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Studies of Thioacids and Their Derivatives

III. Methods for the Preparation of Thiohydrazides

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Several new thiohydrazides (see Table 1) have been prepared from carboxymethyl dithioates and hydrazine or from dithioacids and hydrazine. A number of other potential methods for the preparation of thiohydrazides were tried without success. An excess of carboxymethyl dithioate leads generally to the formation of thiadiazoles; in two cases, however, dithioacylated hydrazines were obtained.

For the preparation of thiohydrazides the reaction between carboxymethyl dithioates and hydrazine, originally used by Holmberg [1] for the preparation of thiobenzhydrazide, has proved to be most convenient. The carboxymethyl esters of dithioacids, dissolved in aqueous sodium hydroxide, react rapidly with hydrazine at 0°C. The methyl and ethyl esters may also be used, but the higher alkyl esters seem to be rather unreactive: amyl dithiobenzoate reacts only slowly with hydrazine even at 100°C.

The hydrazides may also be prepared directly from dithioacids. The hydrazinium salts of these acids are rapidly transformed into hydrazides in dilute aqueous solution:

$$RCSS^{-}N_2H_5^{+} \longrightarrow RCSNHNH_2 + H_2S$$

This reaction is accompanied by a decolorization of the red or brown solution. The method is mainly of importance when the dithioacids can be obtained by the reaction of aldehydes with ammonium polysulfide. The preparation of a number of new thiohydrazides by these methods has already been announced (Jensen and Jensen [2]); they are included in Table 1, and details of their preparation are given in the experimental part.

Thiohydrazides with the $-CSNHNH_2$ group attached to an aromatic or a non-basic heterocyclic nucleus can in most cases be prepared without difficulties. Sometimes, however, a thiadiazole is formed as the main product (see No. VI of this series), and we were unable to prepare *m*-nitrothiobenzhydrazide. In this case the carboxymethyl dithioate reacts rapidly with hydrazine with the formation of hydrogen sulfide, and no thiohydrazide could be isolated. Most aliphatic dithioacids and dithioesters react in the same way with hyd-

Table 1. Thiohydrazides, $RCSNHNH_2$.

