The Syntheses of 1,3-Oxathiolan-5-one Derivatives

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The condensations of aldehydes with thioglycollic acid or α-mercaptopropionic acid were carried out; 2-substituted- or 2,4-disubstituted-1,3-oxathiolan-5-ones were thus obtained. The intermediate of the reaction was isolated only when phenylglyoxal and thioglycollic aicd were used.

We can expect to obtain the 1,3-oxathiolan-5-one derivative by the reaction of α-mercapto acid with aldehyde. However, this heterocyclic system has rarely appeared in the literature except for the 2-trihalomethyl-[1,2] and 2,4,4-triaryl-derivatives.[3-5] In this paper, the syntheses of several 1,3-oxathiolan-5-one derivatives (III) and related compounds will be described.

Acetaldehyde (Ia), propionaldehyde (Ib), and butyraldehyde (Ic) were used as the aliphatic aldehydes and were allowed to react with thioglycollic acid (IIa). The reactions were first carried out in refluxing benzene with an azeotropic removal of the water eliminated in the reaction (Method A). The products thus obtained are presented in Table 1. The results of elementary analyses and the NMR spectra were well in accord with the expected structures. When acetic anhydride was used as the dehydrating agent at 60°C, the product, III, was contaminated with diacetoxyalkane and the separation of the two compounds was almost impossible.

$$\underset{\text{(I)}}{RCHO} + \underset{\text{(IIa)}}{HSCH_2COOH} \longrightarrow \underset{\text{(III)}}{RCH\begin{cases} S-CH_2 \\ | \\ O-CO \end{cases}}$$

The III compounds were also obtained by stirring I and IIa at room temperature without any solvent or dehydrating agent, followed by direct distillation (Method B). As may be seen in Table 1, the yields of the products were here somewhat higher than those given by Method A.

The condensation of IIa with benzaldehyde (Id), *p*-nitrobenzaldehyde (Ie), or *p*-tolualdehyde (If) by Method B was unsuccessful. That is, the bisthioglycollic acid derivative (IV), a condensation product of one mole of I and two of IIa, was thus formed in a nearly quantitative yield. When Method A was adopted, large quantities of the starting materials were recovered, while III was obtained in only about a 15% yield. Therefore, *p*-toluenesulfonic acid was used as the catalyst and the reaction was carried out in refluxing benzene (Method C). Both III and IV were formed in about 30% yields (Table 2).

$$I + IIa \longrightarrow III + \underset{\text{(IV)}}{RCH\begin{cases} SCH_2COOH \\ SCH_2COOH \end{cases}}$$

Since Compound V was considered as an intermediate in the reaction, the isolation of V was attempted.

TABLE 1. $RCHO + HSCH_2COOH \longrightarrow RCH\begin{cases} S-CH_2 \\ | \\ O-CO \end{cases}$ (I) (IIa) (III)

Aldehyde	R	Method	Product (1,3-oxathiolan-5-one)	Yield (%)	Bp (°C/mmHg)
Ia	CH_3	A B	IIIa: 2-methyl-	20.5 36.5	71—73/6
Ib	C_2H_5	A B	IIIb: 2-ethyl-	42.3 43.8	74—75/5
Ic	C_3H_7	A B	IIIc: 2-propyl-	49.3 53.8	90—92/5

	NMR spectral data[a]			Anal (%) Calcd C	H	S	Found C	H	S
IIIa	5.66 (q, 1H)	3.76 (s, 2H)	1.68 (d, 3H)	40.68	5.12	27.10	40.40	5.33	26.88
IIIb	5.48 (t, 1H) 1.03 (t, 3H)	3.68 (s, 2H)	2.23—1.67 (m, 2H)	45.45	6.10	24.22	45.28	6.14	24.30
IIIc	5.55 (t, 1H) 1.00 (t, 3H)	3.68 (s, 2H)	2.13—1.19 (m, 4H)	49.31	6.90	21.90	49.10	7.17	21.72

a) Parts per million downfield from tetramethylsilane; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

1) A. Luttringhaus and H. Prinzbach, *Ann. Chem.*, **624**, 79 (1959).
2) H. E. Simmons and D. W. Wiley, *J. Amer. Chem. Soc.*, **82**, 2288 (1960).
3) A. Bistrzycki and B. Brenken, *Helv. Chim. Acta*, **3**, 447 (1920).
4) A. Romo de Vivar and J. Romo, *J. Org. Chem.*, **24**, 1490 (1959).
5) C. Pedersen, *Acta Chem. Scand.*, **20**, 2314 (1966).

