.35;	9.25;	21.67
						Calc.:	51.31;	9.15;	22.44
Ph	Et	Me	$C_{11}H_{15}N_3S$	46	94–95 [c]	Found:	59.70;	6.83;	18.55
						Calc.:	59.68;	6.84;	18.99
Ph	Bu [n]	Me	$C_{13}H_{19}N_3S$	75	64–65 [c]	Found:	62.45;	7.81;	16.69
						Calc.:	62.60;	7.69;	16.85
Ph	$PhCH_2$	Me	$C_{16}H_{17}N_3S$	71	146–147 [b]	Found:	67.70;	6.00;	14.66
						Calc.:	67.80;	6.06;	14.83
Ph	$PhCH_2CH_2$	Me	$C_{17}H_{19}N_3S$	67	140–141 [b]	Found:	68.75;	6.42;	14.06
						Calc.:	68.65;	6.44;	14.13
Ph	Cyclohexyl	Me	$C_{15}H_{21}N_3S$	34	142–143 [b]	Found:	65.60;	7.91;	14.83
						Calc.:	65.40;	7.70;	15.26
o-$MeOC_6H_4$	Me	Me	$C_{11}H_{15}N_3S$	70	160–161 [b]	Found:	55.68;	6.21;	17.67
						Calc.:	55.68;	6.37;	17.71
p-$MeOC_6H_4$	Me	Me	$C_{11}H_{15}N_3S$	62	119–120 [b]	Found:	55.65;	6.47;	17.73
						Calc.:	55.68;	6.37;	17.71
o-$BuOC_6H_4$	Me	Me	$C_{14}H_{21}N_3S$	20	90–91 [a]	Found:	60.05;	7.61;	15.20
						Calc.:	60.19;	7.58;	15.04
$PhCH_2CH_2$	Me	Me	$C_{12}H_{17}N_3S$	77	66–67 [b]	Found:	61.15;	7.36;	17.64
						Calc.:	61.25;	7.28;	17.68
2-Furyl	Me	Me	$C_8H_{11}N_3S$	56	102–103 [b]	Found:	48.83;	5.61;	20.84
						Calc.:	48.73;	5.59;	21.31

Solvents used for recrystallization: a) methanol; b) ethanol; c) ethanol-water; d) pentane; e) pentanediethyl ether.

Thiosemicarbazides

The thiosemicarbazides were prepared by one or more of the following methods:

1. Isomerisation of hydrazinium thiocyanates.
2. Reduction of thiosemicarbazones.
3. Reaction of isothiocyanates with hydrazine or hydrazines.
4. Reaction of hydrazine or hydrazines with reactive thiocarbamic acid derivatives (acid chlorides, thiuram monosulfides).
5. Ammonolysis or aminolysis of monothiocarbazates or dithiocarbazates.
6. Hydrazinolysis of monothiocarbamates or dithiocarbamates.
7. Reaction of cyanohydrazines with hydrogen sulfide.
8. Special methods for preparing 1-methyl derivatives.

For analyses and melting points, see Tables 1—4.

Method 1. Isomerisation of hydrazinium thiocyanates

Potassium thiocyanate (0.05 mole) and the monohydrochloride of the hydrazine (0.05 mole) were dissolved in water (50 ml). When dihydrochlorides, sulfates or oxalates were used, 5 g of $KHCO_3$ was also added. The absence of an excess acid is essential. Ethanol (100—150 ml) was added to precipitate potassium chloride, sulfate or oxalate and the solution was filtered and evaporated to dryness. The residue was either heated until an exothermic reaction took place, usually at about 160°C (with spontaneous increase of the temperature to 180—190°C), or, in the case of alkylhydrazines with secondary or tertiary alkyl groups, kept at a temperature of 160°C for 15—30 min. The reaction product was crystallized from 10—20 ml of water and the residue, if any, crystallized from ethanol. For solvents used for recrystallization, see the tables, The aqueous mother liquors contained much hydrazinium thiocyanate and a second crop of the thiosemicarbazide could be obtained by repeating the evaporation and heating of the solid residue.

The crude products are often very difficult to purify. The following thiosemicarbazides were prepared by this method (yields of recrystallized products in parentheses): 2-methyl (25—37 %), 1-methyl (15 %), 2-ethyl (11 %), 1-ethyl (8 %), 2-propyl (20 %), 1-propyl (15 %), 1-isopropyl (10 %), 2-butyl (20 %), 1-*tert*-butyl (7 %), 2-allyl (14 %), 2-benzyl (16 %), 1-benzyl (9 %), 1-α-methylbenzyl (10 %), 2-phenethyl (25 %), 1-cyclohexyl (30 %), 1,1-dimethyl (20 %), 1,2-dimethyl (20 %), 1,1-diethyl (34 %), 1,1,2-trimethyl (15 %, isolated as the hydrochloride).

2-Methylthiosemicarbazide was obtained in better yields by the following method: Methylhydrazinium thiocyanate was prepared as above. After evaporation of the solution to dryness, 35 ml of xylene was added and the mixture was refluxed for 5 min. After cooling, the solid was filtered, dried and recrystallized twice from water. Yield 2.75 g (52 %) of 2-methylthiosemicarbazide, m.p. 173—174°C. Higher temperature and more prolonged heating diminished the yield. By this method ethyl-, propyl-, and butylhydrazine yielded mixtures of 1- and 2-alkylthiosemicarbazides, from which pure compounds could only be obtained with great loss by recrystallization. However, the isomers have been separated successfully by layer chromatography in the manner described for the separation of 1- and 2-methylthiosemicarbazide; see Method 3d.

2-Methyl-1-phenylthiosemicarbazide was prepared from 1-methyl-2-phenylhydrazine and the equivalent amount of ethoxycarbonyl dithiocarbamate. On mixing the components an evolution of carbonyl sulfide started and the mixture was heated gently until the gas evolution had stopped. On further heating, the resulting oil (which was easily soluble in water and according to qualitative reactions represented the hydrazinium thiocyanate) suddenly solidified to the thiosemicarbazide, which is almost insoluble in water. It was recrystallized from ethanol. Yield 70 %. 2-Ethyl-1-phenylthiosemicarbazide was prepared in a similar manner, except that the mixture was heated to 150°C (it did not solidify until cooled). Yield 42%. This method has also been applied for the preparation of some 1-methylthiosemicarbazides; see Method 8.

Method 2. Reduction of thiosemicarbazones

2a. Reductions with sodium borohydride. A solution of sodium borohydride (2 g) in ethanol (100 ml) was added to a solution of a thiosemicarbazone (0.02 mole) in ethanol (150 ml). The mixture was allowed to stand at room temperature for 3 h and was then heated to boiling, cooled and filtered. The solution was cooled in ice and made slightly acid by addition of concentrated hydrochloric acid. After filtering, the solution was evaporated to dryness *in vacuo* and the product was isolated by extraction with hot absolute ethanol, evaporation of the extract, and recrystallization (in most cases from ethanol, see Tables).

In this way the following thiosemicarbazides were prepared (yields of recrystallized products in parentheses): 1-ethyl (62 %), 1-propyl (63 %), 1-isopropyl (38 %), 1-butyl (51 %), 1-isobutyl (27 %), 1-*sec*-butyl (41 %), 1-cyclopentyl (31 %), 1-cyclohexyl (58 %), 1-benzyl (42 %), 1-phenethyl (25 %), 1-ethyl-4-methyl (56 %), 1-isopropyl-4-methyl (17 %), 1-benzyl-4,4-dimethyl (12 %).

Thiosemicarbazones could not be reduced by the method of Brown and Brown,[99] *i.e.* by adding sodium borohydride to an acid solution of the thiosemicarbazone containing platinum or rhodium catalysts.

2b. Reductions with sodium amalgam. Some thiosemicarbazones which could not be reduced with sodium borohydride were reduced with sodium amalgam according to Hoggarth.[18] Benzophenone thiosemicarbazone (3 g) was dissolved in 100 ml of 80 % ethanol, and sodium amalgam, prepared from 3 g of sodium and 5 ml of mercury, was added in the course of 2 h while refluxing the solution. The solution was yellow at the beginning but became colourless. On evaporation of the filtered solution an oil was obtained, which became crystalline on addition of water and was recrystallized from ethanol. Yield 2 g of 1-benzhydrylthiosemicarbazide (65 %). In a similar way 1-benzyl-2,4-dimethylthiosemicarbazide was prepared from benzaldehyde 2,4-dimethylthiosemicarbazone (yield 40 %).

2c. Reductions with diborane. Thiosemicarbazones of 2-substituted thiosemicarbazides were generally completely hydrolyzed or otherwise decomposed on attempts at reduction with sodium borohydride or sodium amalgam but were successfully reduced with diborane (the very low yields obtained in some of the preparations with sodium borohydride could possibly also be increased by using diborane).

Acetaldehyde 4-*tert*-butyl-2-methylthiosemicarbazone (0.90 g) was dissolved in a cooled 2 M solution of diborane in tetrahydrofuran [100] (5 ml) and the solution was stirred for 2 h under nitrogen with cooling in ice. The solution was evaporated *in vacuo*, water (10 ml) was added with ice cooling and the solution was made alkaline with sodium hydroxide. After 12 h the crystalline precipitate was extracted with benzene, the solution was evaporated to dryness and the residue was recrystallized from ethanol-water. Yield 0.70 g (78 %) of 4-*tert*-butyl-1-ethyl-2-methylthiosemicarbazide (this was used for the preparation of 1-ethyl-2-methylthiosemicarbazide; see Method 3c).

In a similar way 1-ethyl-2-phenylthiosemicarbazide was prepared from acetaldehyde 2-phenylthiosemicarbazone, except that the precipitate was recrystallized directly from ethanol. Yield 89 %.