R	Yield, %, by procedure		M.p., °C	Formula	Analyses							
					Carbon		Hydrogen		Sulfur		Nitrogen	
	I [a]	II [b]			Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.
Benzyl [d]		55	70— 71	$C_8H_{10}N_2S$	57.52	57.82	5.95	6.07	19.25	19.26	16.96	16.86
β-Phenylethyl [e]		78	105—106	$C_9H_{12}N_2S$	59.80	60.00	6.68	6.72			15.69	15.52
o-Tolyl [c]												
p-Tolyl [d]		63	137—138	$C_8H_{10}N_2S$	57.75	57.80	5.85	6.07			17.10	16.83
o-Hydroxyphenyl [e]	40	67	101—102	$C_7H_8N_2OS$	49.98	50.00	4.85	4.80	18.92	19.07	16.95	16.66
m-Hydroxyphenyl [f]	10		146—147	$C_7H_8N_2OS$	49.80	50.00	4.89	4.80			16.64	16.66
p-Hydroxyphenyl [f]	26	77	200—201	$C_7H_8N_2OS$	50.25	50.00	4.73	4.80			16.83	16.66
o-Methoxyphenyl [e]		50	34— 35	$C_8H_{10}N_2OS$							15.30	15.38
p-Methoxyphenyl [d]		80	125—126	$C_8H_{10}N_2OS$	52.85	52.72	5.48	5.53	17.30	17.59	15.31	15.38
o-Propoxyphenyl [e]		78	52— 53	$C_{10}H_{14}N_2OS$	57.22	57.13	6.79	6.71			13.43	13.33
o-*Iso*propoxyphenyl [e]		70	58— 59	$C_{10}H_{14}N_2OS$	57.20	57.13	6.70	6.71			13.33	13.33
o-Butoxyphenyl [e]		70	66— 67	$C_{11}H_{16}N_2OS$	59.10	58.91	7.10	7.19			12.42	12.49
o-Hexyloxyphenyl [e]		29	56— 57	$C_{13}H_{20}N_2OS$	62.05	61.86	8.18	7.99			11.22	11.10
3-Methoxy-4-hydroxyphenyl [f]	13		147—148	$C_8H_{10}N_2O_2S$	48.68	48.48	5.18	5.09			14.06	14.14
m-Chlorophenyl [d]		83	118—119	$C_7H_7ClN_2S$	44.75	45.05	3.87	3.78			15.25	14.99
p-Chlorophenyl [d]		62	123—124	$C_7H_7ClN_2S$	45.00	45.05	3.60	3.78			15.14	14.99
p-Acetamidophenyl [g]	6	70	235—240(d.)	$C_9H_{11}N_3OS$	51.71	51.67	5.38	5.30			20.41	20.09
α-Naphthyl [d]		82	96— 98	$C_{11}H_{10}N_2S$	65.30	65.30	4.93	4.99	15.93	15.84	13.82	13.86
β-Naphthyl [e]		65	163—165	$C_{11}H_{10}N_2S$	65.15	65.30	5.08	4.99			13.85	13.86
2-Furyl [d]	40	55	130—131	$C_5H_6N_2OS$	42.28	42.25	4.44	4.26	22.45	22.52	19.84	19.71
2-Thienyl [h]	56	60	155—156	$C_5H_6N_2S_2$	38.11	37.98	3.58	3.83	40.42	40.53	17.83	17.72
2-Pyrryl [d]		77	121—122	$C_5H_7N_3S$	42.66	42.55	5.29	5.00	22.56	22.67	29.82	29.78
3-Indolyl [h]		75	173—174	$C_9H_9N_3S$	56.97	56.54	5.02	4.75	16.85	16.77	22.16	21.98
tert-Butyl [i]		60	93— 94	$C_5H_{12}N_2S$	45.35	45.40	8.99	9.16			21.24	21.20

a. From 10 g of the aldehyde, b. From 0.01 mole of the carboxymethyl dithioate. c. Isolated as the benzylidene derivative (see text). Solvents used for recrystallisation. d) benzene; e) benzene-light petroleum (b.p. 60—100°C); f) ethanol-water; g) ethanol; h) benzene-ethanol; i) light petroleum (b.p. 60—100°C). In most cases the compounds may also be recrystallised from hot water.

razine. We have tried to prepare the benzylidene derivatives of such thiohydrazides by reaction of dithioesters with benzalhydrazone, but without success. The only purely aliphatic thiohydrazide we have been able to prepare is trimethylthioacethydrazide (thiopivalic hydrazide). Phenylthioacetic hydrazide and β-phenylpropionic thiohydrazides were prepared in good yields but the former is decidedly less stable than aromatic thiohydrazides. *N*-Substituted thiohydrazides could be prepared in all cases (see No. V of this series).

The thiohydrazides are colourless substances which are easily soluble in ethanol or benzene and somewhat soluble in water. They are amphoteric substances and therefore soluble in dilute aqueous solutions of strong acids or bases. Their pK_a values are about 10.5 and their pK_b values about 8.5 as determined from titration curves.

A number of other potential methods for the preparation of thiohydrazides have also been tried, but without success.

a. The reaction of hydrazides with phosphorus pentasulfide generally seems to give a thiadiazole instead of a thiohydrazide. However, Profft *et al.*[3] obtained a small yield of picolinic thiohydrazide in this way. We were unable to prepare nicotinic or *iso*nicotinic thiohydrazide by this procedure, but obtained a 6 % yield of thiobenzhydrazide from benzhydrazide and phosphorus pentasulfide.

