THE REDUCTIVE CLEAVAGE OF 1,3-OXATHIOLANES WITH LITHIUM ALUMINUM HYDRIDE IN THE PRESENCE OF ALUMINUM CHLORIDE OR BORON TRIFLUORIDE[1]

B. E. LEGGETTER AND R. K. BROWN
Department of Chemistry, University of Alberta, Edmonton, Alberta

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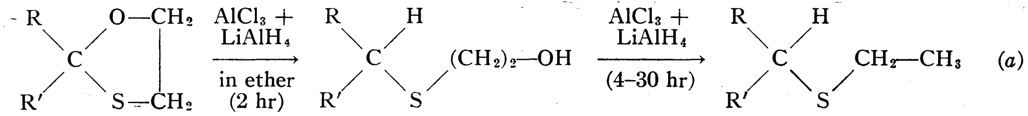
ABSTRACT

A number of 1,3-oxathiolanes and 1,3-dithiolanes were subjected to reduction in ether solution by lithium aluminum hydride in the presence of either aluminum chloride or boron trifluoride. Both of these Lewis acids not only isomerized 1,3-oxathiolanes but also catalyzed their hydrogenolysis to the hydroxy thioethers. Under the same conditions neither aluminum chloride nor boron trifluoride had any effect upon 1,3-dithiolanes. However, in methylene chloride solution, 1,3-dithiolanes are isomerized by both Lewis acids although their hydrogenolysis was not achieved, probably due to the insolubility of the hydride in methylene chloride.

A mechanistic interpretation is discussed to explain the results obtained.

INTRODUCTION

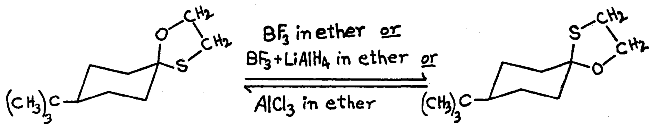
Recently Eliel and co-workers (1, 2) reported the reduction of 13 cyclic hemithioacetals and ketals (1,3-oxathiolanes) with a mixture of lithium aluminum hydride and aluminum chloride in ether solution. They found that in every case cleavage of only the carbon–oxygen bond occurred. Extended reaction times gave further reduction of the hydroxy thioether to the dialkyl sulphide (equation (*a*)).



(*a*)

Attempts by the same authors to reduce a hemithioketal with a mixture of *boron trifluoride* and lithium aluminum hydride were unsuccessful, resulting in practically complete recovery of the hemithioketal.* Thus, boron trifluoride – lithium aluminum hydride reduction of 4-*t*-butylcyclohexanone ethylene hemithioketal gave, in 2 hours, less than 1% of the hydrogenolyzed product, whereas the combination of aluminum chloride and lithium aluminum hydride, under otherwise identical conditions, yielded 85 to 90% of the hydrogenolyzed products, which consisted mainly of the hydroxy thioether along with some dialkyl sulphide.

Although *reduction* of the 4-*t*-butylcyclohexanone ethylene hemithioketal failed to occur with the BF$_3$–LiAlH$_4$ combination, *isomerization* of the two individual isomers of this ketal *did* take place readily and cleanly with the mixture BF$_3$–LiAlH$_4$ *or* with BF$_3$ etherate alone (equation (*b*)). Such isomerization was also obtained by AlCl$_3$ alone in ether solution but accompanied by some further decomposition (1).



(*b*)

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[1] *Taken in part from the thesis of B. E. Leggetter submitted to the Graduate School, University of Alberta, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.*

Reduction of a dioxyketal (a 1,3-dioxolane) with* BF$_3$–LiAlH$_4$, *however, is readily accomplished (Note 18 in ref. 1). Compare also A. R. Abdum-Nur and C. H. Issidorides, J. Org. Chem.,* **27, *67 (1962).*

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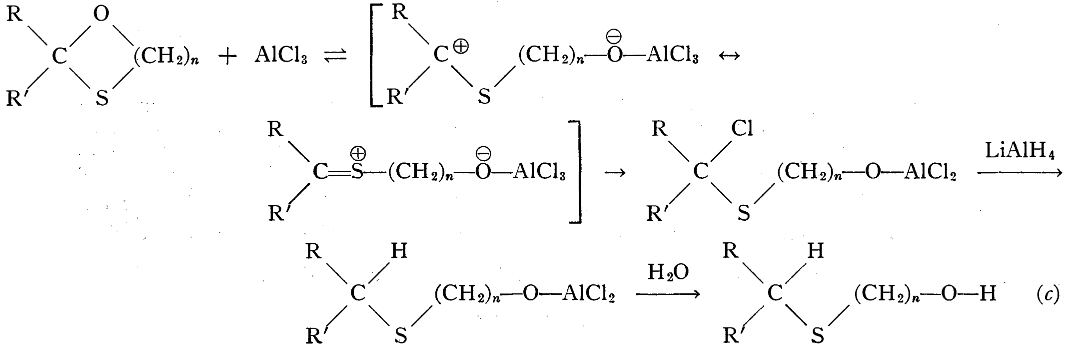
On the basis of this information, a mechanism for the hemithioketal reduction was proposed (1) involving first the formation of the resonance-stabilized sulphocarbonium ion *which could not be reduced by the hydride but did permit isomerization*. Reaction of this ion with the more nucleophilic chloride ion from the aluminum chloride, but not with the less nucleophilic fluoride ion from BF_3, gave the α-halo thioether which in turn could be reduced easily by the hydride to the hydroxy thioether (equation (*c*)).



(*c*)

As part of a program of research in this laboratory it had become necessary to examine the selective cleavage of 1,3-dioxolanes (ketals or acetals), and 1,3-oxathiolanes (hemithioketals or acetals) using as one of the reducing agents lithium aluminum hydride along with a Lewis acid. This paper reports the results obtained and gives data which cast some doubt on the mechanism of reductive cleavage suggested by Eliel (1).