Method 3. Reaction of isothiocyanates with hydrazines

3a. The hydrazine (0.01 mole) was added to a solution of the isothiocyanate (0.01 mole) in ether (10 ml). In most cases the reaction took place with evolution of heat and was finished in a few minutes. Trimethylhydrazine and some dialkylhydrazines reacted slowly and the solution was kept for 24 h. Normally the thiosemicarbazides crystallized from the ether solution. After addition of 10 ml of petroleum ether and cooling, the crystals were filtered and washed with ether or pentane according to their solubility. In this way a more than 90 % yield of almost analytically pure substances could in most cases be obtained. In some cases it was of course necessary to work up the mother liquor. For solvents used for recrystallization, see the tables.

Most of the 4-alkylthiosemicarbazides (Table 1) and di- and trisubstituted thiosemicarbazides (Tables 2 and 3) were prepared by this method. From monoalkylhydrazines the 2,4-dialkylthiosemicarbazide is always the primary product. When the alkyl group

in the 2-position is secondary or tertiary these products may rearrange to 1,4-dialkylthiosemicarbazides during recrystallization. Usually they could be purified without rearrangement by dissolution in warm ether or benzene, addition of petroleum ether until crystallization began, and cooling.

The use in these preparations of the pure, free hydrazine gives the best yields and most easily purified products. It is, however, quite possible to prepare thiosemicarbazides from hydrochlorides or other water-soluble salts of the lower aliphatic hydrazines. A rather concentrated solution (10—20 %) of the salt in water is made strongly alkaline (pH 12—13) and the equivalent amount of the isothiocyanate and enough ethanol to dissolve the isothiocyanate are added with stirring. After several hours enough water is added to dissolve any inorganic salts which may have separated and the mixture is cooled in a refrigerator. In the cases where this method was tested 70—80% of a crude crystalline thiosemicarbazide was obtained. The number of recrystallizations necessary to get a pure product will depend upon the nature of the substituents and the purity of the hydrazinium salt.

The reaction of isothiocyanates with hydrazinium salts in neutral (or slightly acid) solution is extremely slow. At room temperature only traces of the thiosemicarbazide had formed after several months. However, when a solution of methyl isothiocyanate (0.04 mole) and methylhydrazinium chloride (0.04 mole) in 80 % ethanol (40 ml) was refluxed for 2 h 1-(methylthiocarbamoyl)-2,4-dimethylthiosemicarbazide, $CH_3NH-CS-NH-N(CH_3)-CS-NHCH_3$, was formed. The residue obtained on evaporation of the solution was recrystallized twice from water and yielded 1 g (25%) of colourless crystals with m.p. 178—180°C. (Found: C 31.53; H 6.25; N 29.09. Calc. for $C_5H_{12}N_4S_2$: C 31.28; H 6.30; N 29.18).

The thiosemicarbazides obtained as primary products in the reaction between hydrazines and isothiocyanates may be transformed into other thiosemicarbazides by the following methods:

3b. 2,4-Dialkylthiosemicarbazides in which the alkyl group in the 2-position is secondary may be rearranged to 1,4-dialkylthiosemicarbazides by heating a suspension of the compound in water to boiling for 2 h. However, thiosemicarbazides with a methyl group in the 4-position do not rearrange or are more difficult to rearrange than those with a *tert*-butyl or phenyl group in the 4-position. 2-Isopropyl-4-methylthiosemicarbazide and 2-α-methylbenzyl-4-methylthiosemicarbazide did not rearrange and 2-cyclohexyl-4-methylthiosemicarbazide rearranged only on melting. 2,4-Di-α-methylbenzylthiosemicarbazide, on the other hand, rearranged on recrystallization, even from low-boiling solvents.

The method may be illustrated by the following example:

2-Isopropyl-4-*tert*-butylthiosemicarbazide, m.p. 142—143°C, was boiled with water for 2 h. The solid did not change conspicuously but was found to have the melting point 123—124°C. Analytical values for C, H, and N were identical with those of the starting material, but the reaction with $NiCl_2$ was negative and the NH_2 infrared band had disappeared. Thus, the compound was 1-isopropyl-4-*tert*-butylthiosemicarbazide.

In the same manner were prepared 4-*tert*-butyl-1-α-methylbenzylthiosemicarbazide, 4-*tert*-butyl-1-phenethylthiosemicarbazide, 4-*tert*-butyl-1-cyclohexylthiosemicarbazide, 4-*tert*-butyl-1-isobutylthiosemicarbazide, 1-isopropyl-4-phenylthiosemicarbazide, 1-isopropyl-4-α-methylbenzylthiosemicarbazide, and 4-methyl-1-phenylthiosemicarbazide.

With few exceptions thiosemicarbazides with a primary alkyl group in the 2-position do not rearrange, even when they have a *tert*-butyl group in the 4-position (examples: 2-methyl-4-*tert*-butylthiosemicarbazide and 2-butyl-4-*tert*-butylthiosemicarbazide).

Thiosemicarbazides with unsubstituted 4-positions rearrange only when the substituent in the 2-position is tertiary (*tert*-butyl, phenyl) but not if it is secondary (α-methylbenzyl, isopropyl, cyclohexyl) or primary.

tert-Butylhydrazine will normally give 1-*tert*-butylthiosemicarbazides. However, 2-*tert*-butyl-4-methylthiosemicarbazide was obtained from the hydrazine and methyl isothiocyanate when the temperature was kept below —10°C during the reaction. *tert*-Butyl isothiocyanate yielded 1,4-di-*tert*-butylthiosemicarbazide even at low temperature.

3c. Thiosemicarbazides, prepared from *tert*-butyl isothiocyanate may be transformed into thiosemicarbazides unsubstituted in the 4-position by treatment with hot, concentrated hydrochloric acid: 1 g of a 4-*tert*-butylthiosemicarbazide was suspended in 2—5 ml of concentrated hydrochloric acid which was heated to boiling for 1 min. During

the heating *tert*-butyl chloride was formed and the substance went into solution (if necessary some ethanol was added). The solution was at once evaporated to dryness *in vacuo*, the residue was dissolved in water and the solution was neutralized with aqueous ammonia and again evaporated to dryness. The residue was recrystallized from water or ethanol-water with addition of active carbon.

The yields obtained by this method are very variable. Thiosemicarbazide (from 4-*tert*-butylthiosemicarbazide) and 1-phenyl-2-methylthiosemicarbazide were obtained in almost 100 % yields, but the yields of 2-alkylthiosemicarbazides were much lower, the lower the higher the alkyl group was (2-methyl 55 %; 2-propyl 24 %; 2-butyl 7 %; 2-isobutyl 7 %). No thiosemicarbazide was obtained from 2-isopropyl-4-*tert*-butylthiosemicarbazide. 1,1-Dialkyl-4-*tert*-butylthiosemicarbazides could be transformed into 1,1-dialkylthiosemicarbazides in 20—60 % yields. Among the 1,2-dialkylthiosemicarbazides only 1,2-dimethylthiosemicarbazide and 1-ethyl-2-methylthiosemicarbazide could be obtained in this way (yields *ca.* 30%). 1,2-Dialkyl-4-*tert*-butylthiosemicarbazides with higher alkyl groups (ethyl, propyl, isopropyl, butyl) in the 2-position were completely split so that only the hydrazinium chloride could be isolated (when boiling was avoided, the chloride contained unchanged starting material but no 1,2-dialkylthiosemicarbazide).

In this way the following thiosemicarbazides were prepared: 2-methyl, 2-propyl, 2-allyl, 2-butyl, 2-isobutyl, 2-benzyl, 2-cyclohexyl, 1,1-dimethyl, 1-methyl-1-phenyl, 1-methyl-1-benzyl, 1,1-diethyl, 1,2-dimethyl, 1-ethyl-2-methyl, 1-phenyl-2-methyl, 1,1,2-trimethyl (isolated as hydrochloride, yield 5 %).

3d. A trimethylsilyl group can be removed even more easily than a *tert*-butyl group, but trimethylsilyl isothiocyanate often acts as a silylating agent towards hydrazines (such as 1,1-dimethylhydrazine, trimethylhydrazine, isopropylhydrazine, and hydrazobenzene), forming thiocyanic acid. However, 1,2-dimethylhydrazine and methylhydrazine formed 1,2-dimethylthiosemicarbazide and 2-methylthiosemicarbazide, respectively, with trimethylsilyl isothiocyanate. The thiosemicarbazides separated directly from the ethereal solution of equimolecular amounts of the reactants, the trimethylsilyl group being transferred to another molecule of the hydrazine. The yields were quantitative according to this reaction, *i.e.* 50 % relative to the hydrazine. Unexpectedly, the yield of 2-methylthiosemicarbazide relative to trimethylsilyl isothiocyanate was not improved by using two moles of methylhydrazine, but under these conditions 1-methylthiosemicarbazide was also formed as follows.

Trimethylsilyl isothiocyanate (6.5 g) was added slowly to a cooled solution of 4.6 g of methylhydrazine in anhydrous ether. The solution was kept for 12 h at room temperature in a well closed bottle. The crystals of 2-methylthiosemicarbazide which had separated (1.7 g) were filtered and washed with ether. The compound was pure after one recrystallization from water (m.p. 173—174°C). The ether solution yielded, after removal of the ether and crystallization of the residue from ethanol-water, 2.2 g of a crystalline substance with m.p. 133—134°C, consisting of a mixture of 1-methylthiosemicarbazide and 2-methylthiosemicarbazide. It proved impossible to separate the isomers by recrystallization but layer chromatography of the mixture with ethyl acetate on silica gel PF_{254} afforded 0.4 g of 1-methylthiosemicarbazide and 0.8 g of 2-methylthiosemicarbazide. They were pure according to analyses, infrared spectra, and melting points.