b. Thioamides react with hydrazine with evolution of hydrogen sulfide, and dihydrotetrazines or thiadiazoles, but no thiohydrazides, are formed. Junghahn [4] obtained dibenzyldihydrotetrazine from phenylthioacetamide and hydrazine, and McMillan *et al.*[5] obtained a thiadiazole from *iso*nicotinic thiamide and hydrazine; we have qualitatively shown that many other thiamides react in a similar way. It seemed, however, possible that the reaction would be different with a hydrazinium salt instead of free hydrazine (*cf.* Galat and Elion [6]), but attempts to prepare thiohydrazides in this way also gave a negative result.

c. *O*-Alkyl monothioates react with hydrazine with evolution of hydrogen sulfide, and no thiohydrazide is formed. From the reaction product of *O*-ethyl thiobenzoate and hydrazine we have isolated diphenyldihydrotetrazine and diphenyltriazole, *i.e.* the same products which are formed by the reaction of hydrazine with ethyl imidobenzoate (Pinner [7]) or with *N*-phenylthiobenzhydrazide (Wuyts [8]). The preparation of *iso*nicotinic thiohydrazide from *O*-ethyl thio*iso*nicotinate has been described in a Japanese patent [9], but we were unable to duplicate this result.

d. At an early stage of this investigation we tried to prepare thioacethydrazide from acethydrazidine and hydrogen sulfide. The lack of success in this case is understandable because it later became evident that thioacethydrazide is not a stable substance. That thiohydrazides may in principle be prepared from hydrazidines has, however, been shown by Zemplén [10], who has prepared a number of *N*-phenyl-thiohydrazides in this way.

e. Some attempts were made to prepare thiohydrazides from *a*-chlorobenzalazine:

$$\begin{array}{l} C_6H_5C=N-N=CHC_6H_5 \\ \quad\quad | \\ \quad\quad Cl \end{array}$$

Table 2. Thioacylhydrazones, RCSNHN=CHR'

R	R'	M.p., °C	Colour	Formula	% N	
					Found	Calc.
Phenyl	*o*-Hydroxyphenyl	155	yellow	$C_{14}H_{12}N_2OS$	11.09	10.93
Phenyl	*m*-Hydroxyphenyl	158	white	$C_{14}H_{12}N_2OS$	11.08	10.93
Phenyl	*o*-Methoxyphenyl	145	white	$C_{15}H_{14}N_2OS$	10.54	10.37
Phenyl	*p*-Methoxyphenyl	84	white	$C_{15}H_{14}N_2OS$	10.36	10.37
Phenyl	*p*-Nitrophenyl	109	pale yellow	$C_{14}H_{11}N_3O_2S$	14.66	14.73
Phenyl	*p*-Acetamidophenyl	187	white	$C_{16}H_{15}N_3OS$	14.19	14.14
Phenyl	*p*-Succinylamino-phenyl	176	white	$C_{18}H_{17}N_3O_3S$	11.88	11.83
Phenyl	*p*-Dimethylamino-phenyl	125	red	$C_{16}H_{17}N_3S$	14.68	14.83
Phenyl	1-Naphthyl	126	white	$C_{18}H_{14}N_2S$	9.74	9.65
Phenyl	2-Naphthyl	132	white	$C_{18}H_{14}N_2S$	9.76	9.65
Phenyl	2-Quinolyl	138	white	$C_{17}H_{13}N_3S$	14.10	14.42
Phenyl	8-Quinolyl	159	white	$C_{17}H_{13}N_3S$	14.14	14.42
Phenyl	1-Phenyl-pyrryl (2)	118	white	$C_{18}H_{15}N_3S$	13.88	13.76
o-Hydroxyphenyl	*p*-Acetamidophenyl	195	white	$C_{16}H_{15}N_3O_2S$	13.50	13.41
o-Hydroxyphenyl	8-Quinolyl	180	white	$C_{17}H_{13}N_3OS$	13.89	13.68
p-Methoxyphenyl	*p*-Acetamidophenyl	172	white	$C_{17}H_{17}N_3O_2S$	12.94	12.84
p-Acetamidophenyl	*p*-Acetamidophenyl	160 (d.)	yellow	$C_{18}H_{18}N_4O_2S$	15.61	15.81
Benzyl	Phenyl	140	white	$C_{15}H_{14}N_2S$	10.95	11.02
Benzyl	*p*-Methoxyphenyl	152	white	$C_{16}H_{16}N_2OS$	9.76	9.85
Benzyl	2,4-Dichlorophenyl	152	white	$C_{15}H_{12}Cl_2N_2S$	8.80	8.66
Benzyl	*p*-Nitrophenyl	171	pale yellow	$C_{15}H_{13}N_3O_2S$	14.13	14.04
Benzyl	*p*-Acetamidophenyl	207	white	$C_{17}H_{17}N_3OS$	13.20	13.50
Benzyl	*o*-Carboxyphenyl	167	white	$C_{16}H_{14}N_2O_2S$	9.56	9.40
Benzyl	1-Naphthyl	160	white	$C_{19}H_{16}N_2S$	9.36	9.21
Benzyl	2-Furyl	98	white	$C_{13}H_{12}N_2OS$	11.55	11.47
2-Furyl	2-Furyl	138	yellow	$C_{10}H_8N_2O_2S$	12.60	12.72
2-Furyl	*p*-Acetamidophenyl	197	yellow	$C_{14}H_{13}N_3O_2S$	14.63	14.63
2-Thienyl	2-Thienyl	138	yellow	$C_{10}H_8N_2S_3$	11.27	11.11
2-Thienyl	*p*-Acetamidophenyl	205	yellow	$C_{14}H_{13}N_3OS_2$	13.89	13.86
2-Pyrryl	2-Quinoxalyl	250 (d.)	brownish yellow	$C_{14}H_{11}N_5S$	24.84	24.90