Table 2. $RCHO + HSCH_2COOH \longrightarrow RCH(S-CH_2)(O-CO) + RCH(SCH_2COOH)_2$

(I) (IIa) (III) (IV)

Aldehyde	R	Method	Product	Yield (%)	Mp (°C)
Id	C_6H_5	A	IIId	16.8	57—58
		C	IIId+IVd	31.3+36.5	
Ie	p-NO_2-C_6H_4	A	IIIe	13.8	85
		C	IIIe+IVe	22.5+47.6	
If	p-CH_3-C_6H_4	A	IIIf	19.1	99—100
		C	IIIf+IVf	36.1+32.8	

Product (1,3-oxathiolan-5-one)	NMR spectral data[a]			Anal (%) Calcd C	H	S	Found C	H	S
IIId: 2-phenyl-	7.33 (s, 5H)	6.34 (s, 1H)	3.65 (s, 2H)	60.00	4.48	17.77	59.71	4.70	18.01
IIIe: 2-p-nitrophenyl-	8.30 (d, 2H) 3.86 (s, 2H)	7.62 (d, 2H)	6.55 (s, 1H)	48.01	3.13	14.23	48.00	3.13	14.45
IIIf: 2-p-methylphenyl-	7.37 (d, 2H) 3.78 (s, 2H)	7.16 (d, 2H) 2.36 (s, 3H)	6.44 (s, 1H)	61.85	5.19	16.48	62.01	5.48	16.33

a) Parts per million downfield from tetramethylsilane in $CDCl_3$; s=singlet, d=doublet.

Table 3. $RCHO + HSCH(CH_3)-COOH \longrightarrow RCH(S-CH(CH_3)-)(O-CO)$

(I) (IIb) (VI)

Aldehyde	R	Method	Product (1,3-oxathiolan-5-one)	Yield (%)	Bp (°C/mmHg)
Ia	CH_3	B	VIa: 2,4-dimethyl-	30.9	59—60/3
Ib	C_2H_5	B	VIb: 2-ethyl-4-methyl-	33.9	68—69/3
Ic	C_3H_7	B	VIc: 2-propyl-4-methyl-	55.7	84—86/3

	NMR spectral data			Anal (%) Calcd C	H	S	Found C	H	S
VIa	5.58 (q, 1H) 1.51 (d, 3H)	4.10 (q, 1H)	1.65 (d, 3H)	45.45	6.10	24.22	45.21	6.38	24.46
VIb	5.43 (t, 1H) 1.49 (d, 3H)	4.05 (q, 1H) 1.01 (t, 3H)	2.17—1.67 (m, 2H)	49.31	6.90	21.89	49.23	7.16	21.70
VIc	5.47 (t, 1H) 1.48 (d, 3H)	4.03 (q, 1H) 0.97 (t, 3H)	2.15—1.20 (m, 4H)	52.49	7.55	19.98	52.55	7.81	20.23

In all cases involving the above aldehyde, however, this attempt failed. However, phenylglyoxal (Ig) reacted readily with IIa to give (1-hydroxyphenacyl)-thioacetic acid (V, R=C_6H_5CO), which was then converted to IIIg by means of dehydration with acetic anhydride at room temperature:

$RCH(SCH_2COOH)(OH)$ (V)

The reaction of aliphatic aldehyde with α-mercapto-propionic acid (IIb) was also examined (Method B); the corresponding 4-methyl-1,3-oxathiolan-5-one derivatives (VI) were thus obtained (Table 3).

The above reaction was then applied to the synthesis of the 1,3-oxathian-6-one derivative (VIII) from β-mercaptopropionic acid (IIc) and aldehyde. The hetero-ring VIII has not been reported in the literature. Although VIII was not obtained by the reaction of IIc with Ia—f, it *was* obtained when Ig or chloral (Ih) was used as the aldehyde. In both cases, the intermediates (VII) were isolated in high yields.

$RCHO + HSCH_2CH_2COOH \longrightarrow$

(I) (IIc)

$RCH(OH)-SCH_2CH_2COOH \longrightarrow RCH(S-CH_2-CH_2-)(O-CO)$

(VII) (VIII)

Experimental

Method A. Into a solution of 0.2 mol of aldehyde (I) and 100 m*l* of benzene, 0.1 mol of thioglycollic acid (IIa)

was added, and then the mixture was stirred for 2 hr at room temperature. The mixture was then refluxed for about 5 hr, the water formed in the reaction being removed continuously by azeotropic distillation. The reaction mixture was washed with a 10% sodium carbonate aqueous solution. Distillation gave the products shown in Table 1.

