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Studies of Thioacids and Their Derivatives

IV. On 1,2,3,4-Thiatriazoles

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Aromatic and heterocyclic thiohydrazides react with nitrous acid to give compounds which according to their infrared spectra and chemical reactions are thiatriazoles and not thioazides. The same compounds can, in most cases, also be obtained by reaction of carboxymethyl dithioates with sodium azide.

Few compounds containing the 1,2,3,4-thiatriazole ring have hitherto been described in the literature (Freund *et al.*[1], Oliveri-Mandalà [2]). In 1952 Crossland, in this laboratory, observed (unpublished) that the sodium salt of carboxymethyl dithiobenzoate reacted with sodium azide in aqueous solution to form a compound with the composition $C_6H_5CSN_3$, which was shown by its infrared spectrum not to be an azide and therefore probably was the isomeric thiatriazole.

This reaction has proved to be a rather general one. We have tried the reaction of all the carboxymethyl dithioates we have prepared with sodium azide. Most of the dithioates reacted well with sodium azide at room temperature (approximate reaction times are given in Table 1) with formation of the corresponding thiatriazoles:

$$RCSSCH_2COO^- + N_3^- \rightarrow RCSN_3 + {}^-SCH_2COO^-$$

In most cases good yields were obtained (Table 1, Method 1, see also the experimental part). Some of the dithioates did not react with sodium azide after several days of standing at room temperature (see further below).

In a number of cases the same compounds were prepared by the reaction of thiohydrazides with nitrous acid (Table 1, Method 2):

$$RCSNHNH_2 + HONO \rightarrow RCSN_3 + 2\ H_2O$$

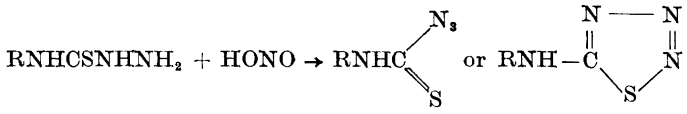
This reaction seems to be the most general one since it gives thiatriazoles in some cases where the dithioates do not react with sodium azide, *viz.* *o*-hydroxyphenyl-, *a*-naphthyl-, 2-pyrryl-, and 3-indolyl-1,2,3,4-thiatriazole.

Table 1. 1,2,3,4-Thiatriazoles, R—C(=N—N)—S—N

R	Yield %		M.p. °C	Formula	Analyses					
					Carbon		Hydrogen		Nitrogen	
	Dithio-ester + NaN_3	Thiohydrazide +HONO			Found	Calc.	Found	Calc.	Found	Calc.
Phenyl [a,b]	80 (24 h)	65	95— 96	$C_7H_5N_3S$					25.76	25.75
o-Tolyl [c]	56 (72 h)		45— 46	$C_8H_7N_3S$	53.85	54.21	4.26	3.98	24.08	23.71
p-Tolyl [d]	95 (24 h)		97— 98	$C_8H_7N_3S$	54.15	54.21	3.92	3.98	23.74	23.70
p-Hydroxyphenyl [e]		88	152—153	$C_7H_5N_3OS$	47.00	46.91	2.88	2.81	23.86	23.45
o-Methoxyphenyl [d]	77 (24 h)		104—105	$C_8H_7N_3OS$	49.85	49.72	3.78	3.65	21.82	21.75
p-Methoxyphenyl [d]	90 (60 h)		104—105	$C_8H_7N_3OS$	49.85	49.72	3.65	3.65	21.90	21.75
m-Chlorophenyl [a,d]	75 (1 h)		83— 85	$C_7H_4ClN_3S$	42.90	42.53	2.50	2.04	21.50	21.26
p-Chlorophenyl [c]	82 (24 h)		101—102	$C_7H_4ClN_3S$	42.60	42.53	2.12	2.04	21.46	21.26
m-Nitrophenyl [b]	66 (½ h)		95— 97	$C_7H_4N_4O_2S$	40.55	40.38	1.93	1.94	27.20	26.92
p-Acetamidophenyl [f]	83 (60 h)		141—142	$C_9H_8N_4OS$	49.30	49.07	3.70	3.66	25.30	25.44
α-Naphthyl [a]	traces	75	46— 47	$C_{11}H_7N_3S$	62.10	61.95	3.40	3.31	19.95	19.71
β-Naphthyl [b]	50 (24 h)	70	96— 97	$C_{11}H_7N_3S$	61.95	61.95	3.37	3.31	19.97	19.71
2-Furyl [a]	43 (3-4 h)	83	63— 64	$C_5H_3N_3OS$	39.00	39.21	1.95	1.97	27.44	27.44
2-Thienyl [d]	67 (72 h)	95	100—102	$C_5H_3N_3S_2$	35.68	35.49	1.93	1.78	24.90	24.84
2-Pyrryl [b]		83	130—131	$C_5H_4N_4S$	39.16	39.46	2.79	2.65	36.74	36.82
3-Indolyl [b]		83	135—136	$C_9H_6N_4S$	53.80	53.45	3.22	2.99	27.73	27.71