No reaction could be induced between this compound and hydrogen sulfide, but with potassium xanthate *a*-ethylxanthylbenzalazine was formed:

$$C_6H_5C(S-CS-OC_2H_5)=N-N=CHC_6H_5$$

It was expected that this compound would be split by ammonia with formation of benzaldehyde-thiobenzhydrazone, but no reaction took place. With hydrazine it reacted rapidly with formation of hydrogen sulfide and diphenyldihydrotetrazine; no thiohydrazide could be isolated.

An excess of carboxymethyl dithioate generally leads to formation of a thiadiazole, but in two cases we obtained dithioacylated hydrazines, *viz.* in

the reaction between hydrazine and carboxymethyl *o-iso*butoxydithiobenzoate or *o*-pentyloxydithiobenzoate.

With the purpose of testing them for antibacterial activity, a number of thioacylhydrazones were prepared by condensation of thiohydrazides with aldehydes in aqueous-alcoholic solution [2]. These hydrazones are listed in Table 2.

EXPERIMENTAL

2-Furanthiocarboxhydrazide. a. From carboxymethyl 2-furancarbodithioate. Carboxymethyl 2-furancarbodithioate (2.0 g) was dissolved in 1 N NaOH (10 ml, 1 equiv.) + 10 ml of water. The solution was cooled in ice and hydrazine hydrate (0.5 g, 1 equiv.) was added. The product separated almost immediately and the orange colour of the solution disappeared. A little 1 N HCl was added to bring the pH to 5—6, and the mixture was kept in ice for one hour. The product was then filtered off, washed with water and dried. The crude product (1.15 g) was recrystallised from benzene, yielding 0.75 g (55 %) of colourless crystals with m.p. 128—29°C. After an additional recrystallisation the compound was pure, m.p. 132—133°C.

Most of the other thiohydrazides shown in Table 1 were prepared in the same way. In two cases, *viz.* the *o*-methylthiobenzhydrazide and the *a*-thionaphthoic hydrazide, the reaction between hydrazine and the carboxymethyl ester was rather slow, 1—2 h being needed. In all the other cases the reaction took place in 1—2 min as seen from the disappearance of the colour of the carboxymethylester and the precipitation of the product.