3e. Acyl isothiocyanates react violently with hydrazines with the formation of 4-acylthiosemicarbazides. When these are derived from monoalkyl- or 1,2-dialkylhydrazines they are transformed spontaneously or on attempts at hydrolysis into thioxotriazolidones.[55] Accordingly, only 1,1-dialkyl- or trialkylthiosemicarbazides can be prepared by this method.

1,1-Dimethylthiosemicarbazide. 1,1-Dimethylhydrazine (0.30 g) was added to a cooled solution of benzoyl isothiocyanate (0.80 g) in petroleum ether (30 ml). The oil, which separated immediately, became crystalline on standing in a refrigerator. The colourless crystals of 1,1-dimethyl-4-benzoylthiosemicarbazide (1.1 g) were recrystallized from cyclohexane and then from ethanol-water. M.p. 120—121°C. (Found: C 53.95; H 5.90. Calc. for $C_{10}H_{13}N_3OS$: C 53.78; H 5.88). The benzoyl derivative was hydrolyzed by boiling with 4 N hydrochloric acid for 1 h. The cooled solution was filtered from benzoic acid, concentrated *in vacuo* and 1,1-dimethylthiosemicarbazide precipitated by addition of aqueous ammonia. Yield 63 %. M.p. 184—185°C after recrystallization from water.

1,1,2-Trimethylthiosemicarbazide. Addition of trimethylhydrazine to a cooled solution of acetyl isothiocyanate in ether afforded an oily precipitate which could not be induced

to crystallize. The ether was decanted from the oil and the latter was extracted with ether, which dissolved most of it. The combined ether solutions were evaporated and the oily residue hydrolyzed by stirring with 4 N hydrochloric acid at 35°C for 6 h. The solution was evaporated to dryness and the crystalline residue was recrystallized from abs. ethanol-ether. Yield 70 % of trimethylthiosemicarbazide hydrochloride, m.p. 176—178°C (decomp.).

Method 4. Reaction of hydrazines with reactive thiocarbonyl compounds

4a. Thiocarbamoyl chlorides and hydrazines. Several 4,4-substituted thiosemicarbazides were prepared from dialkylthiocarbamoyl chlorides and hydrazines. With less reactive hydrazines heating was necessary to complete the reaction. The following examples illustrate the methods used.

4,4-Diethyl-2-methylthiosemicarbazide. Diethylthiocarbamoyl chloride (1.5 g; 0.01 mole) and methylhydrazine (0.92 g; 0.02 mole) were dissolved in anhydrous ether (5 ml) and kept in a refrigerator overnight. The separated methylhydrazinium chloride was filtered and the ether solution evaporated. The oily residue solidified when kept in a refrigerator. It was recrystallized from petroleum ether. M.p. 37—38°C. Yield 0.90 g (56 %).

The following thiosemicarbazides were prepared in a similar manner: 2,4,4-trimethyl, 1,1,4,4-tetramethyl, 1,2,4,4-tetramethyl, and 1,1,4,4-tetraethyl. The two last mentioned failed to crystallize. Their ether solutions were washed with water to remove any hydrazinium chloride, and the thiosemicarbazide hydrochlorides were precipitated from the dried solutions by addition of ethereal hydrogen chloride. These compounds were also prepared by the following method.

Yields as high as 95 % of 2,4,4-trimethylthiosemicarbazide have been obtained from dimethylthiocarbamoyl chloride and methylhydrazine. As shown by thin layer chromatography, the 1,4,4-isomer was not formed in this reaction.

1,2,4,4-Tetramethylthiosemicarbazide. 1,2-Dimethylhydrazine (1.5 g) was added to a suspension of dimethylthiocarbamoyl chloride (2.5 g) in triethylamine (20 ml) and the mixture was refluxed for 1 h. After addition of ether and cooling, triethylammonium chloride was removed by filtration and the solution was fractionated *in vacuo*. The liquid 1,2,4,4-tetramethylthiosemicarbazide was collected between 85 and 87°C at 2—3 mm Hg. Yield 25 %.

2,4,4-Trimethylthiosemicarbazide and 1,1,4,4-tetramethylthiosemicarbazide were prepared in the same way (yields 50—60 %), but distillation was unnecessary since the compounds crystallized on addition of ether and petroleum ether to the residue obtained after evaporation of triethylamine.

2,4,4-Trimethylthiosemicarbazide has further been obtained by reaction of dimethylthiocarbamoyl chloride (6.15 g) with 1-methyl-1,2-bis(trimethylsilyl)hydrazine (9.5 g) in triethylamine (15 ml) at room temperature (24 h) and treatment of the reaction product with boiling water (*cf.* Ref. 16). Yield 4.3 g (81 %) of recrystallized product (m.p. 63—64°C).

Pentamethylthiosemicarbazide was prepared from trimethylhydrazine (3.7 g), dimethylthiocarbamoyl chloride (6 g), and triethylamine (30 ml). The solution had to be refluxed for 5—6 h before the calculated amount of triethylammonium chloride had formed. The residue obtained by evaporation of triethylamine was treated with aqueous ammonia and extracted with ether. The ether solution was dried with $MgSO_4$ and distilled. Yield 3 g (38 %) of colourless liquid, b.p. 83—85°C at 2—3 mm Hg. In some preparations a small amount of a crystalline material separated on cooling the liquid. It was identified as tetramethylthiourea by analyses, m.p. (76—77°C) and infrared spectrum. It could be eliminated by a second distillation. It has, however, not been possible to obtain pentamethylthiosemicarbazide of high purity. It decomposed somewhat on repeated distillation in high vacuum, as shown by the appearance of a weak infrared band at *ca.* 1650 cm^{-1} and further increase of the originally too high N-content. Decomposition also took place on attempts at purification by gas chromatography.

In the preparation of 1,1,4,4-tetraethylthiosemicarbazide by this method, an appreciable amount (25%) of a crystalline by-product was obtained which according to analyses was 1,1-diethyl-2,2-bis(diethylthiocarbamoyl)hydrazine, $(C_2H_5)_2N-N(CSN(C_2H_5)_2)_2$,

formed by reaction of the hydrazine with two moles of diethylthiocarbamoyl chloride. (Found: C 52.60; H 9.58; S 20.23. Calc. for $C_{14}H_{30}N_4S_2$: C 52.83; H 9.43; S 20.13). M.p. 102—103°C after recrystallization from cyclohexane.

4,4-Dimethyl-1-phenylthiosemicarbazide. Dimethylthiocarbamoyl chloride (3.1 g) and phenylhydrazine (5.4 g) were dissolved in ether (10 ml). After 24 h the precipitate, consisting of a mixture of the thiosemicarbazide and phenylhydrazinium chloride, was filtered and washed with water. Yield 2.2 g (50 %) of a not quite pure product. It proved impossible to purify this compound by recrystallization, so it was purified by layer chromatography with benzene-ethyl acetate-acetone (100:5:10) on silica gel $PF_{254+366}$ and recrystallization from methanol. In this way it was obtained chromatographically pure as colourless crystals (m.p. 131—132°C), which soon turned yellow on exposure to air. It gives a red-violet nickel complex in alkaline solution, in agreement with the formulation as the 1,4,4-isomer. The 2,4,4-isomer is not formed in this reaction. The 1,4,4-isomer has also been prepared from sodium phenylhydrazide or by refluxing a solution of equimolecular amounts of dimethylthiocarbamoyl chloride, phenylhydrazine and triethylamine in ether until the calculated amount of triethylammonium chloride had separated. In this way also 2,4,4-trimethyl-1-phenylthiosemicarbazide was prepared from 1-methyl-2-phenyl-hydrazine. Yield 0.30 g (purified by layer chromatography) from 1 g of the hydrazine (14 %).

4,4-Dimethyl-2-phenylthiosemicarbazide. Dimethylthiocarbamoyl chloride (2.5 g) and benzaldehyde phenylhydrazone (3.9 g) were dissolved in anhydrous pure tetrahydrofuran (50 ml). A suspension of sodium hydride (containing 0.72 g of NaH) in tetrahydrofuran was added and the mixture was refluxed for 4 h. The solution was poured into water (250 ml) and the mixture was neutralized with hydrochloric acid and extracted with ether. The dried ether solution on evaporation left an oil, which crystallized on addition of petroleum ether (10 ml) and cooling. On recrystallization from ethanol, benzaldehyde 4,4-dimethyl-2-phenylthiosemicarbazone was obtained as yellow crystals, m.p. 110—111°C. Yield 30 %. (Found: C 67.55; H 6.16; N 14.60. Calc. for $C_{16}H_{17}N_3S$: C 67.82; H 6.03; N 14.84).

The thiosemicarbazone was dissolved in ethanol and an equivalent of ethanolic 2,4-dinitrophenylhydrazine hydrochloride was added. After 12 h the solution was filtered from benzaldehyde 2,4-dinitrophenylhydrazone and neutralized and the solvent removed by evaporation. The residue was extracted with pentane and the solution was treated with active carbon and filtered. Since the thiosemicarbazide could not be obtained crystalline, the hydrochloride was precipitated from the pentane solution.

Unsuccessful attempts were made to prepare this thiosemicarbazide by hydrolysis of 1-acetyl-4,4-dimethyl-2-phenylthiosemicarbazide. The latter compound was prepared by refluxing a solution of equimolecular amounts of 1-acetyl-2-phenylhydrazine, dimethylthiocarbamoyl chloride and triethylamine in methylene chloride for 24 h. It was obtained as colourless needles after recrystallization from carbon tetrachloride and sublimation. M.p. 183—185°C. (Found: C 55.95; H 6.13; N 17.61. Calc. for $C_{11}H_{15}N_3OS$: C 55.80; H 6.33; N 17.72).