Solvents used for recrystallisation: a) ethanol-water; b) benzene-light petroleum (b.p. 60—100°C); c) ether-light petroleum (b.p. 40—60°C); d) light petroleum (b.p. 60—100°C); e) ethanol; f) acetone-water.

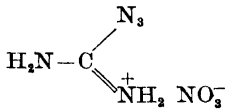
The evidence for the structure proposed by Freund *et al.* for the compounds obtained by nitrosation of thiosemicarbazides has hitherto not been quite unambiguous, the possibility that these compounds are azides not being definitely excluded. In fact Oliveri-Mandalà considered the compounds he prepared to be azides (I):



I II

That this possibility has to be considered seriously is shown by the observation that after reaction of aminoguanidines with nitrous acid often both tetrazoles and the isomeric azides can be isolated (Thiele [3], Jensen and Pedersen [4]).

To decide between the two structures I or II we have studied the infrared spectra of six of the compounds. In all cases these showed complete absence of the characteristic azide band in the 4.5—5 μ range [5]. This eliminates structure I for our compounds and probably also for the compounds of Freund *et al.* For comparison we also took infrared spectra of the nitrosation products of thiosemicarbazide and aminoguanidinium nitrate. The thiosemicarbazide product has no azide band, in accordance with formula II, whereas "diazoguanidinium nitrate", to which Thiele [3] has ascribed the structure III, had a strong band at 4.66 μ. After the completion of this work three papers by Lieber [6] have appeared, confirming structure II for the thiosemicarbazide nitrosation product by infrared and degradative studies.



III

The thiatriazoles do not give colour reaction with iron(III) chloride and are not reduced by hydrogen sulfide, in contrast to the behaviour of azides. Furthermore these compounds do not have thioacylating properties. Thioazides have been proposed as thioacylating agents, but attempts to prepare them were unsuccesful (Mc Omie [7]). It now seems certain that the reactions attempted will only give thiatriazoles without thioacylating properties.

Most of the thiatriazoles prepared were stable at room temperature, but decomposed vigorously when heated to the melting point (and in some cases already during recrystallisation) with formation of a nitrile, sulfur, and nitrogen (see the experimental part). This is in agreement with the finding of Freund and Lieber *et al.* and also does not support structure I, which on heating might be expected to give an *iso*thiocyanate in accordance with the well known behaviour of the corresponding oxygen compounds.

In no cases could thiatriazoles with aliphatic substituents be prepared. Potassium dithioformate and carboxymethyl dithioacetate did not react with sodium azide. Thiopivalic hydrazide, which is the only known aliphatic thiohydrazide (*cf.* Paper No. III of this series), gave an oil on reaction with nitrous acid. This is probably the 5-*tert*-butyl-1,2,3,4-thiatriazole; it is, however, very unstable and decomposes in a few minutes at 0°C with nitrogen evolution and formation of sulfur. Reaction of thiophenylacethydrazide, and thio-β-phenylpropionic hydrazide with nitrous acid also gave oily products which decomposed rapidly. Carboxymethyl dithiophenylacetate and dithio-β-phenylpropionate did not react with sodium azide. Thiosalicylic hydrazide on reaction with nitrous acid gave a solid of melting point 86—88°C (decomp.), it was, however, too unstable to be purified. Carboxymethyl dithiosalicylate reacted slowly with sodium azide with evolution of gas.

