SOME 1,3-OXATHIOLANES AND RELATED COMPOUNDS

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ACKNOWLEDGMENTS

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CHAPTER I

INTRODUCTION

Work on the preparation of 1,3-oxathiolanes was first undertaken by the writer in the early months of 1953. This was done with the original aim of preparing monomers for possible ring-scission polymerization as part of a research project sponsored by the United States Air Force for the study of polymers and copolymers of ethylene sulfide. A 1,3-oxathiolane may be considered as formally derived from the combination of one molecule of ethylene sulfide with one molecule of a carbonyl compound.

At the time this work was begun only two simple oxathiolanes were reported in the literature, those derived, at least formally, from acetone and acetaldehyde. Work on this problem was discontinued by the author for three years, and during this time the literature concerning this type of compound increased considerably. The research project on ethylene sulfide polymers had been completed and summarized; however, it was decided to continue the preparation of 1,3-oxathiolanes independently so as to further clarify preparative methods for aldehydic and ketonic derivatives and to determine some properties and reactions of this type of compound.

Since parts of the early work have been reported by Feldman (17) and Dermer (8) in connection with the aforementioned research project, there will be some unavoidable duplication between material which is

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considered as literature review and material which is included in the experimental section of this paper. An attempt will be made to keep this duplication to a minimum.

CHAPTER II

REVIEW OF THE LITERATURE

Acetals and ketals have been known for many years and the appli-
cation of methods for the preparation of these compounds to the for-
mation of 1,3-dioxolanes is covered quite adequately in the chapter
devoted to dioxolanes in the reference work, Heterocyclic Compounds.
(14). Unfortunately, this work almost completely ignores the oxathi-
olanes and dithiolanes. The literature pertaining to 1,3-oxathioles
and 1,3-oxathiolanes will be briefly reviewed here.

There has not been a great deal of interest shown in these com-
pounds, most of the work done on 1,3-oxathioles and 1,3-oxathiolanes
has been incidental to other research, and the majority of literature
references are since 1950. The simplest compound of this series, 1,3-

oxathiole, $HC_5=CH_4 / O_1 \quad S_3 / C_2H_2$, is unknown, as is 1,3-dioxole. The hydro-

genated from of 1,3-oxathiole, 4,5-dihydro-1,3-oxathiole, 1,3-oxathio-
lane, was first prepared by the writer and is reported only in the
work of his associates. (8, 17).

Preparation of 1,3-oxathiolanes

Methods which have been used to prepare 1,3-oxathiolanes fall
into the four following categories of acid-catalyzed reactions.

These are as follows:

1. The most widely used method, acetal formation with the elimination of water.

$$RC=O + HSCH_2CH_2OH \rightleftharpoons R_2C\begin{smallmatrix}S-CH_2\\O-CH_2\end{smallmatrix} + H_2O$$
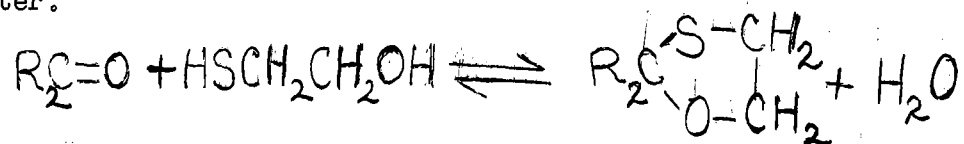
In early work Sjoberg (38) used a mixture of phosphorus pentoxide and sand to condense vicinal mercaptoalkanols with carbonyl compounds. Later, Romo and his associates (35) used fused zinc chloride and anhydrous sodium sulfate for the same purpose. Several workers have successfully applied to 1,3-oxathiolanes a method long applied to the preparation of 1,3-dioxolanes, the method of continuous dehydration using a Stark-Dean apparatus (Barrett water trap) with benzene or toluene as an entrainer, usually with p-toluenesulfonic acid as catalyst. (1, 2, 12, 28). There is also the interesting simplification proposed by Fieser (18), who stated that 1,3-oxathiolanes will often separate from a mixture of ketone and excess 2-mercaptoethanol in glacial acetic acid which is treated with boron trifluoride-etherate, but made no mention of the use of aldehydes or of other catalysts.

2. Acetal interchange of one ketone for another.

$$R_2C=O + R_2'C\begin{smallmatrix}S-CH_2\\O-CH_2\end{smallmatrix} \rightleftharpoons R_2C\begin{smallmatrix}S-CH_2\\O-CH_2\end{smallmatrix} + R_2'C=O$$
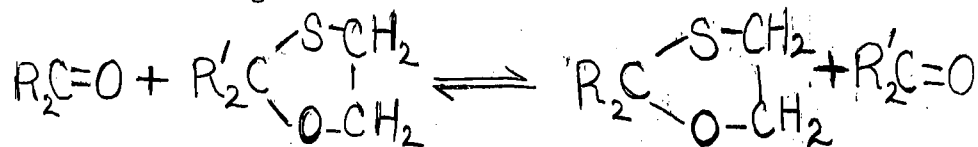
This method seems to be widely applicable to the preparation of the 1,3-oxathiolanes of nonvolatile carbonyl compounds. The carbonyl compound is caused to react with a tenfold excess of the 1,3-oxathiolane of acetone, the acetone being distilled out as the interchange is effected. (11).

3. Interchange of one alcohol for another.

$$R_2C(OR')_2 + HOCH_2CH_2SH \rightleftharpoons R_2C{\overset{S-CH_2}{\underset{O-CH_2}{\diagdown}}} + 2R'OH$$
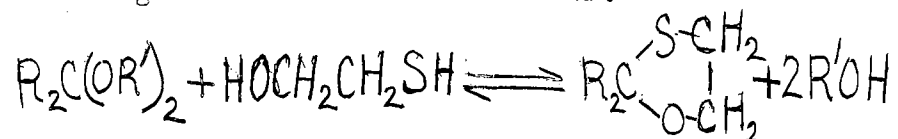
This reaction appears only in a patent by Croxall and Van Hook (6), who claim the reaction of an alkyl _beta, beta_-dialkoxypropionate with 2-mercaptoethanol.

4. The reaction of a vinyl ether with a vicinal mercaptoalkanol.

$$R_2C{=}\overset{H}{C}OR + HOCH_2CH_2SH \rightleftharpoons R_2\overset{H}{\underset{}{C}}{-}\overset{S-CH_2}{\underset{O-CH_2}{C}H} + HOR$$
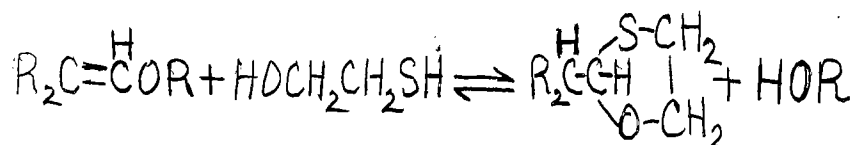
This appears in the patent literature in the work of Copenhaver (5), who reported the preparation of 2-methyl-1,3-oxathiolane by this method, and in the patent by Croxall and Van Hook (6), who claim the reaction of an alkyl _beta_-alkoxyacrylate with 2-mercaptoethanol.

An interesting preparation was used by Stevenson and Smiles (37), for certain 1,3-oxathioles; however, this preparation has no apparent applicability to 1,3-oxathiolanes. A specific example of this preparation is as follows:
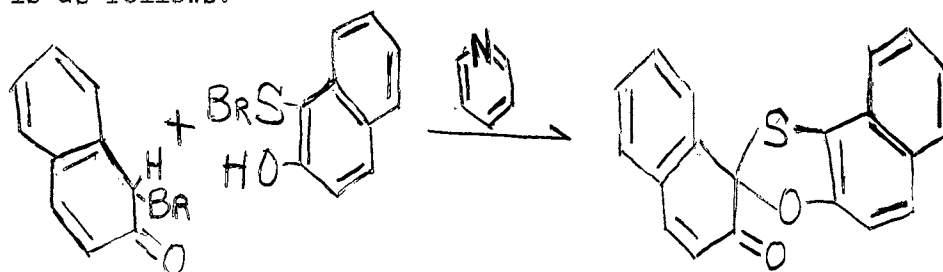
Synthesis of 2-Imino- and 2-Keto-1,3-Oxathioles
and Oxathiolanes

2-Imino-5-methyl-1,3-oxathiolane hydrochloride has been prepared by the careful reaction of an alkali thiocyanate with propylene oxide and hydrochloric acid. (33).

$$H_3C-\overset{H}{\underset{O}{C}}-\overset{H}{C}H + KSCN + HCl \longrightarrow$$
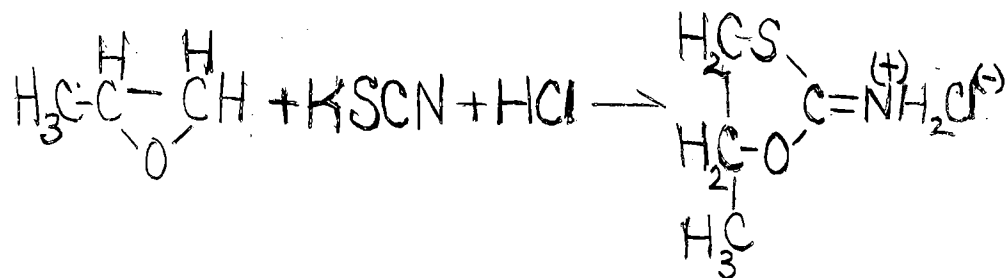
Somewhat similar to the above is the preparation given for 5-(2'-thienyl)-2-imino-1,3-oxathiolane and a 5'-chloro derivative from 2-vinylthiophene, bromine and KSCN in glacial acetic acid. (15).