RESULTS AND DISCUSSION

A number of 1,3-oxathiolanes in ether solution were treated with the combination of lithium aluminum hydride – aluminum chloride or lithium aluminum hydride – boron trifluoride. The results of these experiments are shown in Table I.

Cleavage of C—O but not C—S Bonds

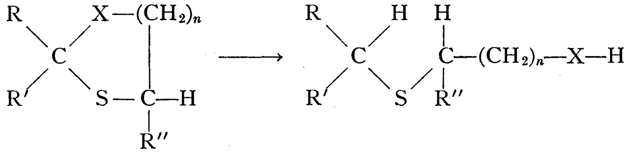
Our results corroborate the findings of the previous workers (1, 2) that in the reduction of 1,3-oxathiolanes the C—O but not the C—S bond is ruptured. No base-soluble mercaptans were isolated. Analyses by v.p.c. and infrared spectroscopy of the individual products as well as the mixtures of products failed to reveal evidence of the presence of the mercapto group. Furthermore, 1,3-*di*thiolanes failed to reduce at all even when the normal reduction time of 2 hours was extended to 48 hours. Only unchanged 1,3-dithiolanes were recovered, and these nearly quantitatively (experiments 6–9).

Hydrogenolysis with BF_3–$LiAlH_4$

As clearly shown in Table I, boron trifluoride *will* catalyze the reductive cleavage of 1,3-oxathiolanes by lithium aluminum hydride in diethyl ether solution (experiments 10–12, 14–15). However, the yield of reduction products is dependent upon the mode of addition of the reagents and upon the physical state of the hydride. In previous work on the reduction of dioxolanes and oxathiolanes using aluminum chloride as catalyst, we have found that when the Lewis acid is added to an ether solution of the dioxolane or oxathiolane *prior* to the addition of hydride, some resinous material was obtained, resulting in a reduced yield of the hydroxy ether. The same occurred but to a much lesser extent when BF_3 was used as the Lewis acid. Our experience in the reduction of these acetals and ketals with $LiAlH_4$–$AlCl_3$ mixture has been that this loss due to resin formation

TABLE I

Reduction of 1,3-oxathiolanes with lithium aluminum hydride in the presence of aluminum chloride or boron trifluoride (solvent, diethyl ether at room temperature)*



Expt. No.	R	R′	R″	X	n	Lewis acid	Total†† product recovery, %	Amount of thioether in the product, %	Amount of recovered 1,3-oxathiolane in product, %
1	H	C_6H_5	H	O	2	$AlCl_3$	—	54	0
2	H	C_6H_5	H	O	1	$AlCl_3$	—	72	0
3	H	n-C_3H_7	H	O	1	$AlCl_3$	—	89†	0
4	CH_3	CH_3	H	O	1	$AlCl_3$	—	87	0
5	C_6H_5	C_6H_5	H	O	1	$AlCl_3$	—	73	0
6	H	C_6H_5	H	S	1	$AlCl_3$	—	0	$\geqslant$96‡
7	CH_3	CH_3	H	S	1	$AlCl_3$	—	0	$\geqslant$96
8	CH_3	H	CH_3	S	1	$AlCl_3$	—	0	92
9	C_6H_5	H	CH_3	S	1	$AlCl_3$	—	0	78
10	CH_3	CH_3	H	O	1	BF_3	95	39	61§
11	CH_3	CH_3	H	O	1	BF_3	73	50	50‖
12	CH_3	CH_3	H	O	1	BF_3	75	56	44¶
13	CH_3	CH_3	H	O	1	BF_3	90	0	100**
14	C_6H_5	H	H	O	1	BF_3	29‡‡	100	0
15	C_6H_5	H	H	O	1	BF_3	90	73	27

*Unless otherwise stated, equimolar mixtures of $LiAlH_4$, Lewis acid, and oxathiolane or dithiolane in ether were used. The Lewis acid was added slowly over a period of 5 minutes to an ether solution of oxathiolane and hydride and then the mixture was stirred 2 hours. After work-up the products were analyzed by distillation and/or v.p.c.

†The solution was stirred for 3.5 hours before work-up.

‡The same result was obtained when the solution was allowed to stand 48 hours.

§The BF_3 etherate was added to the solution of hydride and oxathiolane and then the mixture stirred 3 hours.

‖Solid, finely ground $LiAlH_4$ was added to the stirred solution of BF_3 and oxathiolane in ether and the mixture stirred 3 hours.

¶Some resinous product formed. Here solid lumps of hydride in an ether suspension were added to the stirred ether solution of oxathiolane and BF_3.

**Here a solution of the oxathiolane was added to a stirred ether solution of $LiAlH_4$ + BF_3 as in Eliel's procedure (1), except that equimolar proportions of reagents were used. Eliel used a 4:1 ratio of BF_3:$LiAlH_4$. Our reduction time was 3 hours.

††Total product recovery includes both the recovered oxathiolane (or dithiolane) *and* the thioether.

‡‡Much resinous (polymeric) material remained in the flask after removal of volatile products.

could be avoided, and good control of reduction along with quite satisfactory results could be achieved by careful addition of an ether solution of the Lewis acid to the stirred ether solution of the dioxolane or oxathiolane containing the requisite amount of hydride.* Accordingly this procedure was employed initially in the BF_3-catalyzed reductions of the oxathiolanes. It was found that when equimolar quantities of the oxathiolane and lithium aluminum hydride were treated with ethereal BF_3, 39% of the total isolated product was the hydroxy thioether and the remainder (61%) was unchanged material (experiment 10). However, further investigation showed that if the BF_3 and oxathiolane were mixed *first* and then the hydride added in a finely divided state, a greater proportion of the product was found to be the reduced material (experiment 11). If the hydride was added as in experiment 11, but in the form of small lumps, an even greater proportion of the product was the hydroxy thioether (experiment 12). In both experiments 11 and 12, wherein the oxathiolane and BF_3 were first mixed together, somewhat better reduction did occur, though now with resin formation, than by the method of Lewis acid addition to the

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**Addition of an ether solution of the ketal or acetal to a mixture of* $LiAlH_4$ *and* $AlCl_3$ *in ether was the procedure employed by Eliel et al. (1, 2).*

mixture of hydride and oxathiolane—the procedure found to be much the better when $AlCl_3$ was the Lewis acid.* Finally, a repetition of the procedure used by Eliel and co-workers in the reduction of 4-*t*-butylcyclohexanone ethylene hemithioketal (1), in which 0.05 mole of oxathiolane in ether was added to a 4:1 mixture of BF_3 etherate and $LiAlH_4$ in ether which had been stirred for 5 minutes, gave less than 1% of the reduction product and 99% of the starting material, thus duplicating these authors' results.

