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Synthesis of 2-Ethoxy-1, 3-oxathiolane and 2-Ethoxy-1, 3-dithiolane and Their Some Reactions

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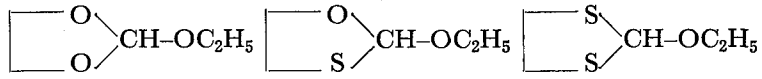
The synthesis of 2-ethoxy-1, 3-oxathiolane(**II**) and 2-ethoxy-1, 3-dithiolane(**III**) from ethyl orthoformate by transesterification reaction was described. The stability toward a trace amount of aqueous acid was found to decrease in the order: 2-ethoxy-1, 3-dioxolane(**I**)>**II**>**III**, and the disproportionation products (or its hydrolysis product) were isolated from the reaction with **II** or **III**. In the reaction with n–BuMgBr, **I** gave 1-ethoxy-1-[2-(hydroxy)ethoxy]pentane and 2-butyl-1, 3-dioxolane, and **II** gave 2-butyl-1, 3-oxathiolane. On the other hand, in the reaction with n–BuLi, both **I** and **II** afforded 5-nonanol and 5-butyl-5-nonanol, and **III** afforded two corresponding thiols. Probable pathways for these transformations are briefly considered.

INTRODUCTION

The chemistry of several kinds of five-membered ring acetals and ketals, such as 1, 3-dioxolanes, 1, 3-oxathiolanes,[1] and 1, 3-dithiolanes[1] have been studied extensively. These compounds are good protective groups for aldehydes and ketones,[2] and are known to be stable to most alkaline and neutral reactions. On the other hand, the action of Grignard reagents or organolithium compounds on certain 1, 3–dioxolanes[3,4] and that of phenyllithium on a 1, 3-dithian[5] lead to ring-cleavage products. In contrast, no descriptions on five-membered orthoesters and thioesters, which correspond to the 2-alkoxy derivatives of the above acetals, are available, except for that on 2-alkoxy-1, 3-dioxolanes.

In this paper, we wish to report the synthesis of two mixed cyclic orthoformates, 2-ethoxy-1, 3-oxathiolane(**II**) and 2-ethoxy-1, 3-dithiolane(**III**), and the results on the reaction of butylmagnesium bromide or butyllithium with these cyclic compounds, including 2-ethoxy-1, 3–dioxolane(**I**) for comparison. Since the fact is known that the disproportionation of acyclic mixed orthoformates, $HC(OC_2H_5)_2SR$, is accelerated by the presence of a trace amount of an acidic substance,[6] the behavior of **II** and **III** toward a trace amount of hydrochloric acid is also examined.



(I) **(II)** **(III)**

RESULTS AND DISCUSSION

Synthesis of II and III. The method developed by Baganz and Domaschke[7]

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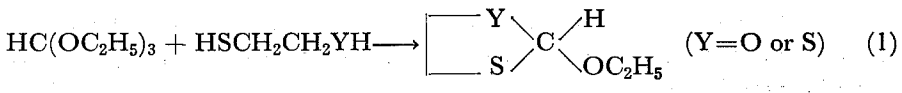
for the synthesis of 2-alkoxy-1, 3-dioxolanes, which involves the transesterification of alkyl orthoformates with 1, 2-ethanediol, was applied to the preparation of **II** and **III**.



$$HC(OC_2H_5)_3 + HSCH_2CH_2YH \longrightarrow \text{(Y, S, C, H, OC}_2\text{H}_5\text{)} \quad (Y=O \text{ or } S) \qquad (1)$$

Though the optimum conditions for the reaction were not ascertained, the yields were generally not so high. As catalysts for these reactions acids as mild as acetic and benzoic acids were satisfactory, and sulfuric acid which is known as an effective catalyst for the preparation of **I**[7] was not suitable for these reactions(Tables I and II).

