Reaction of Mercaptothiocarboxylic Acid with Compounds Containing C=N-Bonds; A Convenient Synthesis of Some 4-Oxotetrahydrothiazole Derivatives[1]

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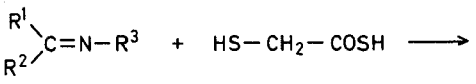
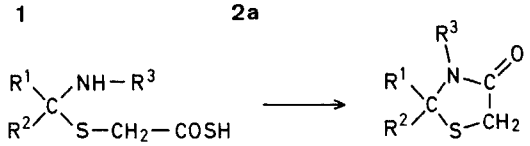
Previously, we have reported on the reactions of mercaptothioacetic acid (**2a**) with compounds containing C=O-bonds to afford 1,3-dithiolanone derivatives[2]. Since the acid **2a** is easily accessible by our method and expected to be a useful synthetic intermediate, it was of interest to investigate extensions of the reactions of **2a**. In this paper, we report the reactions of **2a** with the compounds **1** containing C=N-bonds, such as imines, oximes, and azines, to afford some 4-oxotetrahydrothiazole derivatives **4**.

Several workers have reported that imines[3], oximes[4], or azines[5] react with thioglycollic acid to form 2,3-disubstituted 4-oxotetrahydrothiazoles. However, the compounds **1** used were limited to those derived from aromatic aldehydes, and the reactions of **1** derived from aliphatic aldehydes or from ketones with thioglycollic acid to prepare 2-alkyl- or 2,2-disubstituted-4-oxotetrahydrothiazole derivatives have not been reported in the literature.

The reaction of **2a** with an aldehyde imine **1** was carried out in refluxing ether for 3 h, and the corresponding tetrahydrothiazole derivative **4** was obtained in a good yield (Table 1). Since the compound **3** was considered as an intermediate, the reaction was examined at lower temperature in order to obtain **3**, however, in all cases, this intermediate could not be isolated. Ketone imines such as cyclohexanoneanil reacted similarly with **2a** in refluxing ether for 5 h to give the corresponding derivatives **4**. The reaction of **2a** with aromatic ketone imine gave no product, and the starting materials were recovered.

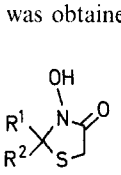


1 **2a**



3 **4**

Oximes and azines also reacted with **2a** to give the 3-hydroxy-4-oxotetrahydrothiazole derivatives **5** and 3-alkylideneamino- or 3-arylideneamino-4-oxotetrahydrothiazole derivatives **6**, respectively (Tables 2, 3). The reaction of an azine with two mol of **2a** also afforded **6**, and no other product was obtained.



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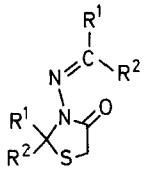

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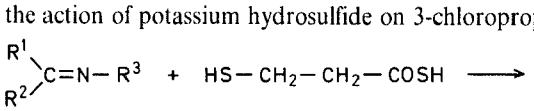
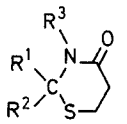
The above reaction was also applied to the synthesis of 4-oxotetrahydro-1,3-thiazine derivatives by the reaction of 3-mercaptothiopropanoic acid (**2b**) with **1**. This acid, which had not been reported in the literature, was prepared by the action of potassium hydrosulfide on 3-chloropropanoyl



1 **2b**



7 R^3 = OH

8 R^3 = $-N=C\begin{matrix}R^1\\R^2\end{matrix}$

Table 1. 4-Oxotetrahydrothiazole Derivatives **4**

Product	R^1	R^2	R^3	Yield [%]	m.p. or b.p./torr	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. m/e (M^+)
4a	*i*-C_3H_7	H	*i*-C_3H_7	77	72–74°/3	$C_9H_{17}NOS$ (187.2)	4.79 (d, 1H); 3.58 (s, 2H); 2.17 (m, 1H); 1.70 (m, 1H); 1.42–0.83 (m, 12H)	187
4b	C_6H_5	H	*n*-C_4H_9	78	142–145°/3	$C_{13}H_{17}NOS$ (235.3)	7.32–7.18 (m, 5H); 5.90 (s, 1H); 3.58 (s, 2H); 1.68–0.77 (m, 9H)	235
4c	C_6H_5	H	C_6H_5	84	131–132°	$C_{15}H_{13}NOS$ (255.3)	7.35–7.15 (m, 10H); 5.96 (s, 1H); 3.78 (s, 2H)	255
4d	4-Cl—C_6H_4	H	C_6H_5	62	137–139°	$C_{15}H_{12}ClNOS$ (289.8)	7.38–7.12 (m, 9H); 6.08 (s, 1H); 3.80 (s, 2H)	289, 291
4e	4-H_3CO—C_6H_4	H	C_6H_5	64	114–115°	$C_{16}H_{15}NO_2S$ (285.3)	7.31–6.75 (m, 9H); 6.01 (s, 1H); 3.75 (s, 2H); 3.65 (s, 3H)	285
4f	4-O_2N—C_6H_4	H	C_6H_5	50	137–139°	$C_{15}H_{12}N_2O_3S$ (300.3)	8.11 (d, 2H); 7.45 (d, 2H); 7.32–7.16 (m, 5H); 6.23 (s, 1H); 3.85 (s, 2H)	300
4g	—$(CH_2)_5$—		C_6H_5	94	172–173°	$C_{14}H_{17}NOS$ (247.3)	7.52–7.06 (m, 5H); 3.57 (s, 2H); 2.16–1.32 (m, 10H)	247
4h	—$(CH_2)_5$—		4-Cl—C_6H_4	82	183–184°	$C_{14}H_{16}ClNOS$ (281.8)	7.50–7.00 (m, 4H); 3.57 (s, 2H); 2.18–1.33 (m, 10H)	281, 283