The failure of a previously prepared 4:1 mixture, in ether, of BF_3–$LiAlH_4$ to effect reductive cleavage of the oxathiolane might be due to destruction of the reducing species before the oxathiolane could be attacked. The work of Shapiro *et al.* (3) on the preparation of diborane indicates that the addition of excess BF_3 to $LiAlH_4$ in ether produces diborane and aluminum fluoride according to the overall reaction given by equation (*d*). Because

$$3LiAlH_4 + 4BF_3 \xrightarrow{\text{ether}} 2B_2H_6 + 3LiF + 3AlF_3 \qquad (d)$$

of its low solubility in diethyl ether, diborane is evolved (4), and in fact the collection of diborane was used as a measure of the rate of formation of diborane (3) from these reagents.

The practically complete loss of the hydride as diborane from the ether solution thus would account for the absence of significant reduction as reported (1),* and as found in the present work when similar experimental conditions were employed.

Shapiro and co-workers (3) observed that no diborane was evolved until the ratio of BF_3 added to $LiAlH_4$ was greater than 1:1, thus indicating a two-step sequence shown by equations (*e*) and (*f*). Complete failure of reduction found in our experiment (No. 13)

$$BF_3 + LiAlH_4 \rightarrow LiBH_4 + AlF_3\downarrow \qquad (e)$$

$$BF_3 + 3LiBH_4 \rightarrow 2B_2H_6 + 3LiF\downarrow \qquad (f)$$

wherein the ratio of BF_3 to $LiAlH_4$ was only 1:1 could thus be attributed to the total conversion of BF_3 to AlF_3. Since the insolubility of AlF_3 makes it an ineffective Lewis acid (5), no reduction of the oxathiolane would occur even though the reducing species, lithium borohydride, was present (equation (*e*)).

In the addition of BF_3 etherate to a mixture of 1,3-oxathiolane and $LiAlH_4$, a competitive reaction must take place between the acetal and the hydride for the Lewis acid. Coordination of the Lewis acid with the oxathiolane would result in subsequent hydrogenolysis while reaction with the hydride would lead to the formation of AlF_3 and B_2H_6. Such a competitive reaction might explain the variability in reduction due to the physical condition of the hydride.

The much faster reduction of 1,3-dioxolanes as compared to that of the 1,3-oxathiolanes (see latter portion of this discussion), and the concept of competition of the dioxolane (or oxathiolane) with the lithium aluminum hydride for the Lewis acid, BF_3, could explain why 1,3-dioxolanes are quite readily reduced by BF_3–$LiAlH_4$ in ether (see first footnote in this paper) but 1,3-oxathiolanes reduce with more difficulty (1) and depend much more upon the order of addition of the reagents than do the dioxolanes.

It is interesting that a new batch of $LiAlH_4$, *which was quite finely divided and appeared light grey in color as compared with the darker grey color and lumpy texture of the batch of hydride used for all our experiments, gave reduction to the hydroxy thioether comparable to that of the darker grey material when the hydride was added to a mixture of the 1,3-oxathiolane and* BF_3 *etherate, but gave only unchanged material if the* BF_3 *was added to the previously mixed hydride and oxathiolane in ether.*

**The small amount of reduction, <1%, reported (1) could be due to the residual* B_2H_6 *remaining in the ether solution or to the presence of some unreacted hydride.*

Comparison of the Ease of Reduction of 1,3-oxathiolanes and 1,3-dioxolanes

A number of reductions were carried out with 2-*n*-propyl-1,3-dioxolane and 2-*n*-propyl-1,3-oxathiolane. Equimolar proportions of reagents were employed and conditions were identical in all cases except for the length of time that each experiment was allowed to proceed. The results are shown in Table II.

TABLE II

Comparison of the ease of reduction of 2-*n*-propyl-1,3-dioxolane and 2-*n*-propyl-1,3-oxathiolane by $LiAlH_4$ in the presence of $AlCl_3$ (solvent, diethyl ether)

Expt. No.	Total reduction time, min	Total recovery,* %	Yield of β-hydroxy thioether, %	Amount of recovered unreacted acetal, %
		For 2-*n*-propyl-1,3-oxathiolane		
1	20	89	51	49
2	40	84	81	19
3	60	91	91	9
4	210	80	>99.8	<0.2
		For 2-*n*-propyl-1,3-dioxolane		
5	20	88	100	0

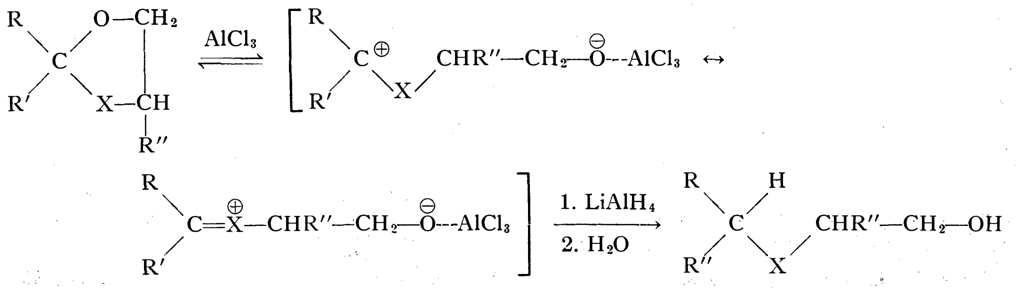
*Total recovery includes the unreacted acetal *and* the β-hydroxyalkyl thioether reduction product. The dialkyl thioethers which Eliel found on continued reduction of the hydroxyalkyl thioethers apparently were not formed during the time of our reduction since v.p.c. analyses failed to reveal their presence.