Table I. 2-Ethoxy-1, 3-oxathiolane from 2-Mercaptoethanol and Ethyl Orthoformate

Acid Catalyst[a]	Yield (%)
$C_6H_5CO_2H$	63
CH_3CO_2H	68
$ClCH_2CO_2H$	49
p-$CH_3C_6H_4SO_3H$	trace
H_3PO_4	18
conc. HCl	18
conc. H_2SO_4	trace
$BF_3\cdot(C_2H_5)_2O$	trace

a) In all runs ca. 1 weight % of catalyst (based on total amount of reactants) was used.

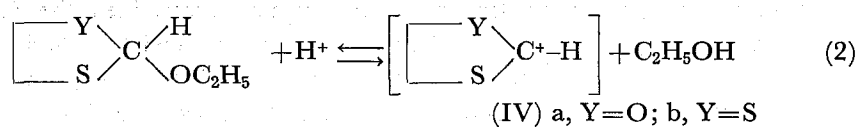
Table II. 2-Ethoxy-1, 3-dithiolane from 1, 2-Ethanedithiol and Ethyl Orthoformate

Acid Catalyst[a]	Yield (%)
$C_6H_5CO_2H$	19
CH_3CO_2H	30
$ClCH_2CO_2H$	17
p-$CH_3C_6H_4SO_3H$	trace
conc. H_2SO_4	trace

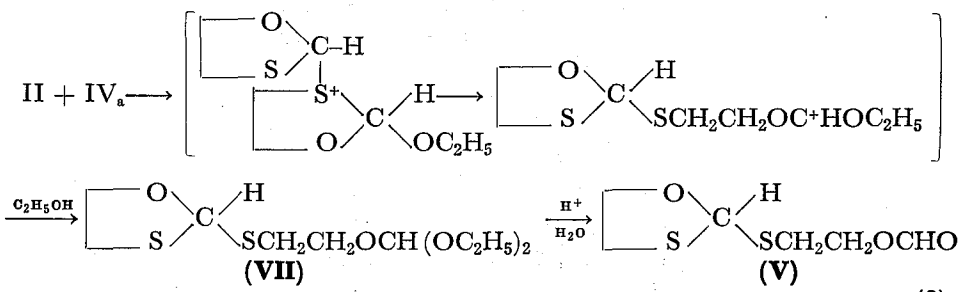
a) ca. 1% of catalyst was used.

Acid-Catalyzed Transformation of II and III. On standing for several days at room temperature **II** became gradually viscous. This change was accelerated by addition of a trace amount of conc. hydrochloric acid, and a liquid product was isolated. The data of its NMR spectrum and of elemental analyses led to 2-[(1, 3-oxathiolan-2-yl)thio]ethyl formate(**V**) as the structure of this product. A similar behavior was also observed for **III**. Addition of a trace amount of conc. hydrochloric

acid to **III** resulted in an exothermic reaction leading to a colorless crystalline product. The analysis of the NMR spectrum defined the product as 2, 2′-(ethylenedithio)di-1, 3-dithiolane(**VI**). In contrast, **I** did not show any transformation at least under similar conditions and most of **I** was recovered. Hence it was found that the stability of three orthoformates toward a trace amount of aqueous acid decrease in the order: **I**>**II**>**III**. For the formation of **V** from **II** and that of **VI** from **III**, a possible rationalization for each is given below.



(IV) a, Y=O; b, Y=S (2)



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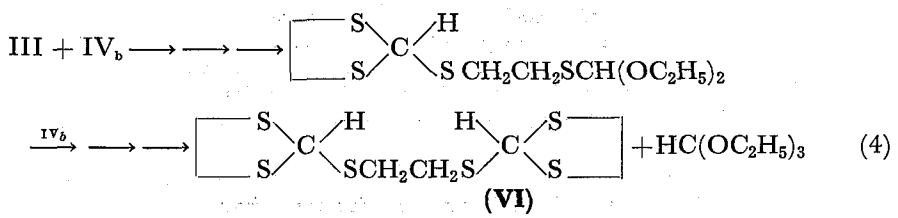