$$Br_2 + 2KSCN \longrightarrow 2KBr + (SCN)_2$$
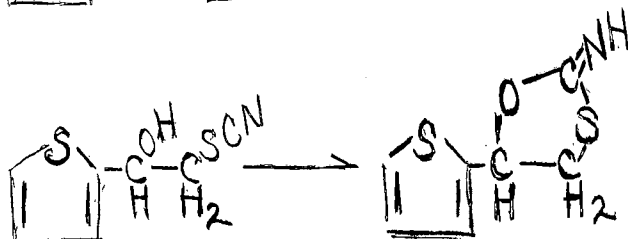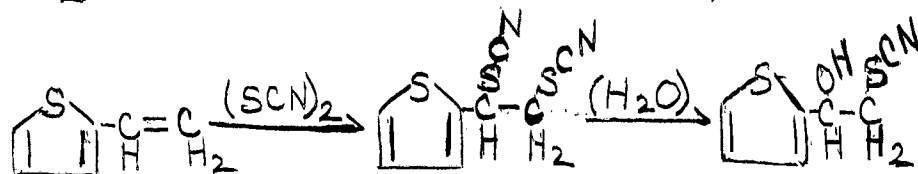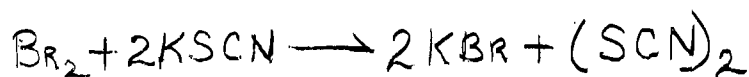
There are several ways by which oxathiolane-2-ones can be prepared. The most direct method is by the reaction of phosgene with vicinal mercaptoalkanols. (7, 27, 20).
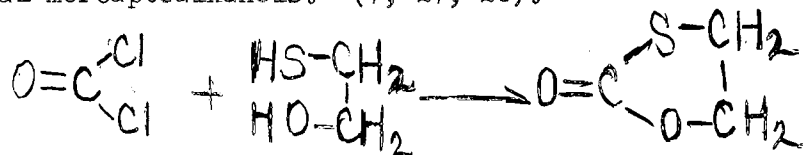
More indirect methods involve the intermediate formation of the 2-imino compound. (27, 32).
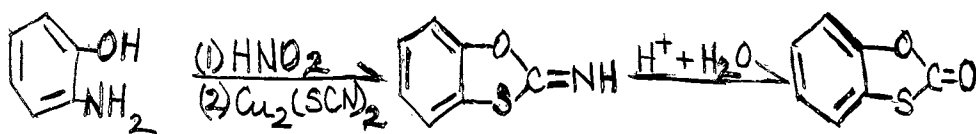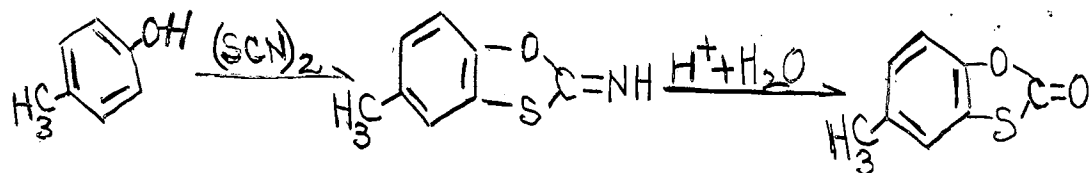
Direct substitution upon the aromatic nucleus will be satisfactory only
if the para position is blocked by a suitable substituent so as to force
ortho substitution. (27).

Types of Reported Compounds and Uses

The simpler 1,3-oxathiolanes of monocarbonyl compounds other than
steroids are listed in Table I at the end of this chapter. The deriv-
atives of steroids are listed in Table II. In connection with some
steroid research, Jaeger and Smith (24, 25, 26) obtained some interest-
ing results with cyclohexane-1,2-dione. They prepared the mono- and
bis-oxathiolane derivatives plus a solid material, isomeric with the
bis-oxathiolane derivative, thought to be an oxathiano-oxathiane,
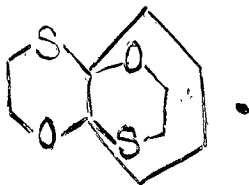
Some derivatives of thioglycerols and a few other vicinal mercapto-
alkanols have been reported (38, 16); a mono-oxathiolane derivative
of benzil has been reported also. (18).

There seem to have been few uses found for 1,3-oxathiolanes as
such. The only patented use found for strictly aliphatic derivatives
is claimed in a German patent on the 2-thiones as insecticides. (9).
Several patents have specified uses for benzoxathioles. The 2-imino-
benzoxathioles have been proposed as dyes (29), as dye and therapeutic

intermediates (43), and as plant-growth stimulants. (42). The 2-keto-1,3-benzoxathioles have been proposed as intermediates for azo dyes and disinfecting agents (43), and as components for dyes to be used in photographic reproduction. (42). 2-Imino-1,3-oxathiolanes derived from vinylthiophenes have been patented as fungicides and insecticides. (15).

Although it is outside the scope of this paper to discuss them further, nine other literature references to benzoxathioles have been listed so as to make the bibliography of this class of compound as nearly complete as possible. (14, 21, 22, 23, 34, 36, 39, 44).

Reactions

The removal of the 1,3-oxathiolane group by the use of Raney nickel has been the most important reaction of this type of compound which has been studied. This desulfurization results generally in the regeneration of the parent ketone and hence has proven to be a very useful preparatory method in steroid research. A ketone group can be protected as the 1,3-oxathiolane while operations are carried out on other parts of the molecule. The oxathiolane grouping can then be removed without resorting to acid hydrolysis. This desulfurization may be written as follows:

$$R_2C \begin{smallmatrix} O-CH_2 \\ | \\ S-CH_2 \end{smallmatrix} + [H] \xrightarrow{\text{RANEY Ni}} R_2C=O + H_2S + H_2C=CH_2 \cdot$$
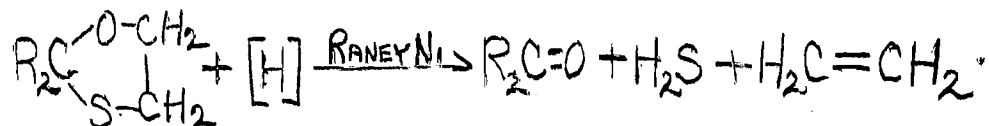
The mechanism of this reaction is somewhat obscure, but may involve some type of biradical intermediate. If oxygen is available either from the air or from an oxygen-containing solvent an alcohol is formed rather than a hydrocarbon. There is also some evidence that the "1-2"

carbon-oxygen bond is sometimes split rather than the "2-3" bond. (12).
The ketone is not always regenerated. Reduction of 2-oxocyclohexane-1-
spiro-2'-1',3'-oxathiolane, also called 6-oxo-1-oxa-4-thiaspiro(4,5)-
decane, produced 2-ethoxycyclohexanone rather than the expected cyclo-
hexane-1,2-dione. (25). Use of catalysts other than Raney nickel
may lead to compounds other than the parent ketone; for example, 1-oxa-
4-thiaspiro(4,5)decane when catalytically reduced with molybdem
trisulfide produced cyclohexanethiol at 230° C. and cyclohexane at
260° C. (4). Noncatalytic reduction of 2-methyl-2-phenyl-1,3-
oxathiolane with sodium and alcohol produced ethylbenzene along with
traces of 1-ethyl-1,4-cyclohexadiene. (33).

Feldman (17) studied the polymerization of 1,3-oxathiolane both
alone and with other substances. He found some polymerization and
copolymerization of 1,3-oxathiolane itself but not of 2-substituted-1,
3-oxathiolanes, which yielded the orginal carbonyl compound and poly-
ethylene sulfide. Dermer (8) reported the similar polymerization of
5-methyl-1,3-oxathiolane. Feldman offers two reaction mechanisms as
explanation of his results. A split between the oxygen atom and the
#5 carbon atom takes place when the split between the oxygen atom and
the #2 carbon atom is inhibited by increased electron density on the
#2 carbon from the inductive effect of alkyl substituents. Feldman's
mechanisms are essentially as follows:

1. $HOCH_2CH_2\text{-}S\text{-}CH_2$ ... $\longrightarrow$ $HOCH_2CH_2S\text{-}CH_2O$ ...
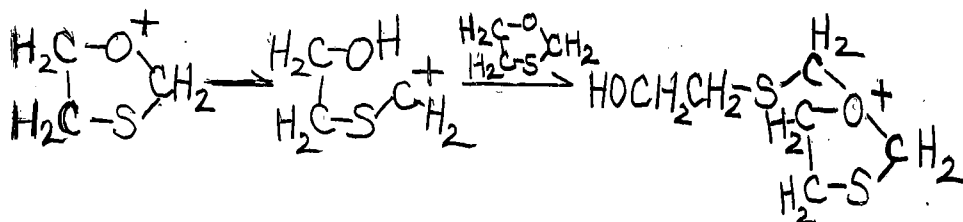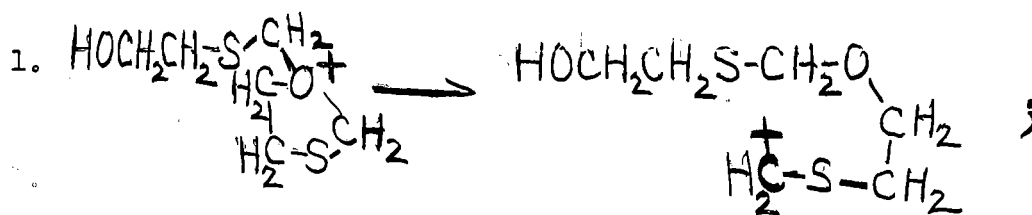
this pattern of reaction is continued, finally terminating with addition

of an anion to the end of the chain. This anion is usually hydroxyl

ion; thus the final production is the telomer, $H[O\text{-}CH_2CH_2\text{-}S\text{-}CH_2]_n OH$.

2. ... $\longrightarrow$ ... $\longrightarrow H^+ + R_2C=O + \bar{S}\text{-}CH_2\overset{+}{C}H_2$

I
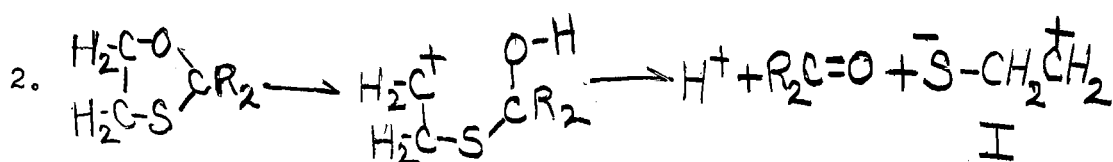
In connection with this second mechanism Feldman states that the polar

form of ethylene sulfide (I above) can react with the oxathiolane

monomer to promote the polymerization of ethylene sulfide. No mech-

anism is given in explanation of this statement.

Although simple 1,3-oxathiolanes are stable to aqueous base, 1,3-

oxathiolane-2,5-diones are unstable to either acid or base, as could

be predicted from their structure (7, 22, 23); and 1,3-oxathiolane-

2-ones may be hydrolyzed by base, a fact that has been used for the

preparation of certain aromatic thiols. (7, 20, 32). The 1,3-

oxathiolane-2,5-diones are more properly considered as anhydrides

than as oxathiolanes, just as the 2-oxo-1,3-oxathiolanes are essen-

tially cyclic thiocarbonates rather than oxathiolanes.

Like other organic sulfides, 1,3-oxathiolanes may be oxidized to

sulfoxides and sulfones. (11, 20). If other functional groups are

present, operations may be carried out which are not dependent upon

the oxathiolane structure. Some reactions of this type have been reported. Some of the work of Jaeger and Smith (25) is representative. By the use of Grignard reactions they formed 2-ethynyl-2-hydroxycyclo-hexane-1-spiro-2'-(1',3'-oxathiolane) and the corresponding 2-ethyl compound from 2-oxocyclohexane-1-spiro-2'-(1',3'-oxathiolane); and by the use of lithium aluminum hydride they prepared 2-hydroxycyclohexane-1-spiro-2'-(1',3'-oxathiolane) from the same precursor.