It is clear that under identical conditions 2-*n*-propyl-1,3-dioxolane is reduced considerably faster than is 2-*n*-propyl-1,3-oxathiolane. The dioxolane had disappeared completely within 20 minutes and it is quite likely that the time for complete reduction is less than this. On the other hand, the oxathiolane was approximately 50% hydrogenolyzed in 20 minutes.

Mechanistic Interpretation

Any mechanistic scheme to explain the reductive cleavage, in ether solution, of these acetals or ketals by lithium aluminum hydride in the presence of a Lewis acid must account for: (i) the direction of ring opening of cyclic acetals (6, 7); (ii) the cleavage of the C—O bond but not the C—S bond in oxathiolanes; (iii) the slower rate of cleavage of oxathiolanes as compared with that of the dioxolanes; (iv) the complete failure of reductive cleavage of dithiolanes.

The two reasonable mechanisms which have been advanced (1, 7, 8) are: (A) direct reduction of the initially formed resonance-stabilized oxocarbonium or sulphocarbonium ion as in equation (*g*).



(*g*)

(X = O or S)

(B) formation of the α-halo ether from the oxo- or sulpho-carbonium ion followed by reduction of the α-halo ether by the hydride as in equation (*c*).

In view of our observation that BF_3–$LiAlH_4$ causes reduction as does $AlCl_3$–$LiAlH_4$, the argument used as the support for the necessary formation of the α-halo ether is no longer valid. However, this does not mean that the concept of prior α-halo ether formation is disproved. It still *may* be, but is not *necessarily*, the pathway of the reaction.

It is noteworthy that both isomers of 4-*t*-butylcyclohexanone ethylene hemithioketal, when reduced by $AlCl_3$–$LiAlH_4$, were found to give a high (86 to 92%) yield of the same isomer, *trans*-4-*t*-butylcyclohexyl β-hydroxyethyl sulphide (1). This indicates that if α-halogenation were in fact a preliminary step, then *either* the α-halo ether must lose the halogen to become a carbonium ion, a common intermediate from both isomers, which is then reduced stereospecifically, *or* a rapid equilibration of the oxathiolanes occurs (cf. equation (*b*) wherein approximately a 1:1 mixture was found at a slowly attained equilibrium (1)) from which only one of the isomeric α-chloro ethers is formed, and this nearly quantitatively, which is then reduced stereospecifically. In the latter case, if the α-halo ether reacts with $LiAlH_4$ via an S_N1 mechanism, as is likely in view of the known S_N1 character of the solvolysis reactions of α-halo ethers (9),* then initial cleavage of the C—Cl bond must occur to form the readily reducible sulphocarbonium ion.

In view of the fact that the sulphocarbonium ion formation is necessary in the isomerization of the oxathiolane, in the formation of the preferred α-halo ether and also in the reduction (S_N1) of the α-halo ether, it is more logical to assume that prior α-halogenation isn't necessary and that the initially formed sulphocarbonium ion (made with the assistance from the Lewis acid) is the species reduced. The α-halogenation might then occur only as a competitive reaction, with the transient α-halo ether being immediately reduced. No evidence has been obtained in our work (cf. Table II) in the partial reduction of oxathiolanes of α-halo ether formation. No carbonyl compound was found in the products after work-up under alkaline conditions, suggesting α-halo ether formation.

As pointed out by Eliel, Pilato, and Badding (1) "only those functional groups are subject to hydrogenolysis (by $LiAlH_4$) which upon departure leave a stabilized carbonium ion". By and large this seems to be the guiding principle in nearly all the reductive cleavages of 1,3-dioxolanes or 1,3-oxathiolanes encountered in our laboratory. The very few exceptions can be rationalized within the framework of the above statement. This, and other aspects of the problem will be reported upon in a subsequent publication.

Regarding the Selective Cleavage of the C—O Bond Rather than the C—S Bond

There is considerable evidence that association of $AlCl_3$ with thioethers is more difficult than similar association of $AlCl_3$ with oxygen ethers. Harnish and Tarbell found in their study of the cleavage of ethers (10–12) that thioethers are more resistant to cleavage by acidic reagents than are their oxygen analogues. Suter and Hanson (13) found that alkyl *p*-methoxyphenyl thioethers were cleaved by an acetic acid solution of HBr to form only alkyl *p*-hydroxyphenyl thioethers with no evidence of cleavage of the C—S bond. Furthermore, when dry aluminum bromide was added to pure phenyl benzyl sulphide, cleavage occurred to give thiophenol and benzyl bromide, but when electron donor solvents such as ethers or nitrobenzene were used as diluents for this reaction, aluminum bromide failed

