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Chemistry of [beta]-keto sulfoxides

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CHEMISTRY OF β-KETO SULFOXIDES

by

Leo Arthur Ochrymowycz

A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of

The Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

In Charge of Major Work

Head of Major Department

Dean of Graduate College

Iowa State University
Of Science and Technology
Ames, Iowa

1969

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INTRODUCTION

Within the highly exploited science of organic chemistry, few specific areas of research endeavor have experienced a greater development in a shorter time than the cumulative chemistry of sulfoxides. The kaleidoscope of chemical versatility displayed by the sulfoxide function defies a comprehensive review. If a descriptive effort in the broadest terms is to be made, the following characteristics of the sulfoxide grouping merit consideration:

The intermediate oxidation state of sulfoxides allows them to function as both oxidizing and reducing agents.

Sulfoxides function as ambident nucleophiles with electrophilic attack at either oxygen or sulfur.

Sulfoxides function as ambident ligands toward metal ions by coordination through either oxygen or sulfur.

Sulfoxides are substances of high polarity, which in part is the basis of not only their remarkable solvent properties, but also their unusual chemical reactivity.
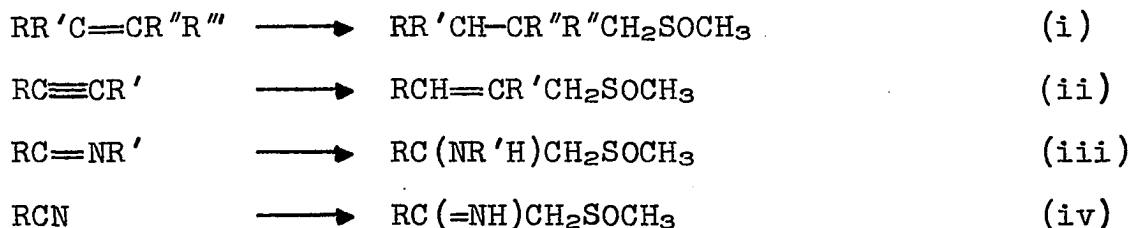
The sulfoxide electronic configuration results in a stable pyramidal structure, allowing for stereochemical study.

The sulfoxide electronic structure is capable of stabilizing adjacent carbanions by a combination of coulombic effects and sulfur d-orbital resonance.

The cumulative properties of sulfoxides are epitomized in their tendency to undergo rearrangement.

Dimethyl sulfoxide (DMSO) is by far the most important sulfoxide. Its dipolar and aprotic nature alone does not single it apart from other solvents possessing these properties. As a solvent, it is unique by the fact that anions, particularly small non-polarizable anions, are poorly solvated in DMSO. This results in enhanced reactivity for such anions.

Beyond its phenomenal solvent properties, DMSO has revealed a tremendous potential as a chemical reagent. It has fulfilled the general synthetic objectives of an oxidizing reagent toward sp^3 carbon with active methylene, halide, alcohol, or alcohol derivative functionality. However, its most dramatic reagent application has involved the utilization of the stabilized carbanion of DMSO, (methylsulfinyl)methide ($CH_3SOCH_2^-$). Nucleophilic incorporation of the methylsulfinyl-methylene group (CH_3SOCH_2—) is a means of adding a carbon atom to a wide variety of organic molecules, (Equations i-viii), such as alkenes, alkynes, multiple carbon-nitrogen bonded molecules, halides, epoxides, ketonic carbonyls and esters.

$$RR'C=CR''R''' \longrightarrow RR'CH-CR''R''CH_2SOCH_3 \qquad (i)$$

$$RC\equiv CR' \longrightarrow RCH=CR'CH_2SOCH_3 \qquad (ii)$$

$$RC=NR' \longrightarrow RC(NR'H)CH_2SOCH_3 \qquad (iii)$$

$$RCN \longrightarrow RC(=NH)CH_2SOCH_3 \qquad (iv)$$

$$RX \longrightarrow RCH_2SOCH_3 \qquad (v)$$

$$RR'C \overset{O}{\triangle} CR''R''' \longrightarrow RR'C(OH)CR'R''CH_2SOCH_3 \qquad (vi)$$