(4)

In the acid-catalyzed hydrolysis of 2-methoxy-1, 3-dioxolane, it has been confirmed that the reaction occurs through initial loss of the exocyclic methoxyl group to give a 1, 3-dioxolenium ion, and that an initial ring C–O bond cleavage can be ruled out as a principal reaction pathway.[8] A route involving the formation of the same cation at the first step is proposed in the reaction of 2-methoxy-1, 3-dioxolane with trityl chloride.[9] Hence the initial formation of the cations **IV** from **II** and **III** would be reasonable. The subsequent attack of another molecule of **II** or **III** on **IV** takes place at the ring S atom. A rather high stability of **I** toward a trace of protic acid, compared with that of **II** or **III**, can be ascribed to the weak nucleophilicity of the O atom in the substrate. A difference in reactivities of the cations **IV** should also participate, *i.e.*, a more stable $\mathbf{IV}_a$ would be less reactive than $\mathbf{IV}_b$, because the cation $ROCH_2^+$ is known to be more stable (by resonance) than $RSCH_2^+$ from the data on acid hydrolysis of chloromethyl ethyl ether and sulfide.[10] It would be worthwhile to note that the disproportionation of **II** was incomplete and the acid hydrolysis of an intermediate ortho ester **VII** leading to **V** preceded the attack of $\mathbf{IV}_a$ on **VII**, whereas with **III** dis-

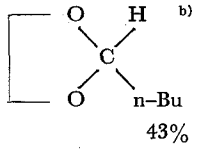
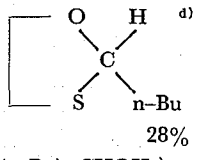
proportionation proceeded completely to afford **VI**. Such a contrast may also be explained by two reasons described above.

Reactions of I, II, and III with n-BuMgBr and with n-BuLi. Both results are presented in Tables III and IV respectively. All of Grignard reactions shown in Table III were carried out under identical conditions (in ether, at 25°C, during 3 hr, under a nitrogen atmosphere), for making a comparison between the cyclic orthoformate **I** and mixed one **II** or **III**.[11]

As can be seen from Table III, when an equivalent amount of n-BuMgBr in ether was allowed to react with **I**, only a β-hydroxy acetal, $HOCH_2CH_2OCH(n\text{-Bu})OC_2H_5$, was formed with ring cleavage, as in the case of 1, 3-dioxolanes.[3] On the other hand, **II** and **III** did not react with the reagent to afford any product. When five equivalent amounts of the Grignard reagent was used, **I** afforded the β-hydroxy acetal and a ring substitution product, 2-butyl-1, 3-dioxolane, the latter of which was the originally expected one. **II** afforded only the substitution product. However, **III** did not react to give any product under at least given reaction conditions.

All of the reactions shown in Table IV were also carried out under identical conditions (in n-hexane, at 25°C, during 3 hr, under a nitrogen atmosphere). The reaction with n-BuLi afforded the products with ring cleavage, which differ from those of the Grignard reaction, *i.e.*, the isolated products from **I** or **II** were 5-nonanol and

Table III. Reaction of the Cyclic Orthoformates with n-BuMgBr

Orthoformate (0.05 mol)	Products and Yields	
	n-BuMgBr (0.05 mol)	n-BuMgBr (0.25 mol)
I	$HOCH_2CH_2OCH(n\text{-Bu})OC_2H_5$[a] 43%	$HOCH_2CH_2OCH(n\text{-Bu})OC_2H_5$[a] 30%  43%
II	$(n\text{-Bu})_2CHOH$[c] trace	 28% $(n\text{-Bu})_2CHOH$[c] 3%
III	unreacted	unreacted