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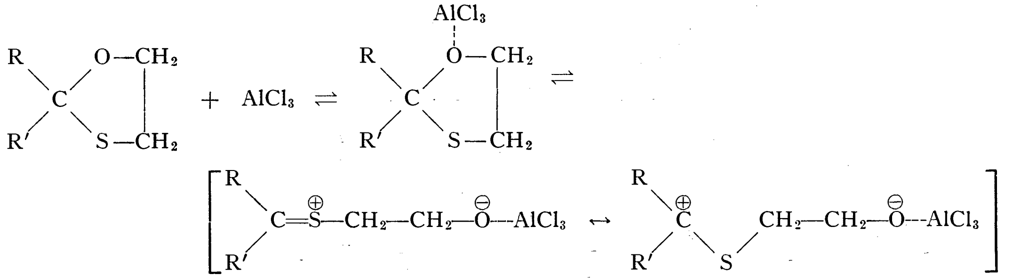
**The reviewer kindly pointed out that α-halo ethers can also react very rapidly by the* S_N2 *mechanism (P. Ballinger, P. B. D. de la Mare, G. Kohnstam and B. M. Prestt, J. Chem. Soc. 3641 (1955). However, since the work done by Ballinger et al. involved* primary *alkyl halides in the α-halo ether structure, while our work concerned itself with* secondary *and* tertiary *alkyl halides of α-halo ether structure, and as well involved the presence of aluminum chloride which could promote dissociation of the halogen as the halide ion, we prefer to consider the* S_N1 *reaction of our α-halo ethers as being more likely, even in the ether solutions employed.*

to cause any cleavage of the thioether (10). The explanation offered was that of preferential coordination of the $AlBr_3$ with the electron donor solvents.

For diethyl ether solutions of 1,3-dioxolanes the acetal oxygen atom can compete quite effectively with the solvent oxygen atoms for the Lewis acid, thus leading to Lewis acid catalysis of the reduction with $LiAlH_4$. Dithiolanes in diethyl ether solution would fail to experience effective association between the Lewis acid and the sulphur atoms and hence would be resistant to $LiAlH_4$ reduction, as has been found. If then the *first* and *necessary* step in the reductive cleavage of the 1,3-oxathiolanes is coordination of the oxathiolane with the Lewis acid, then one must have the reaction shown in equation (*h*) in which the sulphocarbonium ion is formed. This could then undergo isomerization accompanied by some polymerization or be reduced if $LiAlH_4$ is present.


(*h*)

Support for the concept of the inability of the Lewis acid to associate with the sulphur atom of the oxathiolane or dithiolane in diethyl ether solution is obtained from the observation that the high-melting isomer *cis*- (or *trans*-) 4-chloromethyl-2-phenyl-1,3-dithiolane* treated with either BF_3 or $AlCl_3$ in *ether solution* did not isomerize detectably even when the solution was allowed to stand at room temperature for as long as 20 hours. On the other hand, in the solvent methylene chloride, in which the Lewis acids and the dithiolane were quite soluble, equilibration occurred quite readily. Boron trifluoride gave complete equilibration within 90 minutes unaccompanied by polymerization, but aluminum chloride gave equilibration accompanied by extensive gum formation. Detection of isomerization was easily accomplished by n.m.r. analysis of the individual isomers and the mixtures produced, since the signal for the lone proton on C_2 of the dithiolane occurred as a sharp singlet at $\tau = 4.48$ for the low-melting isomer (m.p. 60–62°) and at $\tau = 4.43$ for the high-melting isomer (m.p. 68–69°).

On the assumption that if reduction is to occur there must be prior association of the Lewis acid with the dithiolane, and now knowing that isomerization of dithiolanes does occur in CH_2Cl_2 solution through the agency of a Lewis acid, we attempted to reduce several 1,3-dithiolanes at our disposal. However, the failure of $LiAlH_4$ to dissolve in the CH_2Cl_2 thwarted attempts in this direction and there were obtained only the unchanged dithiolanes. That failure of reduction can be attributed to the insolubility of the $LiAlH_4$ in CH_2Cl_2 is borne out by complete lack of reduction of 2,2,4-trimethyl-1,3-dioxolane in CH_2Cl_2 by the mixture $LiAlH_4$ and $AlCl_3$. This dioxolane is very readily reduced under these conditions if the solvent is ether.

It is possible to explain the more rapid reduction of the dioxolanes as compared with the oxathiolanes. The formation of the stabilized oxocarbonium ion is easier because of the better overlap of the *p*-orbitals of the oxygen atom with the vacant *p*-orbital of the carbonium ion. Similar stabilization of the sulphocarbonium ion in the oxathiolane occurs

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See Note in the experimental section on the preparation of the chloromethyl compounds.

by the less facile overlap of the *d*-orbitals of the sulphur atom. The *formation* of the stabilized carbonium ion then must be involved in the rate-controlling step or steps of the reaction.

EXPERIMENTAL

All compounds mentioned were made by authentic and reported procedures or were newly prepared and characterized. Except where otherwise stated, all v.p.c. analyses were done with a Burrell K-2 Kromotog using a 2-m column packed with 25% of carbowax 20 M on gas-chrom P as the solid stationary phase. Helium, at a flow rate of approximately 80 ml/min was the carrier gas. The column temperature was dependent upon the boiling point of the products. Products were identified by comparison of their retention times with those of authentic samples, and/or by means of infrared spectroscopy as well as n.m.r. analyses with a Varian A-60 spectrometer. Quantitative measurements were made by comparison of v.p.c. peak areas with those obtained from known quantities of authentic reagents.

Typical Reduction Procedure. Reduction of 2-Phenyl-1,3-oxathiane

The compound, 2-phenyl-1,3-oxathiane, was prepared according to published directions (1). However, the boiling point reported was 166° at 1.2 mm while that found by us is 92° at 1.0 mm. Elemental analysis of our preparation agreed closely for the assigned structure.

To a stirred mixture of 2-phenyl-1,3-oxathiane (12.0 g, 0.067 mole) and lithium aluminum hydride (2.7 g, 0.067 mole) in ether (150 ml) at room temperature was added, over a period of 5 minutes, a solution of dry aluminum chloride (8.9 g, 0.067 mole) in 100 ml of ether. The exothermic reaction which took place during the addition required the slow admixture of the $AlCl_3$. The resulting mixture, first stirred 2 hours, was then cautiously diluted with cold water to destroy the aluminum chloride complexes and the excess hydride. In all cases the excess hydride was employed deliberately so that on treatment with water the solution remained basic at all times to avoid isomerization or hydrolysis of any unreacted acetal. The inorganic material was removed by filtration and the ethereal filtrate was dried over magnesium sulphate. Removal of the ether and distillation of the oil under reduced pressure gave a total yield of 6.5 g (54%) of material boiling at 126° at 1.6 mm. Lit. b.p., 185° at 19 mm (14). The infrared spectrum of this material was identical with that of a sample of benzyl γ-hydroxy-*n*-propyl sulphide prepared from benzyl chloride and 3-mercaptopropan-1-ol (14).