TABLE I

KNOWN NONSTEROID 1,3-OXATHIOLANES OF
MONOCARBONYL COMPOUNDS

COMPOUND	B.P., °C. @ ___ mm.	REF.
1,3-Oxathiolane	125-6.5 <u>746</u>	8, 17
2-Methyl-1,3-oxathiolane	<u>129</u>	5
2-Ethyl-1,3-oxathiolane	149.5 <u>743</u>	8, 17
2-Propyl-1,3-oxathiolane	167-8	17
2-Isopropyl-1,3-oxathiolane	29 <u>2.5</u>	28
2-Phenyl-1,3-oxathiolane	86-7 <u>5</u>	28
2,2-Dimethyl-1,3-oxathiolane	70 <u>65</u>	11, 20
2-Methyl-2-ethyl-1,3-oxathiolane	42 <u>8</u>	11, 20
2-Methyl-2-isobutyl-1,3-oxathiolane	41 <u>2</u>	2, 11
2-Methyl-2-phenyl-1,3-oxathiolane	132 <u>16</u>	11, 33
2,2-Dibenzyl-1,3-oxathiolane	M.P. 42-3	11
1-Oxa-4-thiaspiro(4.5)pentane Spiro(cyclohexane-1,2'-1',3'-oxathiolane) 2-Pentamethylenyl-1,3-oxathiolane	62 and 111 <u>12</u>	11, 1
2-(3',4'-Dioxymethylenephenyl)-1,3-oxathiolane	118 <u>1.5</u>	28
2-Methyl-2-(ethoxycarbonylmethyl)-1,3-oxathiolane	117 <u>20</u>	11
2-Methyl-2-ethyl-5-phenyl-1,3-oxathiolane	M.P. 104-5	13

TABLE I (CONTINUED)

COMPOUNDS	B.P., $^{\circ}$C. @ ____ mm.	REF.
2-Methyl-2-isobutyl-4-mercaptomethyl-1,3-oxathiolane		2
5-Methyl-1,3-oxathiolane	134-5 744	8

Note: This table does not include the derivatives of cyclohexane-1,2-dione reported by Jaeger and Smith. (25, 26).

TABLE II

KNOWN STEROID OXATHIOLANES AND OXATHIOLES

COMPOUND	M.P., °C.	REF.
Allopregnan-3β-ol-11-one-20-oxathiolane	175-78	10
Allopregnan-3β,11β-diol-20-oxathiolane 3-acetate	191-3	10
Androstan-17-oxathiolane	119-21	11
Androstan-17β-ol-2-oxathiolane acetate	164-67	35
Δ4-Androsten-2,17-dione-3-oxathiolane	167-70	21, 36
Δ4-Androsten-3,17-bisoxathiolane	203-6	21
Δ5-Androsten-3β-ol-17-oxathiolane	151-3	32
Δ5-Androsten-3β-ol-17-oxathiolane acetate	172-76	11, 35
Cholestan-3-oxathiolane	133-6	11, 18
Δ5-Cholesten-3-oxathiolane	136-7	18
Dehydroepiandrosteroneoxathiolane	183-4	18

Δ4-Androsten-3,17-dione-17-oxathiolane
            D + 46°
            D + 197°
	192-3
	171-3
		35
		35

Estrone-17-oxathiolane	160-2	35
Estrone-17-oxathiolane acetate	124-26	35
Etiocholan-17β-ol-3-oxathiolane acetate	163-5	35
2β-Mercaptocholestan-3β-ol- cyclohexanoneoxathiolane	161-3	13
Δ4-Pregnen-20β-ol-3-oxathiolane acetate	183-5	11
Spiro(1-benzoxathiole-2,3'-androstan-17'- ol 17-acetate)	no mp.	
Spiro(5-benzyloxathiolane-2,3'-cholestane)	148-50	13
Spiro(5-phenyloxathiolane-2,3'-cholestane)	93-4	13
Spiro(4-phenyloxathiolane-2,3'-cholestane)	158-60	13
Δ4-22a-55α-Spirosten-3-oxathiolane	240-42	11
22a-55α-Spirostan-3β-ol-13-oxathiolane acetate	224-5	11
Testosteroneoxathiolane	192-4	11

CHAPTER III

EXPERIMENTAL

Successful Preparations

1,3-Oxathiolane and other low-boiling 1,3-oxathiolanes. 1,3-
Oxathiolane was first prepared by the following procedure in twenty-
nine percent yield. Seven and one-half grams of paraformaldehyde,
seventeen and one-half grams of 2-mercaptoethanol, and one-tenth gram
of p-toluenesulfonic acid were mixed in a round-bottom flask upon
which was mounted a three-ball Snyder distilling column. All readily
distillable material was expelled by heating, leaving behind a brown,
waxy residue. The two-phase distillate was separated and the non-
aqueous layer was distilled. Six and four-tenths grams of liquid
boiling at 123.5° C. were obtained. Analytical data on this and other
major products are found in Table III and IV. The reaction equation
is as follows:

$$[CH_2O]_n + n \ HSCH_2CH_2OH \xrightarrow{H^+} n \ H_2C \overset{S-CH_2}{\underset{O\ CH_2}{\diagdown}} + n \ H_2O;$$
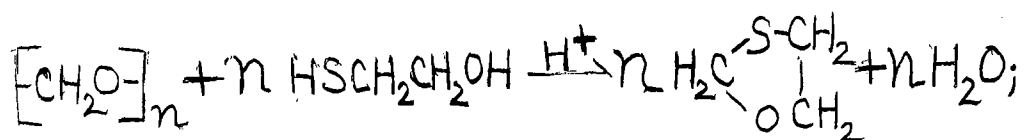
with the acid catalyst serving both to depolymerize the paraformaldehyde
and to promote the acetal formation.

By modifying this apparatus so as to attach the round-bottom flask
directly to a condenser and distilling out the oxathiolane and water
together as they are formed, yields of greater than fifty percent can
be obtained consistently. The reaction is exothermic enough that a

TABLE III

LIQUID 1,3-OXATHIOLANES

COMPOUND	B.P.,°C.	N_D @ ___°C.	d. gm./ml. @ ___°C.	Analysis,% Theory	Found	M. R. Theory	Found	Lit. Ref.
1,3-Oxathiolane	126.5-127	1.5035 27.5	1.1565 27.5	S 35.6	S 35.2	23.5	23.1	8, 17
2-Methyl-1,3-oxathiolane	129	1.4805 27.5	1.0330 27.5	S 30.8	S 30.70	28.1	29.4	5
2,2-Dimethyl-1,3-oxathiolane	138	1.4778 27.5	1.0350 27.5	S 27.7	S 27.5	32.7	32.3	11, 20
2-Ethyl-1,3-oxathiolane	149.5	1.4777 27.5	1.0290 27.5	C 50.9 H 8.5 S 27.7	C 50.99 H 8.46 S 28.00	32.7	32.5	8, 17
2-Methyl-2-ethyl-1,3-oxathiolane	157	1.4375 27.5	1.0040 27.5	S 24.2	S>20.00	37.3	37.0	11
2-N-propyl-1,3-oxathiolane (purity uncertain)	169-170	1.4797 32.0	1.0130 32.0	C 54.4 H 9.1	C 50.79 C 50.81 H 8.91 H 8.93	37.3	37.0	17
2,2-Diisopropyl-1,3-oxathiolane	198	1.4832 20.0	0.9670 27.0	S 18.4	S 18.2	51.3	51.4	---
2-Ethyl-2-n-butyl-1,3-oxathiolane	214	1.4735 32.0	1.0390 32.0	C 62.1 H 10.3	C 61.12 H 10.39	51.3	51.9	---
2-Methyl-2-n-pentyl-1,3-oxathiolane	215	1.4712 32.0	0.9410 32.0	C 62.1 H 10.3	C 61.58 H 10.35	51.3	51.7	---
2-Methyl-2-n-hexyl-1,3-oxathiolane	234 235	1.4692 32.0	1.0260 32.0	C 63.8 H 10.6	C 63.99 H 10.76	55.8	56.6	---
Camphor-1,3-oxathiolane	265	1.5130 30.0	1.0480 30.0	C 66.7 H 9.1	C 68.78 H 9.27	56.0	56.4	---

TABLE IV

PRODUCTS FROM 2-MERCAPTOETHANOL AND DIKETONES

Product Name or Parent Compound	M.P. °C.	Description	Analysis % Theory	Found
Glyoxal	74-76°C.	B.P. 291-294 with decomposition, probably mixture of isomers	S 36.0 ($C_6H_{10}O_2S_2$)	S 34.3
Biacetyl	B.P. 268-270°C.	n_D^{20} 1.5400, d. 25/20 1.15 Yellow oil	S 31.1 ($C_8H_{14}O_2S_2$)	S 27.7
Methylene-bis-2,2'-(2-methyl-1,3-oxathiolane)	53-53.5	Needles similar to benzoic acid	C 49.1 H 7.3 S 29.7	C 48.62 H 6.88 S 28.3
Ethylene-bis-2,2'-(2-methyl-1,3-oxathiolane)	68.5-69.3°C.	Naphthalene-like flakes	C 51.3 H 7.7 S 27.4	C 51.23 H 7.51 S 25.2

portion of the product will distill out without application of external heat; however, further heating with some attendant decomposition is necessary to complete the collection of the oxathiolane. Anhydrous ferric chloride and other Lewis acids may be used as catalysts instead of Brønsted acids. This simple method may be used, with appropriate substitutions of materials, in the preparation of derivatives of the lower molecular weight carbonyl compounds; however, the yield decreases as the molecular weight of the carbonyl compound increases.

1,3-Oxathiolanes in general. The following procedure was found to

$$R_2C=O + HSCH_2CH_2OH \longrightarrow R_2C\begin{matrix} -S-CH_2 \\ | \\ O-CH_2 \end{matrix} + H_2O$$
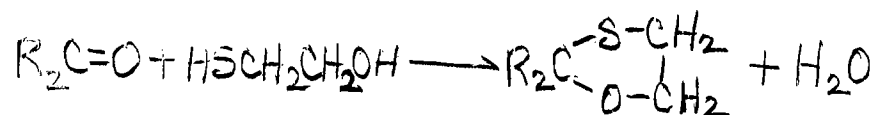
be satisfactory in the preparation of 1,3-oxathiolanes in approximately fifty percent yields. Equimolar quantities of the carbonyl compound and 2-mercaptoethanol are mixed with fifty milliliters of benzene saturated with p-toluenesulfonic acid and heated in a water-removing apparatus, such as was previously described, and the oxathiolane is recrystallized or distilled. This procedure proved to be very satisfactory for the preparation of 2,2-dimethyl-1,3-oxathiolane frome acetone and of 2-methyl-1,3-oxathiolane from paraldehyde. 2-Ethyl-1,3-oxathiolane, 2-methyl-2-ethyl-1,3-oxathiolane, 2-methyl-2-n-hexyl-1,3-oxathiolane, 2,2-diisopropyl-1,3-oxathiolane, and the 1,3-oxathiolane of camphor were also prepared by this procedure. Modifications of this procedure used in the preparation or attempted preparation of oxathiolanes derived from 2,5-hexanedione, 2,4-pentanedione, 2,3-butanedione (biacetyl) and 1,2-ethanedial (glyoxal) will be described separately in detail.