4,4-Diphenylthiosemicarbazide. A solution of diphenylamine (8.5 g) and thiophosgene (5.8 g) in benzene (50 ml) was refluxed for 3 h. The benzene was removed *in vacuo*, the pink, semicrystalline mass was dissolved in ethanol (50 ml) and hydrazine hydrate (2.5 ml) was added. After standing for 12 h the precipitate was filtered, stirred with water to remove hydrazinium chloride and again filtered. The solid was dissolved in ethanol and to the green solution water was added until the colour changed to brown. The solution was heated to boiling, causing some colloidal material to precipitate. The solution was filtered hot, decolourised by addition of active carbon and filtered again. On cooling the thiosemicarbazide separated. It was recrystallized from ethanol. Yield: 33 %. M.p. 154—155°C.

4b. Thiuram monosulfides and hydrazines. The thiuram monosulfides react similarly to the thiocarbamoyl chlorides but not as readily. From thiuram disulfides it has not been possible to prepare thiosemicarbazides.

4,4-Dimethylthiosemicarbazide and 4,4-dibenzylthiosemicarbazide were obtained by refluxing a solution of the thiuram monosulfide (0.05 mole) and hydrazine hydrate (5 ml) in ethanol (50 ml) for 8 h. The thiosemicarbazide crystallized on cooling of the solution and was recrystallized from ethanol. Yields 60—70 %. In a similar experiment with tetraethylthiuram monosulfide, the crystals which separated on cooling (1.7 g) were

found to be thiocarbohydrazide. The thiosemicarbazide was obtained by evaporation of the solution and extraction of the residue with benzene (yield 54 %).

4,4-Diisopropylthiosemicarbazide was prepared by heating a suspension of tetraisopropylthiuram monosulfide (6.7 g) in hydrazine hydrate (15 ml) at 40°C for 2 h. The residue obtained after removal of the solvent under reduced pressure was recrystallized from water (yield 54 %).

2,4,4-Trimethylthiosemicarbazide was obtained by refluxing a solution of tetramethylthiuram monosulfide (10.4 g) and methylhydrazine (4.6 g) in ethanol (20 ml) for 2 h. After removal of the solvent *in vacuo*, the residue was recrystallized from ether (yield 21 %).

Thiuram monosulfides were prepared from thiuram disulfides and sodium cyanide according to von Braun.[101] The following monosulfides have not hitherto been described.

Tetrabenzylthiuram monosulfide. A solution of the disulfide (25.6 g) and sodium cyanide (2.5 g) in ethanol (200 ml) was refluxed for 1 h. On cooling, a semisolid product separated. It was isolated by decantation and was dissolved in hot benzene (100 ml). On addition of ligroin (250 ml) and cooling, 10 g (42 %) of yellow crystals were obtained. M.p. 106—107°C. (Found: C 70.10; H 5.67; N 5.47. Calc. for $C_{30}H_{28}N_2S_3$ C 70.27; H 5.50; N 5.46).

Tetraisopropylthiuram monosulfide. The ethanolic reaction mixture was evaporated, the residue was dissolved in benzene and the solution was filtered. On addition of petroleum ether the monosulfide precipitated as an oil, from which yellow crystals were obtained by dissolution in ethanol and addition of water. Yield 17 %. M.p. 115—116°C. (Found: C 52.60; H 8.81; N 8.80. Calc. for $C_{14}H_{28}N_2S_3$: C 52.50; H 8.75; N 8.75).

4c. Acyl dithiocarbamates and hydrazines. Ethoxycarbonyl dithiocarbamate (prepared according to Ref. 21) reacts with hydrazines with the formation of thiocyanates (which may eventually be transformed into thiosemicarbazides; see Method 1). With certain acylhydrazines it seems to form thiosemicarbazides directly; see Method 8.

Ethoxycarbonyl *N*-alkyldithiocarbamates, which are intermediates in the Kaluza synthesis of isothiocyanates, would be expected to react with hydrazines to form thiosemicarbazides and this was confirmed by preparation of 4-butylthiosemicarbazide and 4-butyl-2-methylthiosemicarbazide from ethoxycarbonyl *N*-butyldithiocarbamate (prepared according to Ref. 29). However, the products were more difficult to purify, and the yields therefore lower, than by use of butyl isothiocyanate.

Ethoxycarbonyl *N,N*-dimethyldithiocarbamate and hydrazines reacted to form hydrazinium dithiocarbamates. No thiosemicarbazides could be isolated. The dithiocarbamate was obtained by adding ethyl chloroformate dropwise and with stirring to a cooled ethanolic solution of potassium dimethyldithiocarbamate and continuing the stirring at room temperature. After removal of KCl by filtration and of the solvent by evaporation, an oil remained which was purified by dissolution in ether, washing with water, drying and evaporation. The compound failed to crystallize and could not be distilled without decomposition. Since, however, analyses were quite satisfactory, it was used without further purification.

4d. Thiocarbonyldi(1,3,4-triazole) and hydrazines. A suspension of 1,2,4-triazole (0.04 mole) and thiophosgene (0.01 mole) in anhydrous ether (100 ml) was shaken mechanically for ½ h. The mixture was then filtered to remove the triazole hydrochloride. Hydrazobenzene (0.01 mole) was added to the resulting solution of thiocarbonyldi(1,2,4-triazole) and the mixture was refluxed for 1 h. The precipitated triazole was filtered and washed with ether. On evaporation of the ether from the filtrate a red semisolid product, believed to be 1,2-diphenylthiocarbazoyltriazole, was obtained. This was used without purification for the next step of the synthesis. It was suspended in 5 ml of concentrated aqueous ammonia and 5 ml of ethanol saturated with ammonia and the mixture was heated to boiling and filtered. The solution yielded on standing for 24 h a slightly reddish precipitate which was filtered and washed with cold ether. It was recrystallized twice from aqueous ethanol to yield 50 % of 1,2-diphenylthiosemicarbazide as colourless crystals, m.p. 182—183°C.

Method 5. Ammonolysis and aminolysis of monothio- and dithiocarbazates

5a. From monothiocarbazates (alkoxythiocarbonylhydrazines, xanthogenhydrazides). Monothiocarbazates with an unsubstituted NH group next to the CS group reacted with ammonia or amines, but either no thiosemicarbazides were formed or the yields were

low because of side reactions: 30 % yields of 1,1-dimethylthiosemicarbazide and 1-*tert*-butylthiosemicarbazide were obtained from $CH_3O-CS-NH-N(CH_3)_2$ and $C_2H_5O-CS-NH-NHC(CH_3)_3$ on standing with aqueous ammonia at room temperature for several months. Ethoxythiocarbonylhydrazine, $C_2H_5O-CS-NH-NH_2$, assumed an intense red colour (probably due to tetrazine formation) on addition of dimethylamine but no thiosemicarbazide could be isolated. Monothiocarbazates of the type $RO-CS-N(CH_3)NH_2$ (R = CH_3, C_2H_5, or n-C_3H_7) were unreactive and could be recovered unchanged after treatment with aqueous ammonia at room temperature or refluxing with piperidine or benzylamine. However, 1,2-diphenylthiosemicarbazide was prepared by treatment of phenoxythiocarbonyl-1,2-diphenylhydrazine with ammonia.

Phenoxythiocarbonyl-1,2-diphenylhydrazine [51] (1.5 g) was dissolved in 100 ml of methanol, 120 ml of 15 % aqueous ammonia was added, and the solution was heated in an autoclave at 125°C for one hour. The solution was evaporated to dryness *in vacuo* and dilute ethanol was added to the residue and evaporated. The residue was taken up in acetone-benzene-petroleum ether (20:40:40) and subjected to preparative layer chromatography on silica gel. One fraction yielded 0.35 g (30 %) of 1,2-diphenylthiosemicarbazide as colourless needles after recrystallization from aqueous ethanol. Its infrared spectrum was identical with that of 1,2-diphenylthiosemicarbazide prepared by method 4d.

5b. From dithiocarbazates. Thiosemicarbazide and 1,1-dimethylthiosemicarbazide have been isolated from ethanolic solutions of $CH_3S-CS-NH-NH_2$ or $CH_3S-CS-NH-N(CH_3)_2$, saturated with ammonia, but the reaction is very slow at room temperature. After 2 months only 20–40 % of the thiosemicarbazide had formed and 60–80 % of the dithiocarbazate could be recovered unchanged. Addition of ammonium chloride as a possible acid catalyst did not increase the yields. Practically no reaction occurred between the dithiocarbazates and sodium amide in liquid ammonia. Even on heating the dithiocarbazates with ethanolic or aqueous ammonia, methylamine, or dimethylamine in an autoclave at 100°C they reacted only slowly, and because of side-reactions usually no thiosemicarbazides could be isolated. By heating methyl dithiocarbazate with 25 % ethanolic methylamine at 100°C for 1 h, however, 4-methylthiosemicarbazide was obtained in slight yield (27 %). With dimethylamine the solution attained an intense red colour and no thiosemicarbazide could be isolated.

Dithiocarbazates of the type $RS-CS-NR'-NH_2$ are even less reactive. $CH_3S-CS-N(CH_3)-NH_2$, dissolved in ethanol saturated with ammonia, was recovered quantitatively after two months at room temperature or after heating for several hours at 100°C. It was also recovered quantitatively after heating for 1 h at 100°C with ethanolic methylamine or after refluxing for 14 h with butylamine. Its acetophenone condensation product was unchanged after refluxing for 32 h with benzylamine. *p*-$NO_2C_6H_4CH_2S-CS-N(CH_3)-NH_2$ was recovered unchanged after refluxing for 10 h with methanolic benzylamine.