The oxathiolanes reduced by this procedure, along with authentic reduction products and their yields, are shown in Table III.

TABLE III

1,3-Oxathiolanes reduced by $LiAlH_4$ and $AlCl_3$ and product yields

1,3-Oxathiolane	Ref.	Reduction product	% yield	Ref.
2-Phenyl-1,3-oxathiolane	15	Benzyl β-hydroxyethyl sulphide	72	18
2-*n*-Propyl-1,3-oxathiolane	(See expt.)	*n*-Butyl β-hydroxyethyl sulphide	89*	18
2,2-Dimethyl-1,3-oxathiolane	16	*i*-Propyl β-hydroxyethyl sulphide	87	1
2,2-Diphenyl-1,3-oxathiolane	17	Diphenylmethyl β-hydroxyethyl sulphide	73	19

*The reaction time in this case was 210 minutes rather than the usual 2 hours.

Attempted Reduction of 2-Phenyl-1,3-dithiolane

To a stirred mixture of 2-phenyl-1,3-dithiolane (18.3 g, 0.1 mole) (20) and lithium aluminum hydride (1.9 g, 0.05 mole) in ether (120 ml) at room temperature was added a solution of dry aluminum chloride (13.4 g, 0.1 mole) in 60 ml of ether over a period of 3 to 5 minutes. The mixture was then stirred for 2 hours. Following treatment of the mixture as for the 1,3-oxathiolanes or 1,3-oxathiane above, there was obtained, by fractional distillation, 17.5 g (96%) of material whose infrared spectrum was identical with that of the original 2-phenyl-1,3-dithiolane.

A second attempt at reduction using the same conditions but with twice the amount of hydride and also with a reaction time of 48 hours gave 96% recovery of the original material. No evidence of reduction was found.

The 1,3-dithiolanes whose reductive cleavage was attempted by the above procedure are shown in Table IV.

Comparative Rates of Reduction of 2-n-Propyl-1,3-dioxolane and 2-n-Propyl-1,3-oxathiolane

The following specific procedure was used for *four* separate reductions of 2-*n*-propyl-1,3-oxathiolane and

TABLE IV

1,3-Dithiolanes subjected to reduction by LiAlH$_4$ and AlCl$_3$

1,3-Dithiolane	Ref.	Recovered 1,3-dithiolane, %	Reduction product, %
2,2-Dimethyl-1,3-dithiolane	21	96	0
2,4-Dimethyl-1,3-dithiolane	(See expt.)	92	0
2-Phenyl-4-methyl-1,3-dithiolane	22	78*	0

*The low recovery was due to accidental loss.

one for 2-*n*-propyl-,13-dioxolane. These differed only in the length of time that the reaction was allowed to proceed after admixture of all reagents. Times of 20, 40, 60, and 210 minutes were chosen for the oxathiolane experiments while a 20-minute reduction time was allowed for the dioxolane.

To a stirred mixture of acetal (0.05 mole) and lithium aluminum hydride (0.05 mole) in 70 ml of ether was added at room temperature over a period of *one* minute a solution of aluminum chloride (0.05 mole) in ether (30 ml). The mixture was then stirred for the requisite time at room temperature and then diluted carefully with cold water. After removal of the inorganic material by filtration, the ether extract was dried (MgSO$_4$). The residual oil obtained on removal of the ether was analyzed by v.p.c. The results are shown in Table II.

2-n-Propyl-1,3-oxathiolane was prepared according to modifications of the general procedure recommended in the literature (16) by condensation of *n*-butyraldehyde with 2-mercaptoethanol. *n*-Butyraldehyde (40 g) and 36 g of 2-mercaptoethanol were dissolved in 200 ml of dry benzene. To this was added 0.3 g of *p*-toluenesulphonic acid and 20 g of anhydrous magnesium sulphate. The solution, which became warm upon the addition of these reagents, was allowed to stand for 20 hours and then poured into aqueous sodium carbonate. The organic layer was separated and dried (MgSO$_4$) and then fractionally distilled. There was obtained 50 g (82%) of 2-*n*-propyl-1,3-oxathiolane boiling at 84° at 34 mm. Calc. for $C_6H_{12}OS$: C, 54.54; H, 9.09; S, 24.24. Found: C, 54.63; H, 9.17; S, 24.01.

2,4-Dimethyl-1,3-dithiolane was prepared according to the above procedure by condensation of acetaldehyde with 1,2-dimercaptopropane. Yield 77%. B.p. 81° at 25 mm. Calc. for $C_5H_{10}S_2$: C, 44.78; H, 7.46; S, 47.76. Found: C, 44.55; H, 7.47; S, 47.91.

n-Butyl β-hydroxyethyl thioether was prepared according to the procedure of Klamann and Bertsh (18). B.p. 68° at 3 mm. Lit. b.p. 106–107° at 14 mm.

Reduction of 1,3-Oxathiolanes with LiAlH$_4$–BF$_3$

In these reductions 2,2-dimethyl-1,3-oxathiolane (16) was used as starting material for experiments 10–13 and was prepared most conveniently in 86% yield by condensation of 2-mercaptoethanol and acetone in the presence of anhydrous magnesium sulphate and a catalytic amount of *p*-toluenesulphonic acid. Excess acetone was removed and the residual oil fractionally distilled, affording 2,2-dimethyl-1,3-oxathiolane. B.p. 57° at 45 mm; lit. b.p. 70° at 65 mm (16).