An alternative procedure which proved satisfactory for the prepara-
tion of ketonic derivatives in 45-50% yields of purified product con-
sists of mixing equimolar quantities of the ketone and mercaptoethanol
with 100 ml. of benzene and three or four drops of concentrated hydro-
chloric acid and treating as in the above procedure save that, after
water removal, the mixture is distilled through a carefully insulated
distilling column (a twelve-ball Snyder column was used by the writer)
without removal of the hydrochloric acid catalyst. The portion boiling
within five degrees above and below the expected boiling point[1] is
saved and redistilled through the same apparatus. 2-Methyl-2-n-pentyl-
1,3-oxathiolane, 2-ethyl-2-n-butyl-1,3-oxathiolane, and 2-methyl-2-n-
hexyl-1,3-oxathiolane were prepared by this procedure.

The first of these two general procedures was tried with para-
formaldehyde in an attempt to prepare 1,3-oxathiolane itself. In this
case, the operation was found to be a complete failure, apparently due
to the high volatility and polymerizability of formaldehyde. The
formaldehyde escaped from the reaction mixture and polymerized within
the reflux condenser of the water-removal apparatus, eventually clog-
ging the condenser completely. No 1,3-oxathiolane could be isolated.

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[1]It was found that derivatives of ketones had boiling points
within three degrees of the estimated value based on the assumption
that the oxathiolane has a boiling point number 8.3 units greater
than the ketone from which it is formed.

2-Mercaptoethanol and glyoxal.

(EXPECTED REACTION)
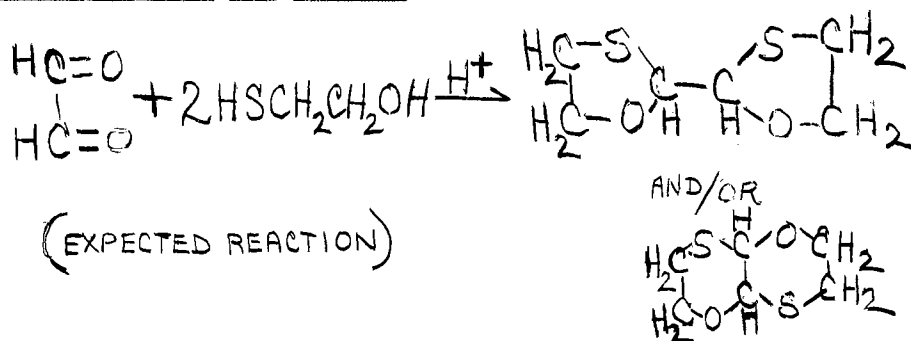
Thirty-two milliliters of 2-mercaptoethanol and 48 ml. of 30% aqueous

glyoxal were mixed with 50 ml. of benzene and placed in the usual dehy-

dration apparatus. After the removal of 36.5 ml. of water, 50 ml. of

benzene saturated with p-toluenesulfonic acid were added. Seven milli-

liters more water were removed. The reaction mixture, a reddish-purple

liquid, was washed with dilute sodium hydroxide, changing in color to

a light yellow in the course of the washing. The benzene solution and

the aqueous layer were both returned to the reaction vessel and the

reaction apparatus was used to remove the benzene. The material

remaining after the removal of the benzene was poured into ice water.

The aqueous phase was decanted and the crude product, now a yellow

wax, was dissolved in warm methanol. Upon cooling brownish oil sepa-

rated which crystallized into yellowish-white crystals. This crude

product dissolved in acetone and frozen out at dry-ice temperatures

yielded 10 g. of off-white cyrstals melting at 68-74° C. This repre-

sents 11% yield.

Repeated recrystallization from acetone, methanol, and benzene

in rotation followed by short-path distillation at 1-2 mm. produced

beautiful white crystals with a melting point of 88.5 to 89.5° C.

Infrared spectra indicate that this material is the major component

of crude material melting at 68-74° C. Unfortunately, this product

was inadvertently destroyed before elemental analysis could be performed upon it.

Simply separating the crude material into ether-soluble and ether-insoluble portions yields an ether-soluble portion with a melting point of 76-78° C. and a waxy ether-insoluble portion. Whereas the theoretical sulfur content for $C_6H_{10}O_2S_2$ is 36%, the ether-soluble material contained 34.3% sulfur[2]; the ether-insoluble material was not analyzed. A yellow oil was recovered from the acetone and methanol from which the main product was crystallized. This oil, which very slowly crystallized into waxy pale-yellow crystals, was not analyzed.

2-Mercaptoethanol and biacetyl.
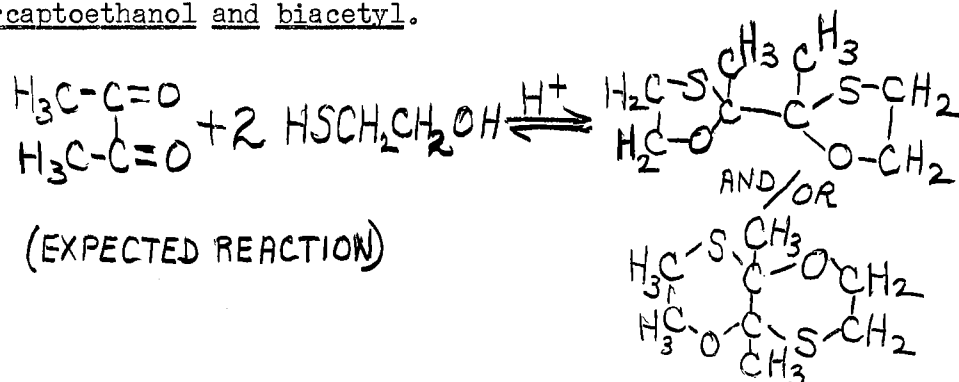
A mixture of three-fourths of a mole of biacetyl, one and one-half moles of 2-mercaptoethanol, 50 ml. of benzene, and 50 ml. of benzene saturated with p-toluenesulfonic acid was heated in the dehydration apparatus for four hours, during which time 25 ml. of water were collected. The resultant mixture, a beautiful orange in color, was washed with sodium hydroxide solution, the orange color thereupon fading to a dull yellow. The aqueous and nonaqueous phases were

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[2] The sulfur analyses reported in this paper were carried out by the method of oxidation in a Parr peroxide bomb followed by gravimetric determination as sulfate. Carbon and hydrogen analyses were performed by Geller Microanalytical Laboratories, Bardonia, New York.

separated and the nonaqueous layer was distilled. All distillate to
150° C. was discarded. The portion boiling above 150° C., after treat-
ment with "Norite" in ether, amounted to 92 g. of yellow oil, b.p.
265-272° C. A portion of this was redistilled to a range of 268-70° C.
For an assumed molecular weight of 206, the experimental molar refrac-
tivity of this final product is 56.1 ml./mole. Sulfur analysis resulted
in values of 27.3 and 27.7% sulfur, compared with a value of 31.1% for
$C_8H_{14}O_2S_2$. Thus either the identity or the purity of the compound is
in error.

Repeated attempts at forced crystallization of this oily product
from acetone and from methanol at low temperatures (acetone and "dry-
ice") followed by rapid filtration through a chilled funnel finally
led to the isolation from methanol of a very small amount of a semisolid
mass. This after three weeks crystallized into beautiful white crystals
which recrystallized from diisopropyl ether melted at 68-70° C. No
further information was obtained about this product.

2-Mercaptoethanol and 2,4-pentanedione.

$$H_3C\overset{O}{\underset{||}{C}}CH_2\overset{O}{\underset{||}{C}}CH_3 + 2\ HSCH_2CH_2OH \overset{H^+}{\rightleftharpoons} H_3C\overset{CH_3}{\underset{S}{C}}-CH_2-\overset{CH_3}{\underset{S}{C}}\overset{CH_3}{}$$
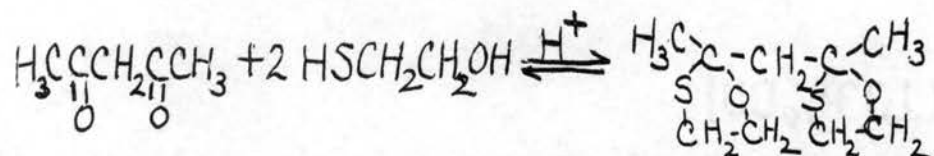
Two-sevenths of a mole of 2-mercaptoethanol, one-seventh of a mole of
2,4-pentanedione, and 50 ml. of a saturated solution of p-toluenesulfonic
acid in benzene were refluxed in the dehydration apparatus for twelve
hours, during which time 5.5 ml. of water were collected. The result-
ant, red solution was washed with dilute sodium hydroxide solution.
The color became a pale yellow. The benzene was evaporated and the

crude product was dissolved in acetone, frozen with dry ice and rapidly
freed from oil by filtration through a chilled Buchner funnel.

The white crystalline product, melting slightly above room temper-
ature, was dissolved in a minimal quantity of warm methanol, two drops
of water were added, and the mixture was cooled in an ice bath. The
yield of product thus recrystallized was 4 g. or 13% of the theoretical
yield. This product, recrystallized from ether-petroleum ether as
needles reminiscent of benzoic acid, showed a melting point of 53-53.5° C.

2-Mercaptoethanol and 2,5-hexanedione.

$$H_3C-C-CH_2CH_2CCH_3 \overset{H^+}{\rightleftarrows} H_3C-C-CH_2-CH_2-C-CH_3$$
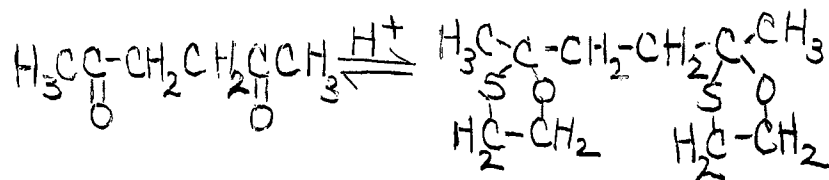
One-half mole of 2,5-hexanedione, one mole of mercaptoethanol, and 50
ml. of benzene saturated with p-toluenesulfonic acid were heated on a
steam bath in the usual apparatus. In two hours 14.5 ml. of water
had been collected. The wine-red solution was shaken with sodium
hydroxide solution, the color changing successively from red to dark
blue, to blue-green, light green and finally to yellow. The reaction
mixture was washed twice with sodium hydroxide solution and then with
water. The organic layer was separated, the benzene removed by simple
distillation, and the residue subjected to steam distillation. Eleven
milliliters of water-immiscible oil (unreacted hexanedione) were
recovered from the steam distillate. The residual material was poured
into ice water. The yellow curds which separated at this point were
filtered out and washed with cold water, then dissolved in a minimal
quantity of hot methanol. Two drops of water were added to the
methanol solution and the mixture was chilled in an ice bath. This

procedure resulted in the precipitation of 17 g. of white crystals. This represents a 15% yield of the expected product. The remaining methanol solution yielded upon evaporation an additional 30 g. of a yellow wax of undetermined composition. The white crystalline product, recrystallized again from methanol containing a trace of water and then from ether-petroleum ether, yielded naphthalene-like flakes having a melting point of 68.5-69.3° C.