$$RR'CO \longrightarrow RR'C(OH)CH_2SOCH_3 \qquad (vii)$$

$$RCO_2R' \longrightarrow RCOCH_2SOCH_3 \qquad (viii)$$
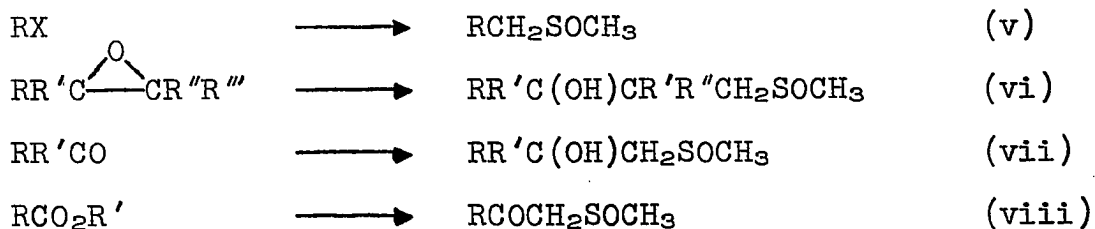
Of the various products derived from (methylsulfinyl)-methide condensation, the β-keto sulfoxides, Equation viii, resulting from condensation with carboxylic esters, have proven to be as fascinating reagents as DMSO itself. Within the past six years, Professor Russell and co-workers have extensively utilized the bifunctional nature of β-keto sulfoxides to devise practical synthetic procedures for a host of sulfur-containing and sulfur-free compounds. The present study is in part a continuation and supplementation of this elegant synthetic groundwork developed through the complementary efforts of Dr. Hans-Dieter Becker, Dr. Gerard J. Mikol (1) and Dr. Edward T. Sabourin (2).

Of particular interest to this study is the ability of the sulfoxide group to function as a potential carbonyl protecting-group by means of its facile transformation to the mercaptal function, Equation ix.

$$RCOCH_2SOCH_3 \longrightarrow \longrightarrow RCOCH(SCH_3)_2 \qquad (ix)$$
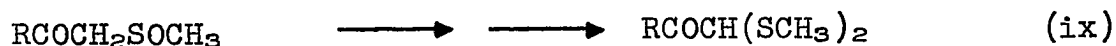
In this fashion, the extensive synthetic application of β-keto sulfoxides is coupled with the novel chemistry of α-keto mercaptals.

Both as a matter of practical limitation and experimental convenience, the study has been mainly concerned with ω-(methylsulfinyl)acetophenone ($C_6H_5COCH_2SOCH_3$). This β-keto sulfoxide can be conveniently prepared in high yield and in a high state of purity. Furthermore, the various products derivable from ω-(methylsulfinyl)acetophenone and the methyl-mercaptal of phenylglyoxal ($C_6H_5COCH(SCH_3)_2$) possess ideal physical, chemical, and spectral properties for isolation, purification and identification by conventional chromatographic and instrumental techniques. In terms of general application, it is envisioned that the synthetic procedures devised are not unique to the aryl derivatives.

LITERATURE SURVEY

The preparation, structure and chemistry of sulfoxides is discussed in general reviews. Dimethyl sulfoxide has received particular emphasis because of its unique chemical and solvent properties and the discovery of pharmacological applications (3-13). Unpublished reviews dealing with the generation and properties of the methylsulfinylcarbanion have been compiled (1, 2).

Methylsulfinylcarbanion has been prepared under equilibrium conditions and in an irreversible fashion. Equilibrium generation has been achieved by equilibration with alkali metal alkoxides (14-17). Two values for the equilibrium constant

$$CH_3SOCH_3 + \underline{t}\text{-BuOK} \xrightleftharpoons{\text{Keq}} CH_3SOCH_2K + \underline{t}\text{-BuOH} \qquad (1)$$

(Keq) have been reported, Keq = 1.5 x 10^{-7} at 25°C (17) in the presence of a large excess of $\underline{t}$-butanol and Keq = 3.3 x 10^{-5} at 25°C (18) in pure dimethyl sulfoxide. Although the carbanion concentration is low since Keq favors the alkoxide, rapid and nearly quantitative adduct formation on reaction of methyl-sulfinylcarbanion with benzophenone (19, 20) is taken as evidence that equilibrium, Equation 7, is rapidly established (21).

$$Ph_2CO + CH_3SOCH_2K \xrightleftharpoons{} Ph_2C(OK)CH_2SOCH_3 \qquad (2)$$

Irreversible formation of the methylsulfinylcarbanion can be affected with alkali metal hydrides, amides and alkyllithium

compounds (14, 19, 22).   The carbanion generated in this

$$CH_3SOCH_3 + MH \longrightarrow CH_3SOCH_2M + H_2 \qquad (3)$$

$$CH_3SOCH_3 + MNH_2 \longrightarrow CH_3SOCH_2M + NH_3 \qquad (4)$$

$$CH_3SOCH_3 + \underline{n}\text{-BuLi} \longrightarrow CH_3SOCH_2Li + \underline{n}\text{-BuH} \qquad (5)$$
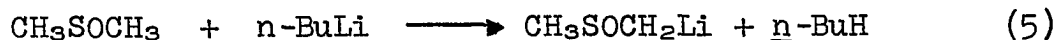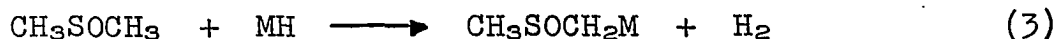
manner is extremely reactive and the term "dimsyl" anion has been coined to distinguish it from methylsulfinylcarbanion prepared under equilibrium conditions (23). This distinction is pertinent in view of the range of basicity, H^-, available in different solvent and base systems. H^- increases from 12 to 19 as the solvent is changed from pure methanol to 5% methanol-95% dimethyl sulfoxide in the sodium methoxide-methanol-dimethyl sulfoxide system (24). In the same system, 0.02% alcohol content raises the basicity, H^-, to 27 (23), while the H^- of dimsylsodium has been placed between 31 ~ 33 (21, 23).