(a) Experiment 10

A mixture of 2,2-dimethyl-1,3-oxathiolane (0.15 mole) and finely divided lithium aluminum hydride (0.05 mole) in 75 ml of anhydrous ether was stirred while boron trifluoride etherate (0.05 mole) was added dropwise. After the addition, the solution was stirred for 3 hours at room temperature. After cautious addition of water, followed by removal of inorganic precipitate, the ether layer was separated and dried (MgSO$_4$). Removal of the ether left an oil (95% yield) which v.p.c. analysis showed to consist of 39% *i*-propyl β-hydroxyethyl sulphide and 61% of unchanged 2,2-dimethyl-1,3-oxathiolane.

(b) Experiment 11

In this experiment, a mixture of 2,2-dimethyl-1,3-oxathiolane (0.05 mole) and boron trifluoride etherate (0.05 mole) in ether (75 ml) was stirred whilst powdered hydride (0.05 mole) was added in small batches. The remainder of the procedure followed that for experiment 10. Total yield of material was 73%, of which 50% was the hydrogenolized product, *i*-propyl β-hydroxyethyl sulphide, and 50% the unchanged oxathiolane. The low yield (73%) was due to the occurrence of considerable resinous material.

(c) Experiment 12

The same procedure as in experiment 11 was followed except that the hydride was added in the form of lumps. The overall total yield was 75%, 56% of which was *i*-propyl β-hydroxyethyl sulphide and the remainder (44%) unreacted starting material. Here again the formation of resinous material lowered the yield.

(d) Experiment 13

The procedure of Eliel *et al.* (1) was used to reduce 2,2-dimethyl-1,3-oxathiolane with the modification that equimolar proportions of reagents were employed and the reaction time extended to 3 hours. During the mixing of the hydride and boron trifluoride a vigorous evolution of gas took place. This had not been noted in the previous experiments. Presumably the gas was B_2H_6. The overall yield of recoverable material was 90%, of which <1% was the hydroxy sulphide and the remainder unchanged oxathiolane.

(e) Experiment 14

A quantity of 2-phenyl-1,3-oxathiolane was reduced by the procedure used in experiment 12. All of the product (29% yield) was benzyl β-hydroxyethyl sulphide. The residual material in the flask was resinous. No starting material was recovered. Analyses by v.p.c. were done with a 2-m column of 25% silicone rubber on Gas-Chrom P at a temperature of 250°. The n.m.r. spectrum agreed with the structure.

(f) Experiment 15

Reduction of 2-phenyl-1,3-oxathiolane by the procedure used in experiment 10 gave a 80% yield of material of which 73% was benzyl β-hydroxyethyl sulphide and 27% was starting material.

Preparation of cis- and trans-2-Phenyl-4-chloromethyl-1,3-dithiolane.

The method of Roberts and Cheng (22) was employed to prepare the 3,5-dinitrobenzoate of 4-hydroxymethyl-2-phenyl-1,3-dithiolane. The method of separation of the cis and trans isomers of this ester devised by Roberts and Cheng proved to be unsatisfactory. However, good separation was achieved by fractional crystallization from benzene. The higher-melting isomer, 118–119° (lit. 112–113° (22)), precipitated, leaving the lower-melting isomer, 99–100° (lit. 100–101° (22)), in solution. Concentration of the mother liquor afforded the latter in 15% yield based upon the hydroxymethyldithiolane used. A 33% yield was obtained for the 118–119° melting isomer.

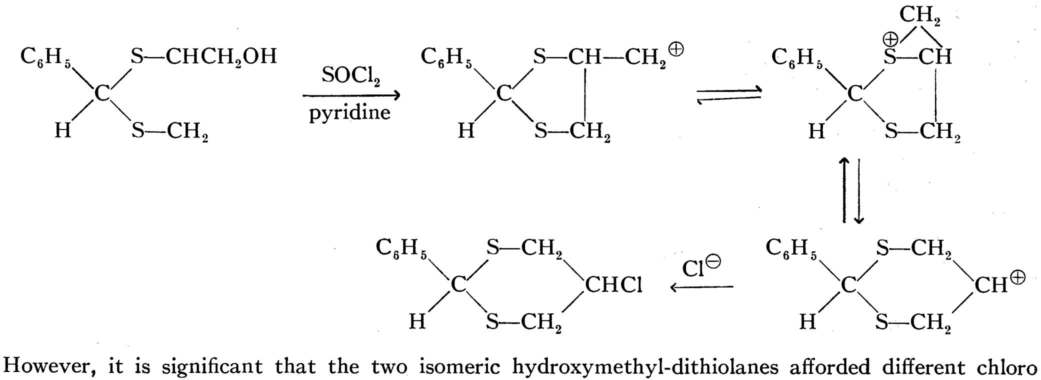
Both isomeric 3,5-dinitrobenzoates were hydrolyzed to the *cis*- and *trans*-4-hydroxymethyl-2-phenyl-1,3-dithiolanes most satisfactorily by refluxing the esters for 45 minutes in a 1:1 mixture of aqueous ethanol containing 8% of potassium hydroxide. Use of only aqueous KOH as advocated by Roberts and Cheng gave less satisfactory results since much of the material remained unhydrolyzed. The high-melting isomeric ester gave a 77% yield of crude alcohol which was purified by chromatography on alumina with ether as eluant. Subsequent crystallization from benzene–skellysolve afforded the pure alcohol, m.p. 90°; lit. m.p. 88.5–89° (22). The low-melting ester gave a 74% yield of crude alcohol which after purification as above melted at 88°. Lit. m.p. 87.5–88° (22).