Comments on preparative procedures. There is no claim implied that the foregoing procedures are the best possible; they are simply the procedures which were used by the writer in the exploratory preparation of the compounds listed in Table III. Some comment may be made on the matter of catalysis which seems to be somewhat critical. It was found that in general Lewis acids produced lower yields than did Brønsted acids, and that use of greater quantities of catalyst than those quoted resulted in sharply curtailed yields. Some further methods which have not been fully tested as yet, as well as some other material of interest, will be covered in the following section of material which is peripheral and/or amplificatory to that recorded in this section.

Attempted Preparations

Ethylene sulfide and carbonyl compounds.

$$H_2C-CH_2 + R_2C=O \underset{H^+}{\overset{H^+}{\rightleftharpoons}} R_2C \begin{matrix} S-CH_2 \\ | \\ O-CH_2 \end{matrix}$$

(DESIRED REACTION)
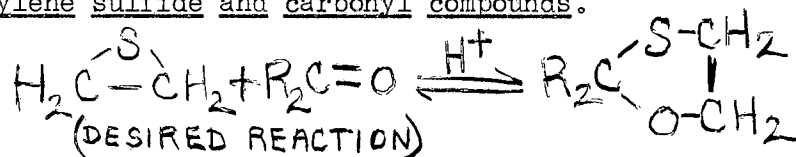
Ethylene sulfide, prepared by essentially the procedure reported by Dermer (8), was caused to react in approximately 20 mole-percent solution in acetone at 0° C. Although a variety of catalysts were

tried, including dilute sulfuric acid, boron trifloride, concentrated hydrochloric acid, ammonium chloride, and stannic chloride, all attempts to isolate the hoped for 2,2-dimethyl-1,3-oxathiolane failed completely. The only isolable product was ethylene sulfide polymer. Attempted reaction of paraldehyde with ethylene sulfide gave the same type of results. Methylal also proved to be a good inert medium in which to carry out the polymerization of ethylene sulfide.

Ethylene oxide, hydrogen sulfide, and carbonyl compounds.

$$H_2C\overset{O}{-}CH_2 + H_2S + R_2C{=}O \underset{\longleftarrow}{\overset{H^+}{\longrightarrow}} R_2C\overset{O-CH_2}{\underset{S-CH_2}{<}} + H_2O$$
(DESIRED REACTION)
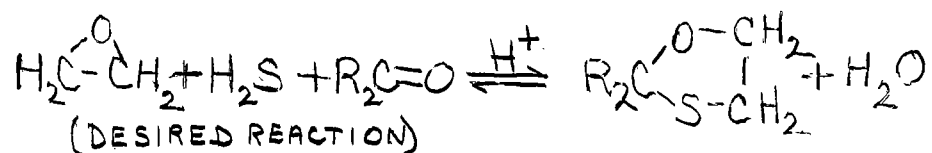
Attempted preparation of 1,3-oxathiolane from ethylene oxide, hydrogen sulfide and formalin resulted in a minuscule yield of a liquid which from its odor was a mixture of mercaptans. Attempted preparation of 2-methyl-1,3-oxathiolane from acetaldehyde, ethylene oxide, and hydrogen sulfide at 0-10° C. produced a mixture of products, none of which was 2-methyl-1,3-oxathiolane.

2-Mercaptoethanol and aldehydes without catalyst. After the failure of reactions of the type discussed in the previous two topics to produce 1,3-oxathiolanes, attention was turned to preparations from 2-mercaptoethanol and carbonyl compounds, culminating in the preparative methods reported previously. Early in this investigation it was noted that aldehydes would react exothermally with 2-mercaptoethanol without acid catalyst; however, this was attributed to the formation of a hemiacetal,

$$HSCH_2CH_2OH + R\overset{H}{C}{=}O \underset{\longleftarrow}{\overset{H^+}{\longrightarrow}} RCH(OH)SCH_2CH_2OH.$$
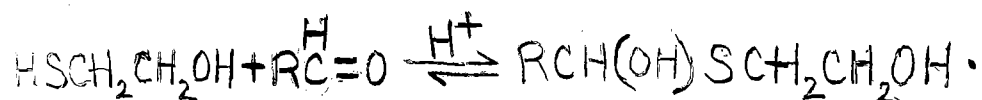
When it was realized that the hemiacetal of mercaptoethanol and
propionaldehyde would most likely be water-soluble, whereas the
material obtained by the "uncatalyzed"[3] reaction of propanal and
2-mercaptoethanol showed no signs of water solubility, it was con-
cluded that the observed exothermic reaction might involve cyclization
to the 1,3-oxathiolane. To test the hypothesis that the use of cata-
lyst in the formation of oxathiolanes from aldehydes is unnecessary,
the following procedure was used for the preparation of aldehyde
derivatives.

Equimolar quantities of the aldehyde and 2-mercaptoethanol were
mixed with 100 ml. of benzene in the usual Stark-Dean apparatus. The
theoretical amount of water was collected and the reaction mixture
was distilled through an insulated twelve-ball Snyder column. A
biphenyl chaser was used and all material boiling within ten degrees
of the expected product was collected. This material was redistilled
to a boiling point range of three degrees and again to a range of one-
half degree. In this manner 2-ethyl-1,3-oxathiolane was prepared from
freshly distilled propanal. The yield of product, b.p. 147-50° C.,
was 35%.

Attempted preparation of 2-propyl-1,3-oxathiolane from commercial
butanal not further purified produced a 23% yield of material boiling
at 163-170° C. Although this could be further purified to a product
boiling at 169-170° C. with molar refractivity in good agreement with

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[3]Although this writer believes this reaction to be truly uncata-
lyzed, the possibility has not been eliminated that it is actually cata-
lyzed by traces of the corresponding organic acid, or by traces of
acid absorbed from the air.

the theoretical value for 2-propyl-1,3-oxathiolane, it cannot be categorically stated that this product _is_ 2-_n_-propyl-1,3-oxathiolane. The hydrogen analysis fits this compound almost perfectly, but the usually more accurate carbon percentage fits a homologue having one less carbon atom. It is possible that some impurity boiling in the same range is responsible for the faulty composition.

As considerable thermal decomposition was noted during distillation of these oxathiolanes derived from aldehydes, any further work should employ vacuum distillation for compounds of this type.

Two further methods of condensation were tested. The first procedure is a modification of that suggested by Fieser. (18). One-tenth mole of butanal and one-tenth mole of 2-mercaptoethanol were mixed in glacial acetic acid and allowed to stand. When no separation of layers occurred, the mixture was diluted to turbidity with water and allowed to stand overnight. The nonaqueous layer was separated and was found to have a density and refractive index which agreed closely with those found for the 169-170° C. cut previously described. Yield of crude product was approximately 80%.

The second procedure was even more successful. One-tenth mole of butanal and one-tenth mole of 2-mercaptoethanol were mixed together over 1 g. of sodium sulfate and allowed to stand for several hours, after which the two-phase mixture was separated. The nonaqueous phase was a very nearly quantitative yield of a liquid having the physical properties of the expected product. This procedure was checked using propanal. In this case the yield of 2-ethyl-1,3-oxathiolane was also very nearly quantitative.

This method appears to be a simple and very useful means of preparing oxathiolane derivatives of aldehydes. If this method works as well for other aldehydes as it did for the two tested, the oxathiolane derivatives of aldehydes may be made in very good yields with little further purification by simply using carefully weighed amounts of purified starting materials.

2-Mercaptoethanol and biacetyl without catalyst.
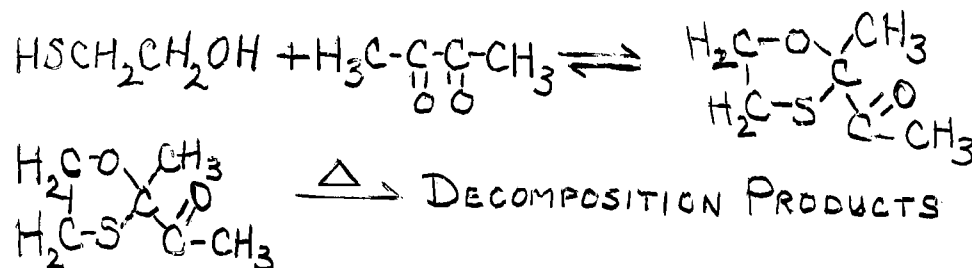
A mixture of 2,3-butanedione and 2-mercaptoethanol in the usual dehydration apparatus without catalyst was found to produce water in a quantity which suggested reaction of the 2-mercaptoethanol with but one of the two carbonyl groups. On the basis of this, an attempt was made to prepare 2-methyl-2-acetyl-1,3-oxathiolane from 2-mercaptoethanol and biacetyl trimer.[4] The reaction was begun with a two-to-one mole ration of 2-mercaptoethanol to biacetyl. When azeotropic water collection ceased at a quantity equal to the reaction of one-half of the 2-mercaptoethanol added (as had been expected), enough additional biacetyl trimer was added to allow for reaction of the entire quantity of 2-mercaptoethanol. Distillation of the reaction

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[4]Biacetyl trimer, m.p. 107-107.5° C., which was formed spontaneously upon the storage of the monomer in an aluminum container is easily weighed and readily reconverted to biacetyl by heating. Since it was available it was chosen as a source of pure biacetyl despite its own interest as a laboratory curiosity of unknown structure.

mixture produced, in addition to the benzene and biacetyl removed below 100° C., an intermediate fraction boiling at 148-180° C., and a high-boiling fraction above 200° C. A very small cut obtained at 180° C. had physical properties agreeing closely with those to be expected for 2-methyl-2-acetyl-1,3-oxathiolane. Redistillation of the entire intermediate fraction produced a quantity of water and biacetyl below 110° C., a quantity of 2-mercaptoethanol at 158-60° C., and a fraction boiling above 220° C. This last fraction proved to be identical to the fraction boiling at 268-270° C. formed in the acid-catalyzed reaction of 2-mercaptoethanol and biacetyl.

From the above it was concluded that it is probable that 2-methyl-2-acetyl-1,3-oxathiolane is formed initially, but that this compound undergoes a pyrolytic reaction at temperatures near its boiling point to form a number of decomposition products. It may be concluded also that only vacuum distillation should be involved in any work aimed at the isolation of the acetyl-oxathiolane. A chromatographic separation may be necessary as it has been reported that the only satisfactory method for separation of the 1,3-oxathiolane derivatives of 1,2-cyclohexanedione is a chromatographic separation on alumina. (25).