When $CH_3S-CS-NPr^i-NH_2$ was heated with conc. aqueous ammonia in an autoclave at 100°C, most of the starting material could be recovered after 8, 24, or 32 h. After 75 h at 100°C or 3 h at 125°C, the starting material had disappeared but no 2-isopropylthiosemicarbazide could be isolated. However, in a similar experiment with $CH_3S-CS-N(CH_2C_6H_5)-NH_2$ (75 h at 100°C) 2-benzylthiosemicarbazide crystallized on cooling of the solution (yield 33 %). It was pure after one recrystallization from ethanol. Its identity was proved by m.p. (172°C) and infrared spectrum. In Ref. 13 this reaction has been stated to give 1-benzylthiosemicarbazide, but the melting point given for the dithiocarbazate used (123–124°C) corresponds to neither of the two isomers (92 and 59°C) [102] and according to our experience the reaction between benzylhydrazine, carbon disulfide, potassium hydroxide, and methyl iodide affords only the 1,1-isomer.[51]

Method 6. Hydrazinolysis of thiocarbamates and dithiocarbamates

6a. Monothiocarbamates (thiourethans, xanthamides) react with hydrazine to give thiosemicarbazide or 4-substituted thiosemicarbazides, usually in slight yields and together with much thiocarbohydrazide. On heating, a more complex reaction sets in with evolution of hydrogen sulfide or methanethiol (*cf.* that $CH_3O-CS-N(CH_3)_2$ has been found to form 1,1-dimethylurea and hydrogen sulfide on heating with aqueous ammonia [103]).

O-Methyl thiocarbamate, $CH_3O-CS-NH_2$ (3 g), and hydrazine (1.7 g) were dissolved in ethanol (5 ml). There was a slight evolution of heat and after a few minutes thiosemicarbazide began to separate. Yield 0.8 g (27 %). A similar experiment with *O*-ethyl thiocarbamate only yielded 0.3 g of thiosemicarbazide. *O*-Phenyl thiocarbamate gave a 35 % yield.

In similar experiments *O*-methyl *N*-methylthiocarbamate, $CH_3O-CS-NHCH_3$, or the corresponding *O*-phenyl derivative reacted with hydrazine to give 35—45 % yields of 4-methylthiosemicarbazide, but in some experiments only thiocarbohydrazide was obtained. Addition of a small amount of potassium hydroxide seems to favour the formation of the thiosemicarbazide. *O*-Methyl *N,N*-dimethylthiocarbamate, $CH_3O-CS-N(CH_3)_2$, did not react with hydrazine in ethanol at room temperature and after refluxing the solution only thiocarbohydrazide was isolated. However, a similar experiment with *O*-phenyl *N,N*-dimethylthiocarbamate afforded 4,4-dimethylthiosemicarbazide in almost quantitative yield.

The alkylhydrazines react slowly with thiocarbamates and it has only been possible to isolate thiosemicarbazides from the reactions with methylhydrazine.

O-Methyl thiocarbamate (1.8 g) was added to a solution of potassium hydroxide (0.3 g) in methanol (5 ml) and methylhydrazine (1 g) was added to the filtered solution. On standing in a refrigerator for 12 h, 2-methylthiosemicarbazide separated (yield 0.45 g; 21 %). *O*-Phenyl thiocarbamate and methylhydrazine gave a similar yield of 2-methylthiosemicarbazide. From *O*-methyl or *O*-phenyl *N*-methylthiocarbamate, 20—30 % yields of 2,4-dimethylthiosemicarbazide could be isolated. Trimethylthiosemicarbazide could not be prepared by reaction of *O*-phenyl *N,N*-dimethylthiocarbamate with methylhydrazine.

6b. Dithiocarbamates differ from the monothiocarbamates in that the *N*-monosubstituted derivatives, $RNH-CS-SR'$, react almost as well with hydrazines as the isothiocyanates. The reason is that these dithiocarbamates are rapidly transformed into isothiocyanates in the presence of bases. On additing one drop of 2 N sodium hydroxide to 1 g of methyl *N*-methyldithiocarbamate, $CH_3NH-CS-SCH_3$, and heating for 1 min at 50°C, the carbamate was transformed almost quantitatively into methyl isothiocyanate.

The procedure for preparing thiosemicarbazides from *N*-alkyl dithiocarbamates is illustrated by the following example.

Methyl *N*-methyldithiocarbamate (3 g) was dissolved in ethanol (3 ml) and methylhydrazine (1.15 g) was added. There was a violent evolution of methanethiol and on cooling of the solution in ice 2,4-dimethylthiosemicarbazide crystallized. The reaction took less than 1 min. The crystals were filtered and washed with a few ml of ethanol and recrystallized from water (15 ml). Yield 1.6 g (53 %) of recrystallized product, yield of crude product almost quantitative. Phenyl *N*-methyldithiocarbamate gave a similar yield of 2,4-dimethylthiosemicarbazide.

In the same manner the following thiosemicarbazides were prepared (yields of recrystallized products in parentheses): 4-methyl (60 %), 2-butyl-4-methyl (65 %), 2-isopropyl-4-methyl (30 %), 2-isobutyl-4-methyl (65 %), 2-cyclohexyl-4-methyl (40 %), 1-*tert*-butyl-4-methyl (30 %), 1,1,4-trimethyl (40 %), 4-methyl-2-phenyl (10 %). No reaction took place between $CH_3NH-CS-SCH_3$ and hydrazobenzene.

Methyl dithiocarbamate, $H_2N-CS-SCH_3$, reacted well with hydrazine to give thiosemicarbazide (71 %) and with methylhydrazine to give 2-methylthiosemicarbazide (75 %), but negative results were obtained with isopropylhydrazine, 1,1-dimethylhydrazine, trimethylhydrazine, and α-methylbenzylhydrazine.

The *N,N*-disubstituted dithiocarbamates are very unreactive, even toward hydrazine. From a solution of $(CH_3)_2NCSSCH_3$ and hydrazine in ethanol, the unchanged dithiocarbamate was recovered quantitatively after refluxing the solution for several hours. Also, phenyl *N,N*-dimethyldithiocarbamate was practically not attacked by hydrazine (*cf.* the behaviour of the corresponding *O*-phenyl monothiocarbamate).

6c. (Thiocarbamoylthio)acetic acids or carboxymethyl dithiocarbamates (Table 5) offer certain advantages over the ordinary dithiocarbamates: they are prepared and purified more easily, they are soluble in aqueous sodium hydroxide so that the reactions can be carried out in aqueous solution, and the formation of methanethiol is avoided.

Solutions of carboxymethyl *N-tert*-butyldithiocarbamate or carboxymethyl *N*-isopropyldithiocarbamate in the equivalent amount of 2 N sodium hydroxide yielded 4-

tert-butylthiosemicarbazide, 4-*tert*-butyl-2-methylthiosemicarbazide, 1,4-di-*tert*-butylthiosemicarbazide, 4-*tert*-butyl-2-isopropylthiosemicarbazide, 4-isopropylthiosemicarbazide and 4-isopropyl-2-methylthiosemicarbazide on addition of hydrazine or the appropriate alkylhydrazine. The reactions proceeded rapidly at room temperature and the yields were almost quantitative. 1,4-Di-*tert*-butylthiosemicarbazide was formed directly and not by rearrangement of the 2,4-derivative (*cf.* 1-*tert*-butyl-4-methylthiosemicarbazide, Method 3).

The unsubstituted carboxymethyl dithiocarbamate $H_2N-CS-SCH_2COOH$, gave a 90 % yield of thiosemicarbazide on addition of hydrazine, but only a very small amount of 2-methylthiosemicarbazide with methylhydrazine. No thiosemicarbazides could be obtained from reactions with isopropylhydrazine, cyclohexylhydrazine, benzylhydrazine, or phenethylhydrazine. The reason for these negative results is that this dithiocarbamate is cleaved into thiocyanic acid and mercaptoacetic acid more rapidly than it reacts with most alkylhydrazines.

The carboxymethyl *N*,*N*-dialkyldithiocarbamates are rather unreactive. However, some 4,4-dialkylthiosemicarbazides have been obtained earlier [1] from their reaction with hydrazine, although in slight yields and with much thiocarbohydrazide as by-product. 4,4-Dialkylthiosemicarbazides have now been prepared in 20—50 % yields by the same method from most of the carboxymethyl dithiocarbamates listed in Table 5. No thiosemicarbazides could be obtained from alkylhydrazines in this way.

Generally it seems preferable to dissolve the dithiocarbamate directly in hydrazine hydrate (*cf.* Ref. 73).

Carboxymethyl ethylmethyldithiocarbamate (9.0 g) was dissolved in hydrazine hydrate (15 ml) and the solution was heated to 60°C for 30 min. After cooling, 10 ml of water was added and the precipitated crystals were filtered and recrystallized from water. Yield 4.0 g (60 %). In a similar manner the following thiosemicarbazides were prepared: 4,4-dimethyl (58 %), 4-methyl-4-phenyl (67 %), 4,4-diisopropyl (40 %). Under these conditions methylhydrazine also reacted slowly with carboxymethyl dithiocarbamates.

Carboxymethyl dimethyldithiocarbamate (7.2 g) was dissolved in methylhydrazine (8 ml) and the solution refluxed for 1 h. The cooled solution was extracted with ether and the residue obtained by evaporation of the ether was crystallized from water. Yield 0.40 g (7.5 %) of 2,4,4-trimethylthiosemicarbazide, m.p. 63—64°C.