EXPERIMENTAL

1,2,3,4-Thiatriazoles from carboxymethyl dithioates and sodium azide

5-Phenyl-1,2,3,4-thiatriazole. Carboxymethyl dithiobenzoate (2.1 g, 0.01 mole) was dissolved in 1 equiv. (10 ml) of 1 N NaOH, and a solution of sodium azide (1.3 g, 0.02 mole) in 10 ml of water was added. After 15 min crystals began to separate, and after 24 h at room temperature the red colour of the carboxymethyl ester had disappeared. The product was filtered off and washed with water. Colourless crystals, yield: 1.3 g (80 %), m.p. 94—95°C. After two recrystallisations from benzene-light petroleum (b.p. 60—100°C) the product was pure. The compound could also be obtained from methyl dithiobenzoate and sodium azide. It is insoluble in water and in aqueous solutions of strong acids or bases and reacts neither with methyl iodide nor with bromine.

In this way all the reactions between carboxymethyl dithioesters and sodium azide were performed. In a few cases it was necessary to add more water to prevent separation of the sodium salt of the carboxymethyl ester. The completion of the reactions was easily seen from the disappearance of the colour of the carboxymethyl ester. Prolonged heating should be avoided during recrystallisations to prevent decomposition. Further data are given in Table 1.

1,2,3,4-Thiatriazoles from thiohydrazides and nitrous acid

5-Phenyl-1,2,3,4-thiatriazole. Thiobenzhydrazide (0.5 g) was dissolved in 7.2 ml (2 equiv.) of 1 N hydrochloric acid. The solution was cooled in ice and stirred, and a solution of 0.25 g (1.1 equiv.) of sodium nitrite in 5 ml of water was added during 5 min. The product separated immediately and was filtered off and washed with water. Recrystallisation from ethanol-water gave 0.35 g (65 %), m.p. 92—94°C.

The same procedure was used in all the other cases where thiatriazoles were prepared from thiohydrazides (Table 1).

Formation of nitriles

p-*Hydroxybenzonitrile.* 5-(*p*-Hydroxyphenyl)-1,2,3,4-thiatriazole (0.46 g) was added in portions to a test tube, which was kept at 150°C in an oil bath. Each addition caused a vigorous evolution of nitrogen. The product was recrystallised from benzene-light petroleum (b.p. 60—100°C) giving 0.24 g (78 %) of colourless crystals with m.p. 103—

106°C. After three additional recrystallisations pure *p*-hydroxybenzonitrile was obtained, m.p. 107—109°C (lit.[8] 113°C). (Found: C 70.40; H 4.20; N 11.62. Calc. for C_7H_5NO: C 70.58; H 4.23; N 11.76).

p-*Acetamidobenzonitrile*. 5-(*p*-Acetamidophenyl)-1,2,3,4-thiatriazole (0.19 g) was heated to 190°C for *ca.* 10 min, until the nitrogen evolution had ceased. The product was recrystallised from water. Yield 0.08 g (58 %), m.p. 201—202°C. An additional recrystallisation gave pure *p*-acetamidobenzonitrile, m.p. 202—203°C (lit.[9] 200°C). (Found: C 67.40; H 4.99; N 17.88. Calc. for $C_9H_8N_2O$: C 67.48; H 5.04; N 17.49).

p-*Methoxybenzonitrile*. 5-(*p*-Methoxyphenyl)-1,2,3,4-thiatrazole (0.35 g) was added in portions to a test tube kept at 130°C in an oil bath. The residue was recrystallised from light petroleum (b.p. 60—100°C) giving 0.16 g (66 %) of colourless crystals with m.p. 54—56°C. Two more recrystallisations provided an analytical sample, m.p. 61—62°C (lit.[10] 59—61°C). (Found: C 72.20; H 5.45; N 10.49. Calc. for C_8H_7NO: C 72.16; H 5.30; N 10.52).

Benzonitrile (isolated as thiobenzamide). 5-Phenyl-1,2,3,4-thiatriazole (1 g) was decomposed at 130°C as described above. The product was dissolved in 1 ml of pyridine + 1 ml of triethylamine. Hydrogen sulfide was passed through the solution for 2 h, and the mixture was then kept overnight. Addition of dilute hydrochloric acid precipitated a yellow solid, which, after two recrystallisations from benzene-light petroleum (b.p. 60—100°C) gave 0.45 g (54 %) of thiobenzamide with m.p. 115—117°C. The mixed melting point with an authentic sample of thiobenzamide showed no depression.

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