2-Mercaptoethanol and halogenated aldehydes.

$$HSCH_2CH_2OH + R_2CX\overset{H}{C}=O \rightleftharpoons R_2CX\overset{H}{\underset{O-CH_2}{C}}\overset{S-CH_2}{\big|}$$

$$HSCH_2CH_2OH + R_2CX\overset{H}{C}=O \xrightarrow{H^+} H[O-CH_2CH_2-S-\underset{R_2CX}{C}-]_n OH$$
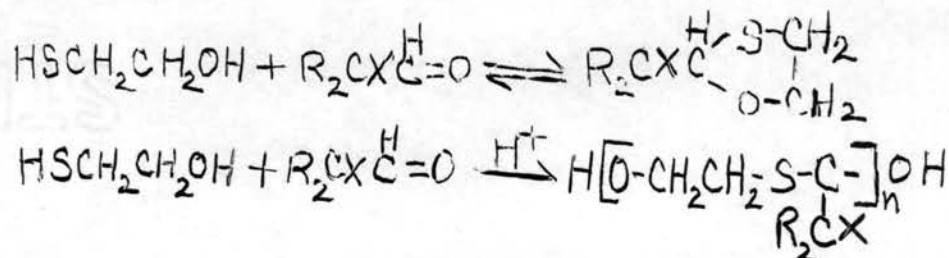
One-tenth of a mole of 2-mercaptoethanol mixed with one-tenth mole of chloral hydrate in 50 ml. of water gave rise to some 10 ml. of a white oil which separated spontaneously from the aqueous solution. If it is

the desired oxathiolane, this represents a yield of approximately 50%.
On standing, this oil took on a definite yellowish color; and it de-
composed completely on attempted distillation.

In the presence of an acid catalyst chloral hydrate and 2-mercapto-
ethanol produced a greyish-white wax with the evil, penetrating odor of
chloral. This material was completely intractable to any attempts at
crystallization or distillation, decomposing completely in the latter
case.

One-tenth of a mole of 2-mercaptoethanol mixed with an excess of
a 30% solution of chloroacetaldehyde reacted immediately and exother-
mally to give a brown gum difficultly soluble in alcohol. Since the
chloracetaldehyde undoubtedly contained some chloroacetic acid, it is
felt that this gum is probably analogous to the white wax formed in
the acid-catalyzed condensation of chloral with 2-mercaptoethanol.

Oxidation of Oxathiolanes

It was decided to use three readily available oxidants, 30%
hydrogen peroxide, benxoyl peroxide, and peracetic acid, in attempts
to prepare sulfones of 1,3-oxathiolanes. The use of benzoyl peroxide
either alone or in a variety of solvents resulted in the recovery of
unchanged benzoyl peroxide, with no evidence of any reaction having
taken place. Hydrogen peroxide in acetone[5] and peracetic acid in

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[5]When hydrogen peroxide appeared to be immiscible with 1,3-
oxathiolanes, acetone was added in large excess as a solvent. Acetone
is known to form peroxides, but only under highly acid conditions, so
that it was felt that oxidative attack on the sulfur would proceed
very rapidly and with minimum complications from the solvent. This
proved to be a somewhat short-sighted assumption in view of the fact
that oxidative attack on the sulfur occured so readily at the temper-
ature of boiling acetone that a strong acid was formed in the reaction
mixture.

ether-acetic acid produced some degree of success. The desired reaction

(a) and some possible complicating reactions are as follows:

(a) $R_2C\underset{\text{O}-CH_2}{\overset{\text{S}-CH_2}{\big<}} \xrightarrow{H_2O_2} R_2C\underset{\text{O}-CH_2}{\overset{\text{S}(O)-CH_2}{\big<}} \xrightarrow{H_2O_2} R_2C\underset{\text{O}-CH_2}{\overset{\text{S(O)}_2-CH_2}{\big<}}$

(b) $RCH\underset{\text{O}-CH_2}{\overset{\text{S}-CH_2}{\big<}} \xrightarrow{H_2O_2}$ $\underset{H_2C-O}{\overset{H_2C-S}{\big>}}R\text{-}C\text{-O-O-}C\text{-}R\underset{\text{O}-CH_2}{\overset{\text{S}-CH_2}{\big<}}$

(c) $RC\underset{\text{O}-CH_2}{\overset{\text{S(O)}_2-CH_2}{\big<}} \xrightarrow{H_2O_2} R_2C{=}O + HO\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}\text{-}CH_2CH_2OH$

(d) $RCH\underset{\text{O}-CH_2}{\overset{\text{S(O)}_2-CH_2}{\big<}} \xrightarrow{H_2O_2}$ $\underset{H_2C-O}{\overset{H_2C-S(O)}{\big>}}RC\text{-O-O-}C\text{-}RO\underset{\text{O}-CH_2}{\overset{\text{S(O)}-CH_2}{\big<}}$

(e) $R_2C{=}O \xrightarrow{H^+ + H_2O_2}$ (cyclic peroxide structures) AND (cyclic peroxide structure).
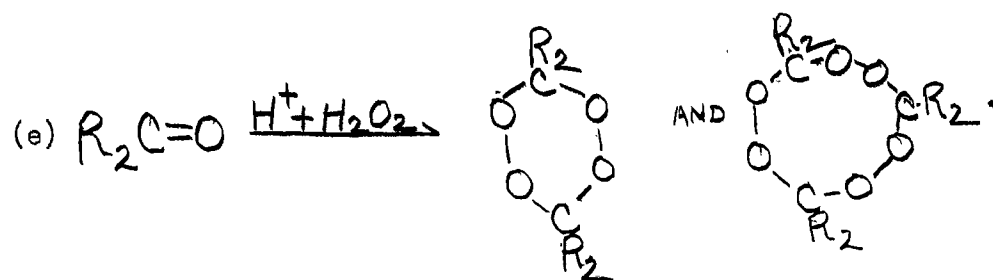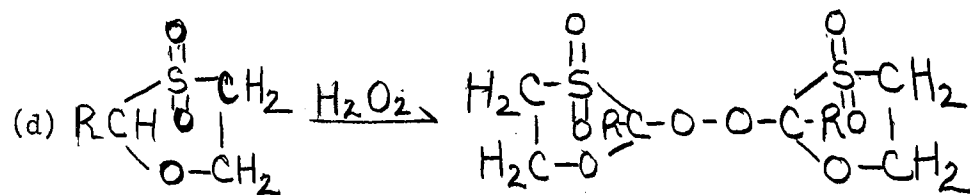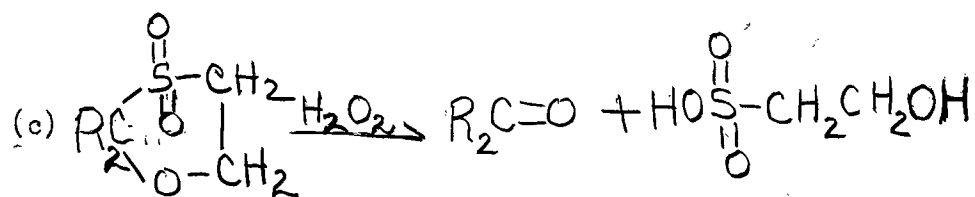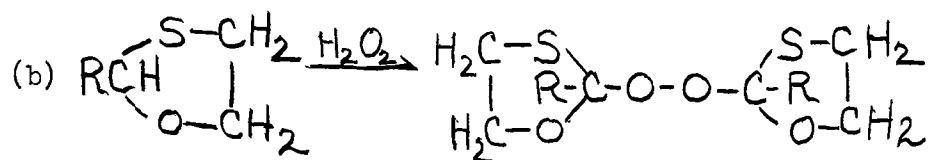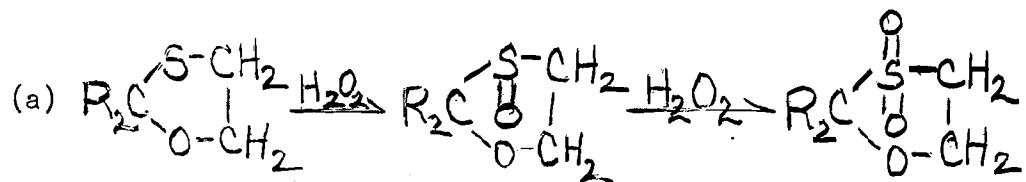
Two milliliters of 1,3-oxathiolane were treated with excess
hydrogen peroxide in acetone solution. A strongly exothermic reaction
took place, causing the acetone solvent to boil. After the subsidence
of the exothermic reaction, the remaining acetone was removed on the
steam bath. The residual material, a yellow oil, quickly solidified
to a crystalline mass containing some entrapped oil. This mixture was
washed twice with hot benzene. The oily residue remaining after the

benzene washing, dried at 105° C., became a brown water-soluble, acetone-insoluble semisolid. In water solution this semisolid proved highly acid. The cooled benzene extract precipitated white crystals still contaminated with a white oil. Dissolution of these crystals in hot acetone produced a two-phase system, the bottom phase being a yellowish oil. This yellow oil was washed with acetone twice more and the acetone washings were combined. When the acetone solution was evaporated, white crystals melting at 78-82° C. were obtained. This material, recrystallized from methanol and air-dried, melted at 81-82° C., had a faint sweet odor, and contained 25.4% sulfur. The calculated value for $C_3H_6O_3S$ is 26.5%. Analytical data on this and other sulfones are found in Table V.

When oxathiolanes other than 1,3-oxathiolane itself were oxidized with excess hydrogen peroxide in acetone solution and the resultant solutions were allowed to evaporate until crystals formed, the following results were noted. 2-Methyl-1,3-oxathiolane and methylene-bis-2,2'-(2-methyl-1,3-oxathiolane) gave no detectable crystalline product, but only a highly acid oil. The 2-ethyl-, 2-methyl-2-ethyl-, 2,2-dimethyl-, and 2-methyl-2-hexyl-1,3-oxathiolanes produced explosive crystalline compounds, or mixtures of compounds, melting between 88 and 125° C., the latter value being noted for the material obtained from the oxidation of 2-ethyl-1,3-oxathiolane.

Analysis of the previously listed explosive compounds showed sulfur to be completely absent. Comparison of the infrared spectra of these compounds leads to the conclusion that they are all primarily "dimeric acetone peroxide," 3,3,6,6-tetramethyl-1,2,4,5-tetraoxacyclohexane. The spectra appear to be identical and are definitely different

TABLE V

SULFONES PREPARED

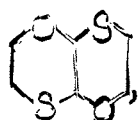| Parent Compound	M.P. $^{\circ}$ C.	Description	Analysis %	
			Theory	Found
1,3-Oxathiolane	81-82° C.	White crystals, faint, sweet odor	C 29.5 H 4.9 S 26.2	C 28.50-28.98 H 5.47- 5.32 S 25.4
3,2-Oxathiano-1,4- oxathiane	172-175° C.	Acetone-soluble white crystals	S 26.5 ($C_6H_{10}O_6S_2$)	S 24.8
By-product of above 1,4-oxathiane	d. 238-40° C.	Acetone-insoluble salt-like	S 26.5 ($C_6H_{10}O_6S_2$)	S 21.3
Product from 2-mercaptoethanol and biacetyl	d.>180° C.	Similar to above	S 23.7 ($C_8H_{16}O_6S_2$)	S 21.4

from the spectrum of a known sample of "trimeric acetone peroxide,"
3,3,6,6,9,9-hexamethyl-1,2,4,5,7,8-hexaoxacyclononane, made for compar-
ison purposes by the oxidation of acetone with 30% hydrogen peroxide in
concentrated hydrochloric acid.