The reaction between carboxymethyl *N*,*N*-diphenyldithiocarbamate and hydrazine proceeded smoothly in aqueous solution. Carboxymethyl *N*,*N*-diphenyldithiocarbamate (2.03 g) was dissolved in 2 N sodium hydroxide (3.3 ml) with addition of hydrazine hydrate (0.60 g) and the solution was refluxed for 2 h (separation of a crystalline precipitate began after 1 h). After cooling, the crystals were filtered and recrystallized from 50 ml of ethanol. Yield 1.2 g (75 %) of 4,4-diphenylthiosemicarbazide, m.p. 154—155°C.

Method 7. Cyanohydrazines plus hydrogen sulfide

Hydrazines react in ethereal solution with cyanogen bromide to form cyanohydrazines. Although the isolated cyanohydrazines often seem to be dimeric,[104] satisfactory yields of thiosemicarbazides have generally been obtained by treatment of the ethereal solutions with hydrogen sulfide. From monosubstituted alkylhydrazines the 2-alkylthiosemicarbazides were formed, except from α-methylbenzylhydrazine and *tert*-butylhydrazine. In these last cases the reaction with nickel chloride showed that the crude products contained the 2-substituted thiosemicarbazide, but this disappeared completely during recrystallization (even from petroleum ether). The method is illustrated by the following example.

Solutions of isopropylhydrazine (1.52 g) in ether (10 ml) and cyanogen bromide (1.0 g) in ether (10 ml) were mixed under ice cooling and slowly heated to boiling. After cooling, the solution was washed with water, 20 % ethanolic dimethylamine (1 ml) was added and the solution was saturated with hydrogen sulfide. After 12 h the solution was evaporated to dryness and the residue was recrystallized three times from water. Yield 0.80 g (65 %). According to analyses, m.p., reaction with nickel chloride, and infrared spectrum, the compound was 2-isopropylthiosemicarbazide.

In the same manner and with similar yields (40—65 %) the following thiosemicarbazides were prepared: 2-butyl, 2-isobutyl, 1-α-methylbenzyl, 2-phenethyl, 2-cyclohexyl, 1,2-dimethyl, 1,1-dimethyl, 1-ethyl-1-methyl, 1,1-diethyl, and 1-*tert*-butyl.

The product prepared in this way from 1-methyl-2-phenylhydrazine (colourless crystals from water) showed analyses corresponding to unreacted cyano(methyl)phenylhydrazine. (Found: C 65.42; H 6.26; N 28.21. Calc. for $C_8H_9N_3$: C 65.30; H 6.16; N 28.55). Also cyanotrimethylhydrazine did not react with hydrogen sulfide, even at elevated temperature or on heating with thioacetamide in dimethylformamide (*cf.* Taylor and Zoltewicz [105]).

Acylthiosemicarbazides could not be prepared from acylhydrazines by this method.

Method 8. Preparation of 1-methyl- (and 1-allyl-) thiosemicarbazides

1-Methylthiosemicarbazides and 1-allylthiosemicarbazides were mostly obtained by hydrolysis of 1-acylthiosemicarbazides, obtained from acylhydrazines and isothiocyanates. 1-*tert*-Butoxycarbonyl-1-methyl- (or 1-allyl-) hydrazine reacted smoothly at room temperature with isothiocyanates, giving the corresponding thiosemicarbazides in 90—95 % yield. 1-Acetyl-1-methylhydrazine was less reactive and did not react with *tert*-butyl isothiocyanate. However, other isothiocyanates reacted to give 1-acetyl-1-methylthiosemicarbazides. Acyl derivatives of 1-methyl-2-phenylhydrazine could not be induced to react with isothiocyanates.

1-*tert*-Butoxycarbonyl-1-methyl- (or 1-allyl-) thiosemicarbazides, unsubsituted in the 4-position, were obtained from the corresponding *tert*-butoxycarbonylhydrazines and ethoxycarbonyl dithiocarbamate. No reaction occurred between 1-acetyl-1-methylhydrazine (or 1-trifluoroacetyl-1-methylhydrazine) and ethoxycarbonyl dithiocarbamate.

Table 7. 1-Acylthiosemicarbazides, $R^1CONR^2-NR^3-CS-NHR^4$.

R^1	R^2	R^3	R^4	Formula	M.p., °C	Yield, %	Analyses (C, H, N, S)			
Me	Me	H	Me	$C_5H_{11}N_3OS$	188—190 [a]	62	Found:	37.18;	6.96;	26.02
							Calc.:	37.26;	6.88;	26.08
Me	Me	H	Et	$C_6H_{13}N_3OS$	187—188 [b]	29	Found:	41.20;	7.52;	23.77; 18.14
							Calc.:	41.13;	7.48;	23.99; 18.26
Me	Me	H	Cyclohexyl	$C_{10}H_{19}N_3OS$	217—219 [c]	22	Found:	52.60;	8.54;	18.48; 14.12
							Calc.:	52.38;	8.35;	18.33; 13.96
Me	Me	$PhCH_2$	Me	$C_{12}H_{17}N_3OS$	175—176 [a]	86	Found:	56.77;	6.52	
							Calc.:	57.33;	6.82	
EtO	Me	H	Me	$C_6H_{13}N_3O_2S$	127—128 [d]	76	Found:	37.70;	6.82;	21.94
							Calc.:	37.69;	6.85;	21.98
Bu^{t}O	Me	H	H	$C_7H_{15}N_3O_2S$	174—175 [e]	58	Found:	40.44;	7.07;	20.53
							Calc.:	40.95;	7.38;	20.47
Bu^{t}O	Me	H	Me	$C_8H_{17}N_3O_2S$	133—134 [f,d]	95	Found:	43.77;	7.80;	19.19
							Calc.:	43.81;	7.81;	19.16
Bu^{t}O	Me	H	Et	$C_9H_{19}N_3O_2S$	104—106 [a]	92	Found:	46.34;	8.21	
							Calc.:	45.79;	8.11	
Bu^{t}O	Me	H	Bu^t	$C_{11}H_{23}N_3O_2S$	155—156 [d]	90	Found:	50.65;	8.77;	16.04
							Calc.:	50.60;	8.81;	16.10
Bu^{t}O	Me	H	Ph	$C_{13}H_{19}N_3O_2S$	134—135 [d]	90	Found:	55.60;	6.88;	14.82
							Calc.:	55.50;	6.81;	14.94
Bu^{t}O	Allyl	H	H	$C_9H_{17}N_3O_2S$	158—160 [b]	65	Found:	46.24;	7.20;	17.72
							Calc.:	46.72;	7.42;	18.17
Bu^{t}O	Allyl	H	Me	$C_{10}H_{19}N_3O_2S$	141—143 [a]	56	Found:	49.07;	7.79;	16.98
							Calc.:	48.94;	7.82;	17.13
Bu^{t}O	Allyl	H	Ph	$C_{15}H_{21}N_3O_2S$	143—144 [a]	79	Found:	58.40;	6.97;	13.94
							Calc.:	58.60;	6.90;	13.67

Solvents used for recrystallization: [a]) ethanol-water; [b]) ethanol; [c]) methanol; [d]) water; [e]) ethyl acetate; [f]) ethanol-ether.

The reaction between acylhydrazines and dialkylthiocarbamoyl chlorides is a complex one. It has only been used in the preparation of 1,4,4-trimethylthiosemicarbazide (*q.v.*).

The following examples illustrate the procedures used in the preparation of the 1-acylthiosemicarbazides listed in Table 7. The preparation of 1-alkoxythiocarbonylthiosemicarbazides will be described in another paper.[108]

1-tert-*Butoxycarbonyl-1,4-dimethylthiosemicarbazide.* 1-*tert*-Butoxycarbonyl-1-methylhydrazine (1.5 g) and methyl isothiocyanate (0.70 g) were dissolved in a mixture of ether (5 ml) and petroleum ether (5 ml). On standing for 24 h, a crystalline precipitate separated. Yield 2.1 g (95 %), m.p. 129—131°C. Recrystallization three times from ethanol-ether raised the melting point to 133.5—134°C. The other 1-*tert*-butoxycarbonylthiosemicarbazides, substituted in the 4-position, were prepared similarly.

1-tert-*Butoxycarbonyl-1-methylthiosemicarbazide.* 1-*tert*-Butoxycarbonyl-1-methylhydrazine (2.2 g) and *S*-ethoxycarbonyl dithiocarbamate (2.5 g) were dissolved in benzene (15 ml) and the solution was refluxed for 24 h. On cooling, a crystalline precipitate slowly separated. Yield 1.8 g (58%). The allyl homologue was prepared in the same manner, except that the benzene was evaporated and the oily residue was treated with ether and petroleum ether to induce crystallization. Yield 65 %.

1-Acetyl-1,4-dimethylthiosemicarbazide. A solution of methyl isothiocyanate (11.7 g) in ethanol (20 ml) was added with stirring to a solution of 1-acetyl-1-methylhydrazine (13.5 g) in ethanol (20 ml). There was a spontaneous increase of temperature and crystals soon began to separate. After 24 h the precipitate was filtered, washed with chloroform-hexane and recrystallized from ethanol-water. Yield 62 %. The other 1-acetylthiosemicarbazides were prepared in the same manner.