Conversion of the 4-hydroxymethyl-2-phenyl-1,3-dithiolane to the 4-chloromethyl-2-phenyl-1,3-dithiolane was accomplished by treatment of the alcohol with an equivalent quantity of thionyl chloride in the presence of a catalytic amount of pyridine, all in refluxing diisopropyl ether. Removal of the ether and other volatile substances gave a pale yellow solid which was purified by chromatography on alumina using skellysolve as eluant. Crystallization from skellysolve gave an analytical sample.

The isomeric alcohol melting at 90° gave the 4-chloromethyl-2-phenyl-1,3-dithiolane in 46% yield based on the alcohol used. An analytical sample melted at 68–69°. Calc. for $C_{10}H_{11}ClS_2$: C, 52.06; H, 4.77; Cl, 15.40; S, 27.77. Found: C, 51.74; H, 4.52; Cl, 15.17; S, 28.01.

The isomeric alcohol melting at 88° gave, by the same procedure, a 58% yield of the 4-chloromethyl-2-phenyl-1,3-dithiolane, melting at 60–62°. Calc. for $C_{10}H_{11}ClS_2$: C, 52.06; H, 4.77; Cl, 15.40; S, 27.77. Found: C, 51.80; H, 4.64; Cl, 15.61; S, 27.61. The n.m.r. spectrum in CS_2 with tetramethylsilane as reference compound supported the structure assigned and gave a sharp singlet for the C_2 proton at $\tau = 4.48$.

(Note: The possibility arises that during the conversion of the 4-hydroxyethyl-2-phenyl-1,3-dithiolanes to the chloromethyl compounds, expansion of the 1,3-dithiolane ring may occur as illustrated by the following scheme.



However, it is significant that the two isomeric hydroxymethyl-dithiolanes afforded different chloro derivatives upon treatment with thionyl chloride. This observation would argue against ring expansion. The n.m.r. spectrum also favors the 5-membered ring structure. *Absolute* identification however must await the synthesis of authentic 6-membered ring structures for comparison. However, the main point of the use of these dithiolanes is not affected.)

The unresolved mixture of *cis*- and *trans*-4-hydroxymethyl-2-phenyl-1,3-dithiolane gave a 65% yield of a mixture of *cis*- and *trans*-chloromethyl compounds which melted over the broad range of 57–62°. Elemental analysis of this mixture gave the following results. Calc. for $C_{10}H_{11}ClS_2$: C, 52.06; H, 4.77; Cl, 15.40; S, 27.77. Found: C, 51.83; H, 4.44; Cl, 15.59; S, 27.90. The integrated areas for proton absorption in the n.m.r. spectrum obtained in CS_2 supported the structural designation. The signal position of the C_2-proton, using tetramethylsilane as internal standard, indicated the expected mixture of the two isomers by the presence of the two singlets at 4.44 τ and 4.49 τ. The relative areas of these two signals indicated a 4:1 ratio of high-melting isomer to low-melting isomer which had occurred as result of a 3-fold crystallization from skellysolve. Further crystallization from the same solvent decreased the content of low-melting isomer in the mixture.

Attempted Reduction of 1,3-Dithiolanes by $LiAlH_4$–$AlCl_3$

A mixture of the dithiolane (0.05 mole) and lithium aluminum hydride (0.05 mole) in 60 ml of dry ether was stirred while a solution of aluminum chloride (0.05 mole) in 20 ml of ether was added dropwise. The reaction mixture was then stirred under nitrogen until a total reaction time of 2 hours had elapsed. Decomposition and subsquent treatment of the reaction mixture in the usual manner afforded only the original unchanged material in at least 90% yield. No alkali-soluble materials were obtained. Vapor phase chromatographic analyses gave no indication of a product other than starting material. Increase in reaction time to 24 hours also failed to yield any hydrogenolyzed products. The compounds subjected to this treatment are shown in Table I, experiments 6–9, and in Table IV.

Equilibration of cis- and trans-4-Chloromethyl-2-phenyl-1,3-dithiolane

In Diethyl Ether as Solvent

A solution of 230 mg of the isomer melting at 68–69° in 20 ml of ether was treated with 135 mg of anhydrous aluminum chloride in 10 ml of ether. The reaction mixture was allowed to stand at room temperature for 20 hours and then poured into aqueous sodium bicarbonate. The ether layer was separated and dried. Evaporation of the solvent afforded 100 mg of product melting sharply at 67–68°. Nuclear magnetic resonance analyses indicated that no equilibration had occurred since only one sharp singlet occurred at $\tau = 4.43$ characteristic of the C_2-proton of the high-melting isomer.

When boron trifluoride etherate was used as the Lewis acid, the same results were obtained.

In Methylene Chloride as Solvent

A quantity (290 mg) of the isomer melting at 68–69° was dissolved in methylene chloride previously dried for 48 hours over $CaCl_2$. Anhydrous boron trifluoride was bubbled into the solution for several minutes and the resulting solution allowed to stand for 90 minutes. The solution was then poured into aqueous sodium bicarbonate. The organic layer was separated, washed with aqueous bicarbonate, then with water, and finally dried (Na_2CO_3). Evaporation of the solvent gave 225 mg of material melting at 51–54°. An n.m.r. spectrum (CS_2) of this product indicated a mixture of *cis*- and *trans*-4-chloromethyl-2-phenyl-1,3-dithiolane in which the high-melting isomer predominated slightly over the low-melting isomer as determined by the integrated areas and by visual inspection of the two singlets at $\tau = 4.43$ and 4.48.

The same reaction was carried out using $AlCl_3$ as the catalyst rather than BF_3, and allowing the reaction mixture to stand for 20 hours. When the mixture was worked up as before, a resinous material was obtained. An n.m.r. spectrum of this substance indicated extensive decomposition and nothing definite concerning isomerization.

A repetition of the reaction with $AlCl_3$ as catalyst, but for a period of 4 hours, gave a resinous oily product whose n.m.r. spectrum showed a somewhat broader and poorly resolved signal at 4.46 τ, indicating that isomerization had occurred along with decomposition.

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