The explosive compounds formed by oxidation of ethylene-bis-2,2'-
(2-methyl-1,3-oxathiolane) and, in one case, from the oxidation
of the "bis-1,3-oxathiolane" of glyoxal were found to be identical to
each other but to differ from the explosive compounds previously de-
scribed. Careful comparison of the spectra of these two derivatives
with that of "trimeric acetone peroxide" leads to the conclusion that
these products are probably identical to this compound.

Oxidation of the derivatives of biacetyl and glyoxal produced
somewhat different results than those quoted above. The present para-
graph deals with the oxidation of the various products (pg. 20) derived
from glyoxal. Upon oxidation with hydrogen peroxide or peracetic acid
the ether-soluble material, m.p. 74-76° C., yielded an acetone-soluble
material with a melting point of 176-8° C. and a sulfur content of
24.8%. The ether-insoluble portion upon oxidation gave a hard acetone-
insoluble, salt-like material, with a sulfur content of 21.3%, which
decomposed slowly at temperatures above 180° C. Oxidation of the
yellow oil recovered from the methanol and acetone from which the main
product was crystallized produced a white solid which melted with
decomposition at 238-240° C. Comparison of infrared spectra showed
that this solid was probably the main component of the acetone-insol-
uble oxidation product previously mentioned.

The trends of polarity indicated by the solubilities and melting
points of the two "oxathiolanes" under consideration and the solubil-
ities and melting points of their oxidation products, taken in

conjunction with the fact that their oxidation was a very high-yield

reaction in comparison with oxidation of most 1,3-oxathiolanes, lead

to the conclusion that the ether-insoluble material cannot be an

oxathiolane, and is probably a linear or branched-chain compound of

unknown structure. The ether-soluble material is probably the con-

densed-ring compound, 3,2-oxathiano-1,4-oxathiane. The oxida-

tion products should be the sulfones. As the theoretical sulfur con-

tent for a compound with formula $C_6H_{10}O_6S_2$ is 26.5%, the sulfone of

the oxathiano-oxathiane obtained may not have been of greater than

94% purity; as the structure of the other parent compound has not

even been postulated, it is impossible to estimate the purity of the

salt-like companion product.

Oxidation of the oil, b.p. 268-70° C., formed in the acid-cata-

lyzed reaction of 2-mercaptoethanol with biacetyl with either 30%

hydrogen peroxide or peracetic acid produced only a hard crystalline

compound similar, if not identical, to that noted from the ether-

insoluble fraction of the product from glyoxal. The sulfur content

of this last oxidation product was 21.4%, as compared with 21.3% noted

for the previous derivative.

Oxidation with hydrogen peroxide of the waxy material formed

from the acid-catalyzed reaction of chloral hydrate and 2-mercapto-

ethanol readily produced an amorphous white solid whose character lends

further credence to the writer's belief that this material is poly-

meric in nature and that the products of the acid-catalyzed reaction

of halogenated aldehydes with 2-mercaptoethanol are polymers analogous

to those derived from 1,3-oxathiolane by Feldman (17), and from 5-methyl-
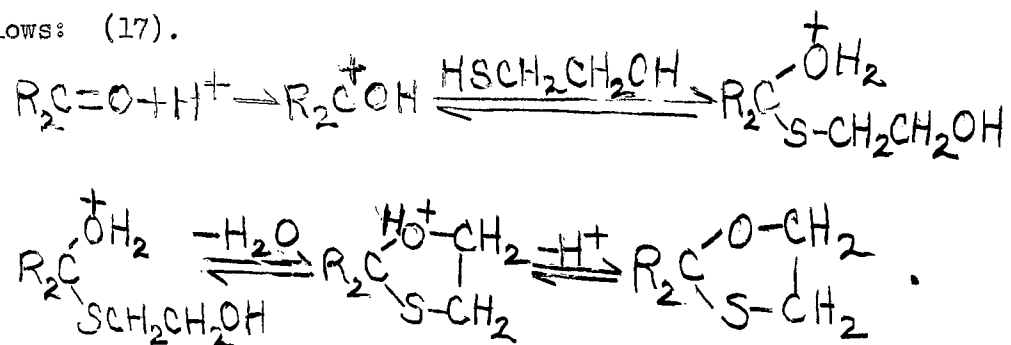
1,3-oxathiolane by Dermer. (8).

Oxidation of 2-substituted oxathiolanes with peracetic acid in ether-acetic acid solution produced only the free parent carbonyl compound as a readily identifiable product. 1,3-Oxathiolane itself was not tested with peracetic acid.
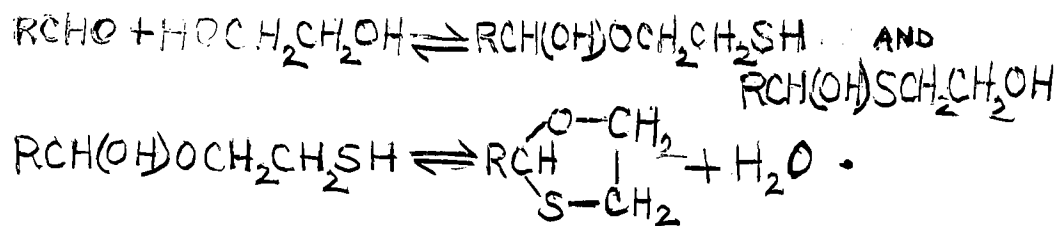
CHAPTER IV

DISCUSSION

Mechanisms

2-Mercaptoethanol reacts with carbonyl compounds to form cyclic
acetal-type compounds. These compounds are of two types, which differ
in certain properties, notably thermal stability, and may well be formed
through two slightly differing reaction mechanisms. The reaction of
2-mercaptoethanol with ketones to form the quite thermally stable
ketonic derivatives is the standard acid-catalyzed acetal (ketal)
formation which has been represented for this particular case as
follows: (17).

$$R_2C=O + H^+ \longrightarrow R_2\overset{+}{C}OH \xrightarrow[\;]{HSCH_2CH_2OH} R_2C\begin{smallmatrix}\nearrow \overset{+}{O}H_2 \\ \searrow S-CH_2CH_2OH\end{smallmatrix}$$

$$R_2C\begin{smallmatrix}\nearrow \overset{+}{O}H_2 \\ \searrow SCH_2CH_2OH\end{smallmatrix} \underset{-H_2O}{\rightleftharpoons} R_2C\begin{smallmatrix}\nearrow \overset{+}{H}\overset{+}{O}-CH_2 \\ \searrow S-CH_2 \end{smallmatrix} \underset{-H^+}{\rightleftharpoons} R_2C\begin{smallmatrix}\nearrow O-CH_2 \\ \searrow S-CH_2 \end{smallmatrix} \;.$$

The uncatalyzed reaction of 2-mercaptoethanol with aldehydes, how-
ever, probably involves attack upon the neutral aldehyde molecule rather
than upon the oxonium-carbonium ion system derived therefrom. The first
step in this reaction would be the formation of the hemiacetal
which is in equilibrium with the aldehyde and the alcohol, this hemi-
acetal would then cyclize with the elimination of water. This series
would be as follows:

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$$RCHO + HOCH_2CH_2OH \rightleftharpoons RCH(OH)OCH_2CH_2SH \quad \text{AND} \quad RCH(OH)SCH_2CH_2OH$$

$$RCH(OH)OCH_2CH_2SH \rightleftharpoons RCH\begin{array}{c} O-CH_2 \\ \big| \\ S-CH_2 \end{array} + H_2O \,.$$

The assumption that the cyclization takes place on the hemiacetal

form derived from the hydroxyl end of the mercaptoethanol is contrary

to the fairly well accepted mode of attack in the acid-catalyzed reac-

tion. As the mode of attack is unproven, any mechanism must neces-

sarily be only tentative; however, it is well known that both alcohols

and mercaptans readily form hemiacetal structures with aldehydes. It

seems reasonable that after the formation of the hemiacetal by the

alcohol end of the mercaptoethanol molecule, owing to the distinct

difference in the basicities of the hydroxyl oxygen of the hemiacetal

and the thiol sulfur of the mercaptoethanol residue, hydrogen transfer

between these two atoms with subsequent (or concurrent) loss of water

and cyclization would readily take place. The basicity of the hydroxyl

oxygen of the hemiacetal should be slightly enhanced by resonance

effects, whereas the basicity of the thiol sulfur would be strongly

decreased by the adjacent hemiacetal group with its difinite tendency

toward inductive electron withdrawal. It is felt that these effects

would be much less in the case of the thiohemiacetal[1] and that in the

case of this compound the differences in basicity between the hydroxyl

oxygen of the thiohemiacetal and the hydroxyl oxygen of the mercapto-

ethanol residue would not be sufficient to cause a facile reaction.

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[1]It may be well to note the distinction being made in this paper
between the terms "thiohemiacetal," RCH(OH)SR, a hemiacetal having
one oxygen replaced by sulfur, and "hemithioacetal," RCH(OR)SR, an
acetal having one of the two oxygens replaced by sulfur.

This is supported in part by the observation that acid is necessary for good yields in the preparation of dioxolanes. (14).
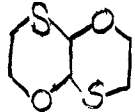
Thermal Stabilities

The derivatives of aldehydes seem to be considerably less stable to heat than are the ketonic derivatives. For example, 2,2-diisopropyl-1,3-oxathiolane, b.p. 198° C., can be distilled at atmospheric pressure with little apparent decomposition, while 2-n-propyl-1,3-oxathiolane, b.p. 163-4° C. (b.p. reported by Feldman), undergoes quite extensive decomposition at near its boiling point. Apparently activated 1,3-oxathiolanes of ketones, such as the monooxathiolane derivative of biacetyl, also readily undergo pyrolytic decomposition. 1,3-Oxathiolanes derived from aldehydes were found to decompose on prolonged heating to brownish oils or waxes of unknown composition. The mechanism involved is also unknown.

Stereoisomeric Considerations

In the preparation of 1,3-oxathiolane derivatives of polyketones not only is a variety of products possible, but also a variety of isomeric forms. The formation of an oxathiolane ring leads in most cases to the generation of an asymmetric carbon atom. All oxathiolanes formed from RCOR', where R and R' are not identical, will be theoretically resolvable into optical antimers. Possible products of the preparations of the double derivatives of 2,4-pentanedione and 2,5-hexanedione can exist as a pair of d,l-isomers and an isomeric meso form. Mono-derivative and polymeric compounds formed by cross-linking of molecules may be formed as byproducts. In the cases of glyoxal

and biacetyl derivatives not only are these possibilities present,

but also a quadruplet of d,l-cis,trans-forms of the condensed ring

system, . It is quite likely that the purified material

melting at 88.5-89.5° C. which was obtained from the reaction of one

mole of glyoxal with two moles of 2-mercaptoethanol is the d,l-trans-

pair of isomers of the condensed ring system. This compound, presumed

to be trans-3,2-oxathiano-1,4-oxathiane, can be shown with the aid of

Hershfelder models to constitute a planar compound, very similar in

shape to naphthalene, which is much more symmetrical in its dimensions

than other isomers and therefore should have the highest melting point

of the possible forms.