a) A new compound. Bp 116.5~118°C/20 mmHg. *Anal.* Found: C, 60.99; H, 11.56%. Calcd for $C_9H_{20}O_3$: C, 61.33; H, 11.44%. NMR(CCl_4) δ4.61 (t, 1H), 4.05~3.40 (m, 6H), 2.78 (broad s, 1H), 1.90~0.80 (m, 12H). b) Bp 64°C/25 mmHg. *Anal.* Found: C, 64.59; H, 10.73%. Calcd for $C_7H_{14}O_2$:C, 64.58; H, 10.84%. NMR(CCl_4) δ4.99 (t, 1H), 4.30~3.75 (m, 4H), 1.85~0.74 (m, 9H). c) Bp 95°C/17.5 mmHg (Lit.[12] 103°C/27 mmHg). d) Bp 88~89°C/18.5 mmHg. *Anal.* Found: C, 57.01; H,9.58%. Calcd for $C_7H_{14}OS$: C, 57.48; H, 9.65%. NMR(CCl_4) δ5.00 (t, 1H), 4.47~4.10 (m, 1H), 3.95~3.50 (m, 1H), 3.10~2.83 (m, 2H), 2.05~0.78 (m, 9H).

Table IV. Reaction of the Cyclic Orthoformates with n-BuLi

Orthoformate (0.05 mol)	Products and Yields	
	n-BuLi (0.05 mol)	n-BuLi (0.15mol)
I	$(n\text{-Bu})_2$ CHOH[a] 28%	$(n\text{-Bu})_2$ CHOH[a] 32%; $(n\text{-Bu})_3$ COH[b] 4%
II	$(n\text{-Bu})_2$ CHOH[a] 22%; $(n\text{-Bu})_3$ COH[b] 14%	$(n\text{-Bu})_2$ CHOH[a] 36%; $(n\text{-Bu})_3$ COH[b] 19%
III	$(n\text{-Bu})_2$ CHSH[c] 16%; $(n\text{-Bu})_3$ CSH[d] 10%	$(n\text{-Bu})_2$ CHSH[c] 43%; $(n\text{-Bu})_3$ CSH[d] 10%

a) See c) in Table III. b) Bp 82~83°C/2~3 mmHg (Lit.[13] 124~125°C/12 mmHg). c) Bp 105~108°C/34 mmHg (Lit.[14] 72°C/ 7 mmHg). d) A new compound. Bp 144~147°C/31 mmHg. *Anal.* Found: C, 72.16; H, 12.58%. Calcd for $C_{13}H_{28}S$: C, 72.14; H, 13.04%. NMR($CDCl_3$) δ 3.26 (s, 1H), 2.65~0.66 (m, 27H).

5-butyl-5-nonanol, and those from **III** were 5-nonanethiol and 5-butyl-5-nonanethiol. A rather poor coordination ability of Li atom would result in such a difference in products.

In the case of **II** an exclusive C–S bond fission is interesting. This can be explained by the symbiotic effect in HSAB principle proposed by Pearson and Songstad,[15] if the attack of the alkyl anion on the 2–C atom of the ring occurs in a S_N2 manner. Since alkyl anion is a soft base, the cleavage to leave a softer S anion would be more favorable than that to leave a harder O anion.

EXPERIMENTAL

Illustrative examples are given below

Synthesis of 2-Ethoxy-1, 3-oxathiolane(II). A mixture of 11.7 g (0.15 mol) of 2-mercaptoethanol, 22.2 g (0.15 mol) of ethly orthoformate and 0.4 g of acetic acid was brought to reflux for 1 min. As in the case of esterification reaction, the ethyl alcohol formed in the reaction mixture was continuously removed by distillation. The organic residue was then poured into a large quantity of 5% NaOH aqueous solution. The organic layer was separated, combined with an extract of the aqueous phase, dried ($MgSO_4$), and distilled to give 13.7 g (68%) of **II**. Bp 78°C/18 mmHg. *Anal.* Found: C, 44.53; H, 7.92%. Calcd for $C_5H_{10}O_2S$: C, 44.75; H, 7.51%. NMR (CCl_4) δ 6.20 (s, 1H, ring C**H**), 4.26~3.98 (m, 2H, ring O**CH$_2$**), 3.80~3.33 (m, 2H, O**CH$_2$**CH_3), 3.13~2.82 (m, 2H, ring S**CH$_2$**), 1.20 (t, 3H, OCH_2**CH$_3$**).