Phenylthioacethydrazide is rather unstable, and prolonged heating should be avoided during recrystallisation. The compound decomposes in a few months when kept at room temperatur (see No. VI of this series).

b. From furfural. A solution of furfural (10 g) in ethanol (30 ml) is heated to 60°C and 44 ml of a solution of ammonium disulfide, prepared according to the directions of Bost and Shealy [11], are added. The solution is heated to boiling for 10 min, decanted from a precipitate and cooled in ice. After addition of 50 ml of ether, concentrated hydrochloric acid is added with stirring until all the dithioacid has been liberated. The dark red ethereal solution is separated and washed with water and then several times with an aqueous solution of hydrazine hydrate (*ca.* 10 %), totalling about 50 ml. The strongly red-brown coloured solutions of the hydrazinium salt are combined and kept for ½—1 h, in the course of which time the colour of the solution fades and a greyish, crystalline product separates. The solution is acidified with acetic acid and filtered. The thiohydrazide is recrystallised from benzene or from water with the addition of active carbon. The thiohydrazide is rather soluble in boiling water, only slightly in cold water. Yield 5.5 g (40 %).

In the same way were prepared (from 10 g of the aldehyde): 4-hydroxythiobenzhydrazide (3.6 g; 26 %), 3-hydroxythiobenzhydrazide (1.2 g; 9 %), 4-acetamidothiobenzhydrazide (0.7 g; 6 %) and 2-thiophenethiocarboxhydrazide (8.0 g; 56 %). No thiohydrazide could be prepared in this way from benzaldehyde, *p-iso*propylbenzaldehyde, *o*-alkoxybenzaldehydes, chlorobenzaldehydes, cinnamic aldehyde, pyridine aldehydes, quinoline aldehydes, *etc.*

o-*Hydroxythiobenzhydrazide.* a. From carboxymethyl *o*-hydroxydithiobenzoate. Attempts to prepare this compound in the same way as furanthiocarboxhydrazide gave an almost quantitative yield of 2,5-di-(*o*-hydroxyphenyl)-1,3,4-thiadiazole (see No. VI of this series). The following procedure was used for the preparation of *o*-hydroxythiobenzhydrazide:

Carboxymethyl *o*-hydroxydithiobenzoate (1.0 g) was dissolved in 1 N NaOH (4.4 ml. 1 equiv.) and water (10 ml). The solution was cooled in ice and added with stirring to hydrazine hydrate (0.44 g, 2 equiv.). The thiohydrazide separated immediately and the mixture became colourless. The pH was brought to 6 with dilute hydrochloric acid and the solution was extracted with ether. The ethereal solution was dried (Na_2SO_4) and the ether removed *in vacuo*. The residue was recrystallised from benzene-light petroleum (b.p. 60—100°C), giving 0.50 g (67 %) of salicylic thiohydrazide, m.p. 95—97°C. After two additional recrystallisations the compound was pure, m.p. 101—102°C.

b. From salicylaldehyde. A solution of hydrazinium 2-hydroxydithiobenzoate, prepared from salicylaldehyde in the same way as described for the dithiofuroate, does not separate crystals because the thiohydrazide is rather soluble in water (on prolonged standing a precipitate consisting of various transformation products of the thiohydrazide separates). After ½ h the solution was acidified with acetic acid and extracted with ether. The thiohydrazide left after evaporation of the ether was recrystallised as above or from tepid water, from which it separates as large colourless crystals. Yield *ca.* 2 g from 10 g salicylaldehyde (14 %).

In the same way 3-methoxy-4-hydroxythiobenzhydrazide was prepared from vanillin.

o-*Methylthiobenzhydrazide.* This hydrazide was obtained as an oil which could not be brought to crystallisation. When the crude thiohydrazide (from 2.26 g of carboxymethyl dithio-*o*-toluate) was treated with benzaldehyde (0.8 g) in ethanol-water 1.9 g (75 %) of the benzylidene derivative was obtained. Two recrystallisations from petroleum ether gave the pure compound as yellow crystals, m.p. 63—65°C. (Found: C 70.80; H 5.21; N 11.03; Calc. for $C_{15}H_{14}N_2S$: C 71.00; H 5.56; N 11.02.)