1-Methylthiosemicarbazide. a) Camphorquinone methylcyanohydrazone [47] (3 g) was dissolved in diethyl ether (250 ml), a little of a suspension of NH_4HS in ether was added, and the solution was saturated with hydrogen sulfide. On standing overnight a solid (2.5 g) separated which was filtered and boiled for ½ h with 30 ml of 4 N hydrochloric acid. The cooled solution was extracted three times with ether and evaporated to dryness *in vacuo*. The residue was recrystallized from a little ethanol and yielded colourless crystals of 1-methylthiosemicarbazide hydrochloride. This was dissolved in the minimum amount of water and the free thiosemicarbazide precipitated by addition of ammonia. Yield 0.30 g (21 %). M.p. 157—158°C.

b) When 1-*tert*-butoxycarbonyl-4-*tert*-butyl-1-methylthiosemicarbazide (2.2 g) was suspended in 10 ml of 4 N hydrochloric acid, CO_2 was evolved and the mixture was rapidly transformed into a thick crystalline mass of the hydrochloride of 4-*tert*-butyl-1-methylthiosemicarbazide, from which the free thiosemicarbazide was obtained as before. Yield 1.0 g (67 %).

1-Methylthiosemicarbazide was obtained by adding conc. hydrochloric acid (5 ml) to the last-mentioned thiosemicarbazide (0.8 g) and heating to boiling for 2 min. The hydrochloride, which first separated, went into solution with the formation of *tert*-butyl chloride. The solution was evaporated *in vacuo*, the residue was dissolved in water, and the solution was neutralized with ammonia and again evaporated to dryness. The residue yielded, on recrystallization from a little water 1-methylthiosemicarbazide (0.35 g; 60 %). It can, of course, also be prepared directly from the preceding *tert*-butoxycarbonyl derivative; 6 g of this compound yielded 2.1 g (87 %) of 1-methylthiosemicarbazide.

c) 1-Ethoxymethylenethiosemicarbazide [49] (14.7 g) suspended in anhydrous tetrahydrofuran (200 ml) was added dropwise to a suspension of lithium aluminium hydride (5 g) in anhydrous tetrahydrofuran (200 ml), placed in a one-liter flask equipped with mechanical stirrer, drying tube and nitrogen inlet. Stirring was continued for 1 h after the addition had been completed. The mixture was left for 12 h at room temperature and then refluxed for 15 min. It was poured on ice and the tetrahydrofuran was removed *in vacuo*. Conc. hydrochloric acid was added until an almost clear solution had been obtained. This was heated to boiling, filtered through Celite, neutralized with sodium hydroxide and evaporated to dryness *in vacuo*. Absolute ethanol was added and again evaporated, and this was repeated three times to remove water. Finally the residue was extracted with cold abs. ethanol and the filtered solution was evaporated to dryness. Yield 6.6 g (92 %), m.p. 145—150°C. Recrystallization from ethanol raised the m.p. to 156—157°C.

d) When 1-*tert*-butoxycarbonyl-1-methylthiosemicarbazide (0.65 g) was suspended in conc. hydrochloric acid (3 ml), it went into solution with evolution of CO_2. The solution was evaporated *in vacuo*, the residue was dissolved in 2 ml of water and the solution was

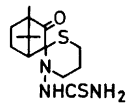
made alkaline with ammonia. On cooling, 1-methylthiosemicarbazide separated as colourless crystals. Yield 0.30 g (90 %). M.p. 158°C after recrystallization from water.

e) 1-Methylthiosemicarbazide has further been obtained as a by-product in the preparations of 2-methylthiosemicarbazide by Methods 1 and 3 d.

The identity of the products obtained by methods a—e was proved by their infrared spectra.

1-Allylthiosemicarbazide. When 1-allyl-1-*tert*-butoxycarbonylthiosemicarbazide (0.5 g) was suspended in conc. hydrochloric acid (2 ml), it dissolved with evolution of CO_2. The solution was diluted with 10 ml of water, neutralized with NaOH and evaporated *in vacuo*. The residue was dehydrated by evaporation with abs. ethanol and extracted with benzene. The solution left on evaporation *in vacuo* 0.20 g (72 %) of 1-allylthiosemicarbazide. M.p. 104—105°C after recrystallization from ethanol-ether.

It was also attempted to prepare 1-allylthiosemicarbazide from camphorquinone cyanohydrazone. This was transformed into *camphorquinone allylcyanohydrazone* in the following way. The cyanohydrazone (4 g) was dissolved in a 10 % solution of sodium carbonate (100 ml). The solution was shaken with allyl bromide (3.1 g) for 16 h, extracted three times with ether and evaporated to dryness. Yield 3.6 g (76 %). M.p. 42—44°C after recrystallization from ether-pentane (Found: C 68.50; H 7.87; N 16.87. Calc. for $C_{14}H_{19}N_3O$: C 68.53; H 7.82; N 17.13). When this compound was treated with hydrogen sulfide in the same manner as the methyl derivative, a compound was obtained which was unattacked by hydrochloric acid and which according to the analyses had been formed by addition of two molecules of hydrogen sulfide to camphorquinone allylcyanohydrazone, probably with the formation of a 1,3-thiazine:



(Found: C 53.3; H 7.0; N 13.1; S 20.8. Calc. for $C_{14}H_{23}N_3OS_2$: C 53.9; H 7.3; N 13.4; S 20.4). M.p. 210—211°C after recrystallization from acetone-petroleum ether. It gives colour reactions with Cu^{2+} (blue) and Ni^{2+} (brown) in ethanolic solution in accordance with the formulation as a thiosemicarbazide.

1-Allyl-4-methylthiosemicarbazide and *1-allyl-4-phenylthiosemicarbazide* were similarly prepared from the *tert*-butoxycarbonyl derivatives.

2-Ethyl-1-methylthiosemicarbazide. 1-*tert*-Butoxycarbonyl-2-ethyl-1-methylhydrazine (1.0 g) and *S*-ethoxycarbonyl dithiocarbamate (1.0 g) were dissolved in benzene (30 ml) and the solution refluxed for 24 h. On evaporation of the solution *in vacuo* a crystalline residue (1.3 g) was obtained which, however, contained much thiocyanate. On recrystallization three times from ethanol-water 0.3 g of thiocyanate-free product was obtained (m.p. 166—167°C). This was treated with hydrochloric acid in the way described for 1-allylthiosemicarbazide and yielded 0.1 g of the thiosemicarbazide. M.p. 80—81°C after recrystallization, first from benzene and then from water.

2-Ethyl-1,4-dimethylthiosemicarbazide. 1-*tert*-Butoxycarbonyl-2-ethyl-1-methylhydrazine and methyl isothiocyanate in petroleum ether yielded an oily *tert*-butoxycarbonyl derivative (1.1 g), which on treatment with hydrochloric acid as described above yielded the thiosemicarbazide (0.4 g). This was obtained crystalline from hexane but because of its low melting point (2—5°C) was transformed into the hydrochloride (0.2 g), m.p. 145—147°C. Recrystallization from ethanol-ether and ethanol-ethyl acetate raised the melting point to 148—149°C.

2-Benzyl-1,4-dimethylthiosemicarbazide was prepared in a similar manner, except that the residue obtained by evaporation with hydrochloric acid was dissolved in water and the thiosemicarbazide precipitated by ammonia. Yield 76 %. M.p. 95—96°C after recrystallization from ethanol-water, benzene-petroleum ether, and again ethanol-water.

It was also attempted to prepare this thiosemicarbazide by hydrolysis of 1-acetyl-2-benzyl-1,4-dimethylthiosemicarbazide. However, the acetyl derivative proved extremely resistant to hydrolysis.

1-Methyl-2-phenylthiosemicarbazide was prepared by reduction of formaldehyde-2-phenylthiosemicarbazone with diborane; see Method 2c. The thiosemicarbazone was prepared in tetrahydrofuran and the residue left after removal of the solvent and water in high vacuum at room temperature was used without further purification. From 1.4 g of 2-phenylthiosemicarbazide, 1.1 g (73 %) of fairly pure 1-methyl-2-phenylthiosemicarbazide was obtained. It was further purified by chromatography on silica gel PF_{254} with benzene-ethyl acetate-acetone, 100:5:10, and recrystallized from ethanol. The melting point (145—146°C) was found to be the same as that of the thiosemicarbazone, but the mixed m.p. showed considerable depression (30°C) and in contrast to the thiosemicarbazone the thiosemicarbazide formed a red nickel complex.

1,4-Dimethyl-2-phenylthiosemicarbazide was prepared in a similar manner. Although the pure thiosemicarbazone was used as starting material, the crude oily reaction product was much more complex in this case, for thin layer chromatography showed the presence of at least 6 compounds. After layer chromatography on silica gel $PF_{254+366}$ with benzene-ethyl acetate (100:5), a 40 % yield was obtained which was recrystallized three times from ethanol-ether. M.p. 104—105°C (m.p. of thiosemicarbazone 70—71°C).

1,4-Dimethylthiosemicarbazide. 1-*tert*-Butoxycarbonyl-1,4-dimethylthiosemicarbazide (2.1 g) was treated with conc. hydrochloric acid (without heating) and went into solution with the evolution of CO_2. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in water, neutralized with ammonia and again evaporated. The residue yielded on recrystallization from hot water 0.9 g (75 %) of 1,4-dimethylthiosemicarbazide.

In a similar way 4-ethyl-1-methylthiosemicarbazide (yield 70 %) and 1-methyl-4-phenylthiosemicarbazide (yield 55 %) were prepared from the corresponding 1-*tert*-butoxycarbonyl derivatives.

b) 1-Ethoxymethylene-4-methylthiosemicarbazide (4.7 g) was reduced with lithium aluminium hydride as described for the preparation of 1-methylthiosemicarbazide. Yield 2.8 g (81 %) of recrystallized 1,4-dimethylthiosemicarbazide.