Method B. Into 0.1 mol of I, 0.1 mol of IIa was added slowly and stirred for 7 hr at room temperature. When the mixture was then distilled, a fraction boiling at 60—110°C/5 mmHg was collected. The distillate was washed with a sodium carbonate solution and then redistilled.

The reaction of α-mercaptopropionic acid (IIb) with aldehyde was carried out in the same manner. The results are shown in Table 3.

Method C. A mixture of 0.2 mol of I, 0.1 mol of IIa, about 0.1 g of *p*-toluenesulfonic acid, and 100 m*l* of benzene was refluxed for about 10 hr, cooled, and washed with a sodium carbonate solution. The benzene was then removed, and the residue was recrystallized from *n*-hexane to give III.

By the acidification of the alkaline solution with hydrochloric acid, IV was precipitated. As IV consists entirely of known compounds,[6] they were confirmed, by studying their melting points and neutralization equivalents to be benzylidenebisthioglycollic acid (IVd) (mp 124°C), *p*-nitrobenzylidenebisthioglycollic acid (IVe) (mp 160—161°C), and *p*-methylbenzylidenebisthioglycollic acid (IVf) (mp 123—125°C). The results are summarized in Table 2.

(1-Hydroxyphenacyl)thioacetic acid (V). To a solution of 0.1 mol of phenylglyoxal (Ig) in 50 m*l* of benzene, 0.1 mol of IIa was added, after with the mixture was stirred for 2 hr at room temperature. The product thus precipitated was collected by filtration and recrystallized from toluene to give V; yield, 81.0%; mp 121°C. Found: C, 52.86; H, 4.31; S, 14.28%; mol wt (neutralization equivalent), 230.4. Calcd for $C_{10}H_{10}O_4S$: C, 53.10; H, 4.46; S, 14.15%; mol wt, 226.2.

2-Benzoyl-1,3-oxathiolan-5-one (IIIg). A solution of 0.05 mol of V, 0.15 mol of acetic anhydride, and 200 m*l* of benzene was stirred at room temperature until the white solid disappeared. When the benzene was then removed under reduced pressure, the residue was poured into a 10% sodium carbonate solution. The product thus precipitated was collected by filtration and recrystallized from ligroin; yield, 58.3%; mp 93—94°C. Found: C, 57.83; H, 3.84; S, 15.33%. Calcd for $C_{10}H_8O_3S$: C, 57.69; H, 3.87; S, 15.37%.

3-(1-Hydroxyphenacyl)thiopropionic Acid (VIIa) and 3-(1-Hydroxy-2,2,2-trichloroethyl)thiopropionic Acid (VIIb). As in the preparation of V, 19.8 g (or 21.4 g) of VIIa (or VIIb) were obtained from 0.1 mol of phenylglyoxal (Ig) (or chloral (Ih)) and 0.1 mol of β-mercaptopropionic acid (IIc). VIIa: yield, 82.5%; mp 107—108°C (recrystallized from toluene). Found: C, 55.23; H, 5.01; S, 13.26%; mol wt (neutralization equivalent), 225.7. Calcd for $C_{11}H_{12}O_4S$: C, 55.00; H, 5.04; S, 13.32%; mol wt, 240.2. VIIb: yield, 84.5%; mp 82—83°C (from ligroin). Found: C, 23.65; H, 2.91; S, 12.88; Cl, 42.08%; mol wt, 245.7. Calcd for $C_5H_7O_3SCl_3$: C, 23.69; H, 2.78; S, 12.65; Cl, 41.95%; mol wt, 253.5.

2-Benzoyl-1,3-oxathian-6-one (VIIIa) and 2-Trichloromethyl-1,3-oxathian-6-one (VIIIb). As in the preparation of IIIg, VIIIa (or VIIIb) was obtained from VIIa (or VIIb). VIIIa: yield, 59.6%; mp 86—87°C (from ligroin). Found: C, 59.27; H, 4.55; S, 14.21%. Calcd for $C_{11}H_{10}O_3S$: 59.46; H, 4.54; S, 14.40%. VIIIb: yield, 48.5%; mp 69—70°C (from hexane). Found: C, 25.58; H, 2.36; S, 13.71; Cl, 44.88%. Calcd for $C_5H_5O_2SCl_3$: C, 25.50; H, 2.14; S, 13.61; Cl, 45.16%.

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6) J. Bongartz, *Ber.*, **21**, 478 (1888).