Thiopivalic hydrazide. Methyl dithiopivaloate (1.0 g) was dissolved in methanol (5 ml). and hydrazine hydrate (0.35 ml) was added. Methanethiol was formed at once, and after 5 min the yellow colour of the dithioester had disappeared. The solvent was removed *in vacuo*, leaving an oil which crystallised on scratching. The product was stirred with water, the pH was brought to 6 with dilute hydrochloric acid, and the crystals were filtered off and recrystallised from petroleum ether. Yield 0.53 g (60 %). This thiohydrazide is rather soluble in water.

The benzylidene derivatives was obtained from thiopivalic hydrazide (0.2 g) dissolved in 1 N hydrochloric acid (5 ml) and a solution of benzaldehyde (0.15 g) in ethanol (5 ml). The compound separated as an oil which crystallised on cooling (0.31 g, 93 %); it was recrystallised from ethanol-water and then from petroleum ether. Colourless crystals, m.p. 100—102°C. (Found: C 65.40; H 7.40; N 12.52. Calc. for $C_{12}H_{16}N_2S$: C 65.50; H 7.35; N 12.72).

Thiobenzhydrazide from methyl dithiobenzoate. Methyl dithiobenzoate (1.0 g) was dissolved in methanol (10 ml), and hydrazine hydrate (0.3 g) was added. After 15 min at room temperature the red colour of the dithioester had disappeared, and the solution smelled strongly of methanethiol. On addition of water and cooling, the thiohydrazide separated as colourless crystals (0.62 g, 70 %).

When ethyl dithiobenzoate was used the reaction was slower and only a 39 % yield of thiobenzhydrazide was obtained. The products were identical with thiobenzhydrazide prepared from carboxymethyl dithiobenzoate (m.p. 72—73°C).

*N,N'-Di-(*o-iso*butyloxythiobenzoyl)hydrazine* and *N,N'-di(*o-*pentyloxythiobenzoyl)-hydrazine.* In attempts to prepare the hydrazides of *o-iso*butyloxythiobenzoic acid and *o*-pentyloxythiobenzoic acid from the carboxymethyl dithioates the hydrazides separated as colourless oils; the reaction mixture was left in an ice box for crystallisation. In the course of three weeks most of the oily products were transformed into intensively yellow crystals, which were separated and recrystallised from ethanol and hexane. Analyses show that these compounds are the dithioacylated hydrazines. (*Iso*butyloxy derivative, Found: C 63.58; H 6.73; N 6.68; S 15.16. Calc. for $C_{22}H_{28}N_2O_2S_2$: C 63.44; H 6.78; N 6.73; S 15.38. Pentyloxy derivative, Found: C 65.30; H 7.13; N 6.64. Calc. for $C_{24}H_{32}N_2O_2S_2$: C 64.84; H 7.26; N 6.30).

a-Ethylxanthylbenzalazine. *a*-Chlorobenzalazine [12] (4.6 g) and potassium xanthate (6.3 g) were dissolved in ethanol (10 ml) and refluxed for 5 h. The solution was filtered hot from the potassium chloride formed in the reaction and cooled in ice. Yield: 4.5 g of colourless crystals which were recrystallised from ethanol-water (4:1). M.p. 80—81°C. (Found: C 61.93; H 4.97, S 19.58, EtO 13.57. Calc.: C 62.14, H 4.91, S 19.51, EtO 13.72)

The compound was recovered unchanged after refluxing an ethanolic ammoniacal solution of it for several hours Addition of hydrazine to an alcoholic solution at room temperature resulted in formation of hydrogen sulfide and diphenyldihydrotetrazine (m.p. 156—157°C; formation of red diphenyltetrazine on exposure to air).

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