[a] All products gave satisfactory microanalyses (C, ±0.30%; H, ±0.29%; N, ±0.29%; S, ±0.29%).

Table 2. 3-Hydroxy-4-oxotetrahydrothiazoles **5**

Product	R^1	R^2	Yield [%]	m.p.	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. m/e (M^+)
5a	CH_3	H	75	99–100°	$C_4H_7NO_2S$ (133.1)	9.90 (s, 1H); 4.90 (q, 1H); 3.50 (s, 2H); 1.62 (d, 3H)	133
5b	*i*-C_3H_7	H	94	85–88°	$C_6H_{11}NO_2S$ (161.2)	9.96 (s, 1H); 4.86 (d, 1H); 3.52 (s, 2H); 1.74 (m, 1H); 1.06 (d, 6H)	161
5c	C_6H_5	H	89	157–159°	$C_9H_9NO_2S$ (195.2)	10.20 (s, 1H); 7.40–7.36 (m, 5H); 5.93 (s, 1H); 3.68 (s, 2H)	195
5d	4-H_3CO—C_6H_4	H	82	147–148°	$C_{10}H_{11}NO_3S$ (225.2)	10.21 (s, 1H); 7.39–7.25 (m, 4H); 6.01 (s, 1H); 3.72 (s, 2H); 3.68 (s, 3H)	225
5e	CH_3	CH_3	78	102–104°	$C_5H_9NO_2S$ (147.1)	9.88 (s, 1H); 3.56 (s, 2H); 1.68 (s, 6H)	147
5f	—$(CH_2)_5$—		87	167–168°	$C_8H_{13}NO_2S$ (187.2)	10.10 (s, 1H); 3.46 (s, 2H); 2.10–1.23 (m, 10H)	187

[a] All products gave satisfactory microanalyses (C, ±0.29%; H, ±0.25%; N, ±0.26%; S, ±0.28%).

Table 3. 3-Alkylideneamino- or 3-Arylideneamino-4-oxotetrahydrothiazoles **6**

Product	R^1	R^2	Yield [%]	m.p. or b.p./torr	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. m/e (M^+)
6a	CH_3	H	87	87–88°/3	$C_6H_{10}N_2OS$ (158.2)	8.26 (q, 1H); 4.90 (q, 1H); 3.50 (s, 2H); 2.02 (d, 3H); 1.61 (d, 3H)	158
6b	*i*-C_3H_7	H	84	93–95°/3	$C_{10}H_{18}N_2OS$ (214.3)	8.28 (d, 1H); 4.87 (d, 1H); 3.56 (s, 2H); 2.50 (m, 1H); 1.72 (m, 1H); 1.21–0.92 (m, 12H)	214
6c	C_6H_5	H	94	158–159°	$C_{16}H_{14}N_2OS$ (282.3)	8.38 (s, 1H); 7.62–7.14 (m, 10H); 6.10 (s, 1H); 3.78 (s, 2H)	282
6d	4-H_3C—C_6H_4	H	85	142–144°	$C_{18}H_{18}N_2OS$ (310.3)	8.30 (s, 1H); 7.61–6.94 (m, 8H); 6.08 (s, 1H); 3.76 (s, 2H); 2.32 (s, 3H); 2.28 (s, 3H)	310
6e	4-H_3CO—C_6H_4	H	86	129–131°	$C_{18}H_{18}N_2O_3S$ (342.3)	8.40 (s, 1H); 7.64–6.96 (m, 8H); 6.08 (s, 1H); 3.80 (s, 2H); 3.94 (s, 3H); 3.70 (s, 3H)	342
6f	CH_3	CH_3	52	96–98° 77–80°/1	$C_8H_{14}N_2OS$ (186.2)	3.60 (s, 2H); 2.17 (s, 3H); 1.90 (s, 3H); 1.58 (s, 6H)	186

[a] All products gave satisfactory microanalyses (C, ±0.29%; H, ±0.25%; N, ±0.27%; S, ±0.30%).