Consideration of the Hershfelder model of 2,3-dimethyl-3,2-oxathiano-

1,4-oxathiane, shows that this compound, in either the cis or the trans

form, should be hindered greatly in formation. The Hershfelder model

can be assembled but it is a very difficult task.

Oxidation Products

Although the products of oxidation of "oxathiolanes" have been

discussed quite extensively previously, it is not malapropos to make

some comment here also. The results of oxidation of compounds of the

oxathiolane type gave somewhat surprising results in that 1,3-oxathiolane

itself and the "oxathiolanes" derived from butanedione and from glyoxal

produced sulfone derivatives accompanied by only very small amounts of

decomposition products, while 2-alkyl-1,3-oxathiolanes reacted under

the same conditions to product only decomposition products, thought to

be primarily the parent ketone or aldehyde and 2-hydroxyethanesulfonic

acid.

The smooth oxidation, with very little apparent side reaction, of the solid white product from glyoxal and 2-mercaptoethanol to form a material quite stable to both acid and base which contains very nearly the theoretical amount of sulfur expected of a "dioxathiolane-disulfone," more particularly, 3,2-oxathiano-1,4—oxathiane-4,4,7,7-tetroxide, in conjunction with the comparatively high melting points of both this derivative and the parent compound, was a primary reason for the conclusion that this parent compound is probably 3,2-oxathiano-1,4-oxathiane rather than 2,2'-bi-1,3-oxathiolane. However, as 1,3-oxathiolane does form a sulfone quite readily, and as negative substituents, even another oxathiolane ring, may tend to stabilize the oxathiolane ring to oxidative scission, this oxidative evidence is far from conclusive.

Comparison of these oxidative results with Feldman's polymerization reactivities (17) shows a certain parallelism. 1,3-Oxathiolane oxidizes to form a sulfone and polymerizes to form a "polyoxathiolane," whereas the 2-alkyl-1,3-oxathiolanes apparently split readily in each case to regenerate the parent carbonyl compound. The small amount of work done with chloral in the course of this investigation suggests that in cases in which the 2-substituent has electron-withdrawing properties rather than electron-releasing properties the polyoxathiolane will be formed upon acid-catalyzed decomposition. This is in agreement with conclusions inferred from the two mechanisms of decomposition given by Feldman (17) and quoted in the historical section of this paper.

Possible Extensions and Related Problems

As is clear from previous comments, the constitution of the products of the reaction of 2-mercaptoethanol with compounds having vicinal

carbonyl groups is far from being solved. The careful preparation, separation, and proof of structure of the products formed by the reaction of mercaptoethanol with glyoxal both with and without acid catalysis would in itself constitute a good unit of research. Any attack upon this problem should be based upon the reaction of mercaptoethanol with a good grade of monomeric, or at least purified, glyoxal. The use of the commercially available 30% aqueous solution of glyoxal obscures and obstructs the problem in several ways. The excess water present makes careful measurement of reactants a difficult proposition and causes mensuration of the extent of reaction by the collection of the water formed in the reaction a virtual impossibility. The glyoxal in such a solution is thought to exist in a polymeric form which must depolymerize before reaction can occur. To further complicate the process, this aqueous glyoxal undoubtedly contains appreciable amounts of glycolaldehyde, ethylene glycol, glycolic acid, and oxalic acid. This makes separation of products very difficult, to say nothing of making it impossible to make any differentiation between the products formed in an acid-catalyzed reaction and an uncatalyzed reaction. It is possible that a chromatographic separation might be necessary. Solution of the problems presented by biacetyl and other vicinal diones might well follow readily from results of a careful investigation of the derivatives of glyoxal.

In the preparation of the derivatives of dicarbonyl compounds a variety of colors was noted. These apparently varied with the acid concentration; and, although their structures are unknown, it is probable that they are oxonium salts. An attempt to determine the structures responsible for the noted colors might give some interesting

information. Possibly some sort of an analytical procedure for oxathiolane groups could be based upon these colored materials.

The dihalogen salts of oxathiolanes, $R_2C\begin{smallmatrix}O-CH_2\\|\\S-CH_2\end{smallmatrix}$, have not

been reported. These might bear investigation, both for their own sake and as a possible analytical method. If these salts can be formed, their hydrolysis to sulfoxides would be a logical further extension. Also careful low-temperature oxidations should be carried out to prepare the oxathiolane sulfones and sulfoxides. Deliberate thermal decomposition of oxathiolanes derived from aldehydes with subsequent identification of products might shed some light on the chemistry of this type of compound.
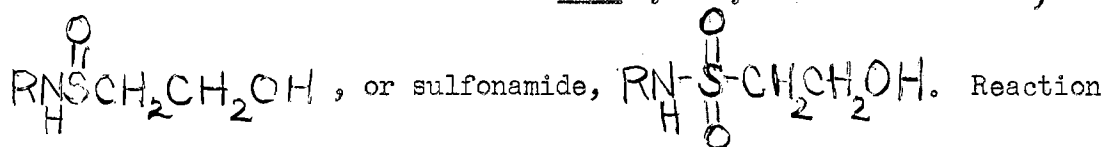
It might be possible to form hemithioacetals in good yields by proper reaction of an aldehyde, alcohol, and mercaptan without the use of an acid catalyst:

$$RCHO + HSR + HOR' \rightleftharpoons RC\begin{smallmatrix}S-R\\H\\O-R'\end{smallmatrix} .$$

This prediction is based upon the guess that the reaction of a mercaptan with a hemiacetal is perferential to the reaction of an alcohol with a hemiacetal or of a mercaptan with a thiohemiacetal. From the results of Feldman (17, pg. 20) as to the stability of dioxolanes, oxathiolanes, and dithiolanes to acid, it may be predicted that acid catalysis of the above reaction would produce a mixture of acetal and dithioacetal.

In two short experiments 2-mercaptoethanol was mixed with 1-nitroso-2-naphthol, and with 2-nitroso-1-naphthol. In each case an exothermic reaction took place, in the first instance with almost explosive violence. In each case two products were formed, a black,

amorphous material and a brownish, base-soluble, acid-insoluble material which was crystalline when dry. No attempt was made to determine the structure of either product. One remote possibility for the crystalline material is that it is a <u>beta</u>-hydroxyethane-sulfinamide,

$$RN\overset{O}{\underset{H}{\overset{\|}{S}}}CH_2CH_2OH \text{, or sulfonamide, } RN\overset{O}{\underset{H}{\overset{\|}{S}}}\text{-}CH_2CH_2OH.$$ Reaction

of 2-mercaptoethanol with these and other analogs of carbonyl compounds probably would produce interesting compounds, although not necessarily cyclic ones. Attempted preparation of cyclic compounds from nitroso compounds and diols might be worth investigation although it is very possible that these, if formed, would spontaneously undergo intra-molecular oxidation-reduction to form entirely unexpected end products.

Investigation of catalysts and conditions for the trimerization of vicinal diketones might prove to be profitable. These trimers might serve as a convenient form for shipping high-purity diones, might have physiological activity, and might have a very interesting cage structure; however, stereochemical factors may prevent the formation of higher analogs of the trimer of biacetyl.

CHAPTER V

SUMMARY

1,3-Oxathiolanes may be formed from carbonyl compounds and 2-mercaptoethanol in an acid-catalyzed reaction similar to that by which dioxolanes are formed. The most satisfactory procedure involves the use of a saturated solution of p-toluenesulfonic acid in benzene as catalyst and entrainer for water removal.

1,3-Oxathiolane may be prepared in reasonable yields by reacting 2-mercaptoethanol and paraformaldehyde with acid catalyst and distilling out the oxathiolane as it is formed. This method may also be used, with somewhat lower yields, on other low-boiling aldehydes and ketones.

1,3-Oxathiolanes of aldehydes are formed without acid catalysis when the monomeric aldehyde and 2-mercaptoethanol are caused to react under dehydrating conditions. The extent to which this reaction goes to completion without dehydration was not determined.

2-Mercaptoethanol with various dicarbonyl compounds produced mixtures of products which were difficult to resolve by crystallization techniques. Solid derivatives of 2,4-pentanedione and 2,5-hexanedione were prepared, as well as a solid thought to be a derivative of glyoxal. Work on biacetyl led to the conclusion that a mono-oxathiolane derivative is readily formed, but this is decomposed by heat to form products which have not been definitely identified.

1,3-Oxathiolanes derived from ketones are relatively stable to heat. Those derived from aldehydes undergo pyrolysis more readily, yielding brownish oils of unknown composition.

1,3-Oxathiolanes derived from chloral and chloroacetaldehyde and other negatively substituted 1,3-oxathiolanes probably undergo polymerization readily.

1,3-Oxathiolane and compounds derived from glyoxal and 2,3-butanedione, upon oxidation with hydrogen peroxide in acetone solution at the temperature of boiling acetone, produced solid derivatives considered to be sulfones. Oxidation of other 1,3-oxathiolanes under these conditions resulted in the regeneration of the parent carbonyl compound with the formation of an acid thought to be 2-hydroxyethane-sulfonic acid. Oxidation with peracetic acid in ether-acetic acid led to similar results.

2-Alkyl-1,3-oxathiolanes produced an explosive product tentatively identified as the dimer of acetone peroxide when reaction mixtures from their oxidation with hydrogen peroxide in acetone solution were allowed to evaporate until crystals formed; in the case of two 1,3-oxathiolane derivatives of diones another product tentatively identified as the trimer of acetone peroxide was formed.

The following previously unreported compounds were prepared and definitely characterized: 1,3-oxathiolane, 2-ethyl-1,3-oxathiolane, 2,2-diisopropyl-1,3-oxathiolane, 2-methyl-2-n-pentyl-1,3-oxathiolane, 2-ethyl-2-n-butyl-1,3-oxathiolane, 2-methyl-2-n-hexyl-1,3-oxathiolane, methylene-bis-2,2' -(2-methyl-1,3-oxathiolane), ethylene-bis-2,2'-(2-methyl-1,3-oxathiolane), 1,3-oxathiolane-3,3-dioxide, and 1,7,7-trimethyl-bicyclo [2.1.2] heptane-2-spiro-2' -1',3'-oxathiolane ("camphor oxathiolane").

Compounds thought to be 3,2-oxathiano-1,4-oxathiane and 3,2-oxathiano-1,4-oxathiane-4,4,7,7,-tetroxide were also prepared as well as a number of compounds which are of unknown structure.

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