The starting material, *1-ethoxymethylene-4-methylthiosemicarbazide*, was prepared by heating a mixture of 4-methylthiosemicarbazide (10.5 g) and ethyl orthoformate (14.8 g) with stirring on a steam bath for 2—3 h. After cooling of the solution in ice and addition of ethanol and petroleum ether, a crystalline product was obtained which was filtered and recrystallized from ethanol. Yield 38 %. M.p. 100—102°C. (Found: C 37.41; H 6.60; N 26.31. Calc. for $C_5H_{11}N_3OS$: C 37.27; H 6.83; N 26.09).

c) 1,4-Dimethyl-1-isopropoxythiocarbonylthiosemicarbazide (0.88 g) was refluxed for 4 h with 10 ml of conc. hydrochloric acid. The solution was evaporated to dryness *in vacuo*, made alkaline with aqueous ammonia and evaporated again. The residue was recrystallized from benzene-ether and from ethanol-ether and yielded 0.30 g (63%) of 1,4-dimethylthiosemicarbazide.

In another experiment the hydrochloride, obtained by evaporation of the hydrochloric acid solution, was dissolved in water and the thiosemicarbazide precipitated by addition of ammonia. It was pure after one recrystallization from water.

Other 1-alkoxythiocarbonyl-1,4-dimethylthiosemicarbazides, such as 1-benzyloxythiocarbonyl-1,4-dimethylthiosemicarbazide, have also yielded 1,4-dimethylthiosemicarbazide on hydrolysis with hydrochloric acid, but in smaller yields.

d) 1-Benzyloxythiocarbonyl-1,4-dimethylthiosemicarbazide [108] (2.69 g) was dissolved in triethylsilane (4.7 g), palladium chloride (50 mg) and triethylamine (100 mg) were added, and the solution was refluxed for 4 h (*cf.* Ref. 106). The filtered solution was diluted with methanol and evaporated *in vacuo*. The residue was stirred with water and ether and the aqueous layer was separated and evaporated *in vacuo*. The residue (0.8 g) yielded on recrystallization from benzene-ether petroleum and then from ethanol-ether pure 1,4-dimethylthiosemicarbazide.

e) 1,4-Dimethyl-1-*o*-nitrobenzyloxycarbonylthiosemicarbazide (0.5 g) was suspended in water (25 ml) with addition of a little ethanol. The solution was heated to boiling and sodium dithionite (3 g) was added in one portion. The solution was filtered and evaporated to dryness *in vacuo* and the residue extracted with abs. ethanol. On evaporation of the ethanol and recrystallization of the residue from ethanol-ether, *ca.* 50 mg of 1,4-dimethylthiosemicarbazide was obtained.

The starting material was synthesized by heating a solution of 1-methyl-1-*o*-nitrobenzyloxythiocarbonylhydrazine [51] (6.2 g) and methyl isothiocyanate (2.9 g) in ethanol (50 ml) to boiling for ½ h. The crystals which separated on standing of the solution for 3 days were filtered and washed with ethanol. Yield 7 g (87 %), m.p. 142—143°C. Recrystallization from ethanol did not change the melting point. (Found: C 42.30; H 4.57; N 17.76. Calc. for $C_{11}H_{14}N_4O_3S_2$: C 42.04; H 4.46; N 17.83). This reaction showed a remarkable solvent effect which has not been observed in the preparation of other thiosemicarbazides: no reaction took place between methyl isothiocyanate and the hydrazine in ether, benzene, or even in boiling cymene.

f) 1-Acetyl-1,4-dimethylthiosemicarbazide (2 g) was dissolved in 30 ml of ethanol and 10 ml of 4 N hydrochloric acid and the solution heated to boiling for 10 min. On evaporation of the solution and recrystallization of the residue from methanol, 1.7 g of the hydrochloride of 1,4-dimethylthiosemicarbazide was obtained. (Found: C 23.64; H 6.56; N 27.47; S 20.07. Calc. for $C_3H_{10}ClN_3S$: C 23.16; H 6.48; N 27.00; S 20.59). On dissolution of the hydrochloride in water and precipitation with ammonia pure 1,4-dimethylthiosemicarbazide was obtained.

The identity of the products prepared according to methods a—f was proved by their infrared spectra.

By the same method *4-ethyl-1-methylthiosemicarbazide* and *4-cyclohexyl-1-methylthiosemicarbazide* were obtained by hydrolysis of the corresponding acetyl derivatives.

1,4,4-Trimethylthiosemicarbazide. 1-*tert*-Butoxycarbonyl-1-methylhydrazine (14.6 g) and dimethylthiocarbamoyl chloride (12.5 g) were dissolved in triethylamine (10 ml) and left at room temperature for 48 h. On addition of excess conc. hydrochloric acid, evaporation of the solution *in vacuo* and addition of water, a crystalline compound was obtained (3.0 g) which according to analyses was *2-dimethylamino-4-methyl-1,3,4-thiadiazol-2-ine-5-thione*. M.p. 110—111°C after recrystallization from water. (Found: C 34.35; H 5.19; N 24.41; S 36.63. Calc. for $C_5H_9N_3S_2$: C 34.26; H 5.19; N 23.98; S 36.55).

On addition of nickel(II) chloride to the aqueous solution, followed by sodium hydroxide to give pH 8, a brown nickel salt of 1,4,4-trimethylthiosemicarbazide precipitated. Yield 3.3 g (21 %), m.p. 211—213°C (decomp.). (Found: C 29.84; H 6.36; N 25.57. Calc. for $C_8H_{20}N_6NiS_2$: C 29.73; H 6.25; N 26.13). The nickel salt was decomposed by shaking with ether containing H_2S and HCl (or alternatively by shaking with ether and aqueous sodium cyanide). The ether solution was neutralized with ammonia (dissolved in ether) and the filtered solution was concentrated *in vacuo*. On addition of pentane and cooling, 0.5—1.6 g (20—60 %) of 1,4,4-trimethylthiosemicarbazide, m.p. 70—71°C, was obtained. Recrystallization from ether-pentane with addition of active carbon afforded colourless crystals, m.p. 71—72°C.

This thiosemicarbazide is rather unstable. It decomposed on standing at room temperature for some months.

1-*tert*-Butoxycarbonyl-1-methylhydrazine was practically unaffected by tetramethylthiuram monosulfide. However, a small amount (10 %) of the above mentioned thiadiazolinethione was isolated after prolonged heating of a mixture of the components without solvent. According to the Ni-reaction, no thiosemicarbazide was formed.

Several other potential methods were tried to prepare this thiosemicarbazide. Dimethylthiocarbamoyl chloride was treated with 1-acyl-1-methylhydrazines (acyl = benzyloxycarbonyl, benzyloxythiocarbonyl, isopropoxythiocarbonyl, formyl, acetyl, trifluoroacetyl), 1,2-dibenzyloxycarbonyl-1-methylhydrazine, 1-methyl-1,2-bis(trimethylsilyl)hydrazine, or with the sodium or lithium salt of methylhydrazine. In most cases a complex mixture resulted which was chromatographed, but 1,4,4-trimethylthiosemicarbazide or its 1-acyl derivatives could not be isolated. Instead, tetramethylthiourea, tetramethylthiuram monosulfide, 2-dimethylamino-4-methyl-1,3,4-thiadiazol-2-ine-5-thione, benzyl dithiocarbamate, 2,4,4-dimethylthiosemicarbazide [16] and unidentified products were isolated. It was also attempted to hydrolyse or hydrogenolyse the crude product from dimethylthiocarbamoyl chloride and 1-benzyloxythiocarbonyl-1-methylhydrazine, but 1,4,4-trimethylthiosemicarbazide could not be isolated, although the colour reaction with Cu^{2+} (violet) suggested that it might have been formed.

4,4-Dimethylthiosemicarbazide did not form a 1-ethoxymethylene derivative with ethyl orthoformate. Instead, *2-dimethylamino-1,3,4-thiadiazole* (b.p. 93—94°C at 0.4 mm Hg) was formed. (Found: C 37.40; H 6.07; N 33.12. Calc. for $C_4H_7N_3S$: C 37.21; H 5.46; N 32.55. The NMR spectrum showed two singlets at 1.63 τ (1 H) and 6.86 τ (6 H) in

agreement with the assigned structure). On reduction with lithium aluminium hydride this compound was completely decomposed with the formation of ionic cyanide and thiocyanate.

Finally, attempts were made to prepare 1,4,4-trimethylthiosemicarbazide by hydrolysis of 2-dimethylamino-4-methyl-1,3,4-thiadiazol-2-in-5-one, but a more thorough decomposition took place. The starting material for this experiment has not been described previously.

2-Dimethylamino-1,3,4-thiadiazolin-5-one. 4,4-Dimethylthiosemicarbazide (4.0 g) was dissolved in 500 ml of boiling benzene. After cooling to 60°C, triethylamine (10 g) and then a 20 % solution of phosgene in benzene (17 ml) were added with stirring. Triethylammonium chloride precipitated immediately and the temperature rose to 75°C. The solution was left overnight, cooled at 8°C and filtered. The filtrate was evaporated and left 4.4 g of an oil, which crystallized on cooling. It was extracted with boiling cyclohexane, the cyclohexane solution evaporated to dryness and the residue recrystallized twice from cyclohexane. Yield 1.4 g (28 %), m.p. 98–99°C. (Found: C 33.36; H 4.82; N 28.76. Calc. for $C_4H_7N_3OS$: C 33.10; H 4.86; N 28.96).

This thiadiazolinone was methylated with dimethyl sulfate in the manner described for 3-phenyl-2-phenylimino-1,3,4-thiadiazolin-5-one.[52] The methyl derivative could not be obtained crystalline. (Found: C 37.3; H 5.76. Calc. for $C_5H_9N_3OS$: C 37.7; H 5.70). On treatment with ethanolic potassium hydroxide it was decomposed without the formation of 1,4,4-trimethylthiosemicarbazide.

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