Table 4. 4-Oxotetrahydro-1,3-thiazines **7** and **8**

Product	R^1	R^2	Yield [%]	m.p. or b.p./torr	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. m/e (M^+)
7a	C_6H_5	H	74	174–176°	$C_{10}H_{11}NO_2S$ (209.2)	9.34 (s, 1H); 7.36–7.25 (m, 5H); 5.78 (s, 1H); 3.27–2.63 (m, 4H)	209
7b	4-H_3CO—C_6H_4	H	50	168–171°	$C_{11}H_{13}NO_3S$ (239.2)	9.40 (s, 1H); 7.40–7.25 (m, 4H); 5.84 (s, 1H); 3.30–2.62 (m, 4H); 3.62 (s, 3H)	239
7c	CH_3	CH_3	63	122–124°	$C_6H_{11}NO_2S$ (161.2)	9.28 (s, 1H); 3.02–2.67 (m, 4H); 1.68 (s, 6H)	161
7d	—$(CH_2)_5$—		53	189° (dec)	$C_9H_{15}NO_2S$ (201.2)	9.10 (s, 1H); 3.11–2.78 (m, 4H); 2.10–1.25 (m, 10H)	201
8a	CH_3	H	81	90–91°/1	$C_7H_{12}N_2OS$ (172.2)	8.04 (q, 1H); 4.82 (q, 1H); 3.13–2.55 (m, 4H); 2.00 (d, 3H); 1.56 (d, 3H)	172
8b	C_6H_5	H	78	122–124	$C_{17}H_{16}N_2OS$ (296.3)	8.28 (s, 1H); 7.42–7.24 (m, 10H); 6.12 (s, 1H); 3.10–2.74 (m, 4H)	296
8c	4-H_3C—C_6H_4	H	79	136–138	$C_{19}H_{20}N_2OS$ (324.4)	8.18 (s, 1H); 7.46–7.02 (m, 8H); 6.00 (s, 1H); 3.04–2.54 (m, 4H); 2.30 (s, 3H); 2.25 (s, 3H)	324

[a] All products gave satisfactory microanalyses (C, ±0.29%; H, ±0.27%; N, ±0.28%; S, ±0.28%).

chloride. The new compounds **7** and **8** were obtained from the reaction of **2b** with an oxime or azine, respectively (Table 4). Imines, however, did not react with **2b** and the starting materials were recovered.

Preparation of 4-Oxotetrahydrothiazoles 4, 5, or 6; General Procedure:

To a solution of compound **1** (0.1 mol) in ether (150 ml) acid **2a** (0.1 mol) is added at room temperature and the mixture is then refluxed for 3–5 h. At the end of this time, evolution of hydrogen sulfide ceases. The solution is concentrated to about 50 ml and cooled. The solid which separates from the solution is collected and recrystallized from ligroin or ethanol to give product **4**, **5**, or **6**. The results are shown in Table 1, 2 or 3. If no solid is obtained, the solvent is removed and the residue is vacuum distilled.

Preparation of 3-Mercaptothiopropanoic Acid (2b):

A solution of potassium hydroxide (90 g) in ethanol (90%, 300 ml) is saturated with hydrogen sulfide at 0°, and 3-chloropropanoyl chloride (25 g, 0.2 mol) is added slowly at about −10°. After the precipitated potassium chloride is removed, the filtrate is concentrated to about 100 ml, acidified with 3 normal hydrochloric acid, and extracted with ether. Distillation gives **2b**; yield: 16 g (67%); b.p. 60–61°/4 torr.

$C_3H_6OS_2$	calc.	C 29.51	H 4.95	S 52.42
(122.1)	found	29.22	5.11	52.19

I.R.: $\nu_{max} = 2550$; 1695 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 5.06$ (s, 1H); 3.17–2.55 (m, 4H); 1.82 ppm (t, 1H).

Preparation of 4-Oxotetrahydro-1,3-thiazines 7 or 8; General Procedure:

To a solution of compound **1** (0.1 mol) in benzene (150 ml) the acid **2b** (0.1 mol) is added at room temperature and the mixture is then refluxed for 5–8 h. After most of the solvent has been removed, the residue is recrystallized from hexane or ethanol to give **7** or **8**. In some instances, the product separates from the reaction solution on cooling. The results are summarized in Table 4.

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