Synthesis of 2-Ethoxy-1, 3-dithiolane(III). **III** was similarly prepared in 30% yield (11.2 g) from 23.5 g (0.25 mol) of 1, 2-ethanedithiol, 37.1 g (0.25 mol)

of ethyl orthoformate and 0.6 g of acetic acid. Bp 103~103.5°C/15 mmHg. *Anal.* Found: C, 39.46; H, 6.99%. Calcd for $C_5H_{10}OS_2$: C, 39.96; H, 6.70%. NMR($CDCl_3$) δ 6.35 (s, 1H, ring C**H**), 3.60 (q, 2H, OCH_2CH_3), 3.45~3.15 (m, 4H, ring SCH_2CH_2–S), 1.21 (t, 3H, OCH_2CH_3).

Acid-Catalyzed Transformation of II. To 5.0 g of **II** was added one drop of conc. HCl. The mixture was allowed to stand at room temperature for 3 hr with occasional shaking. Distillation under vacuum, after usual work-up procedure, gave 1.3 g (36%) of **V**. Bp 120.5°C/1.3 mmHg. *Anal.* Found: C, 36.94; H, 5.31%. Calcd for $C_6H_{10}O_3S_2$: C, 37.09; H, 5.19%. NMR(CCl_4) δ 7.99 (s, 1H, **H**COO), 6.34 (s, 1H, ring C**H**), 4.48~3.95 (m, 4H, OCH_2 in ring and side chain), 3.25~2.65 (m, 4H, SCH_2 in ring and side chain).

Acid-Catalyzed Transformation of III. A small amount of conc. HCl was mixed with **III** at room temperature. After 30 min, the reaction mixture was cooled and the crystal was collected on a filter. This gave a nearly quantitative yield of **VI**. Mp 105~106 °C (from ethanol). *Anal.* Found: C, 31.51, H, 4.81%. Calcd for $C_8H_{14}S_6$: C, 31.76; H, 4.66%. NMR ($CDCl_3$) δ 5.70 (s, 2H, ring C**H**), 3.47~3.20 (m, 8H, ring SCH_2CH_2S), 2.97 (s, 4H, SCH_2CH_2S).

Reaction of II with n-BuMgBr. A Grignard reagent, prepared from 6.08 g (0.25 mol) of Mg, 34.26 g (0.25 mol) of butyl bromide and 50 ml of ether according to the usual procedure, was added dropwise to 6.71 g (0.05 mol) of **II** in 10 ml of ether with stirring at room temperature. At the same temperature the stirring was continued for 3 hr under a nitrogen atmosphere. The reaction mixture was then quenched by aqueous NH_4Cl solution. The organic layer was separated, combined with an ethereal extract of the aqueous phase, dried ($MgSO_4$), and distilled to give 2.02 g (28%) of 2-buty-1, 3-oxathiolane and 0.22 g (3%) of 5-nonanol.

Reaction of II with n-BuLi. To 6.71 g (0.05 mol) of **II** in 50 ml of n- hexane, n-BuLi (70 ml of 20% in n-hexane, 0.15 mol) was added dropwise with stirring under a nitrogen atmosphere. The addition was done very slowly to moderate the exothermic reaction. After the addition was complete,the reaction mixture was stirred at room temperature for 3 hr, and then was poured into a large quantity of ice-water. The organic layer was worked up as above to give 2.60 g (36%) of 5-nonanol and 1.90 g (19%) of 5-butyl-5-nonanol.

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