Further illustration of the difference between dimsyl-anion and equilibrium-generated methylsulfinylcarbanion is observed in their reactions. The topic has been reviewed (25), but one dramatic example deserves mention. Dimsylsodium reacts with 1,2,5,6-tetrabromocyclooctane by direct nucleophilic displacement on halogen to yield 1,5-cyclooctadiene, while potassium methylsulfinylcarbanion dehydrohalogenates to yield cyclooctatetraene (26). This difference has been attributed to potassium $\underline{t}$-butoxide as the predominant basic species in the potassium methylsulfinylcarbanion system.

Reaction of t-butoxide leading to O-H bond formation and de-
hydrohalogenation is considered more favorable than O-Br
bond formation and dehalogenation.

Routine preparation of dimsylsodium is conveniently
achieved by heating an efficiently stirred suspension of
sodium hydride under a static nitrogen pressure at 70 ~ 75°C
(20). The resulting yellowish-brown solution shows no de-
crease of reactivity from slight decomposition. Above 80°C
extensive decomposition results. Caution should be observed
in view of reported explosive decomposition with excessivly
high sodium hydride to dimethyl sulfoxide ratios in the 70 ~
80°C temperature range (27, 28). As the ultimate precaution,
dimsylsodium can be prepared at room temperature by subject-
ing a suspension of sodium hydride in dimethyl sulfoxide to
ultrasonic radiation instead of heat (29). The resulting
preparation is claimed to be colorless and stable indefinite-
ly if stored under a layer of anhydrous mineral oil and frozen
between aliquot extraction. Dimsyllithium, reported prep-
aration in routine fashion with lithium hydride (22) and
n-butyllithium (30), is difficult to prepare at best. Lithium
hydride is of lower relative reactivity to sodium hydride,
and its low density, $\rho = 0.78$, causes it to float in dimethyl
sulfoxide. In order to affect complete dissolution, pro-
longed heating and high-speed stirring is required, which
yields an extensively decomposed solution with little

practical synthetic application. Similarly, n-butyl lithium

yields highly decomposed solutions of dimsyllithium. This may

be due to excessive conversion of n-butyllithium by dimethyl

sulfoxide to yield dimethyl sulfide in an analogous fashion to

the reduction of aromatic alkyl sulfoxides by phenyllithium

(31).

Recently, the preparation of 1,3-dialkali salts of dimethyl

sulfoxide have been reported (32, 33). The preparation was

affected by adding dimethyl sulfoxide to two equivalents of

alkali metal amides in anhydrous liquid ammonia, or two

equivalents of n-butyllithium to a dimethylsulfoxide solution

in hexane-tetrahydrofuran. Chemical reactivity was cited as

$$CH_3SOCH_3 \ + \ 2 \ MNH_2(NH_{3l}) \longrightarrow MCH_2SOCH_2M \qquad (6)$$

$$(M = Li, \ Na, \ K)$$

$$CH_3SOCH_3 \ + \ 2 \ \underline{n}\text{-BuLi (hexane)} \xrightarrow{\text{THF}} MCH_2SOCH_2M + 2 \ \underline{n}\text{-BuH} \qquad (7)$$
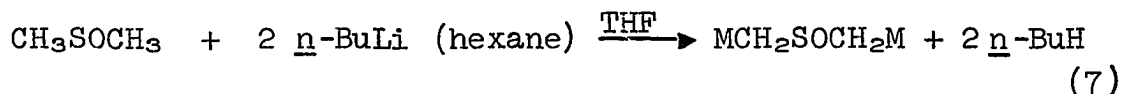
evidence for the 1,3-dianion structure. Reaction with benzo-

phenone yielded the 1,3-diadduct, Equation 8, with only a

trace of monoadduct formation. Further, preformed monoadduct

under identical reaction conditions yielded the sodium amide

adduct of benzophenone (Equation 10) (32).

$$2 \ Ph_2CO + MCH_2SOCH_2M \ \underset{\xleftarrow{\hspace{1cm}}}{\xrightarrow{\text{NH}_3}} \ Ph_2C(OM)CH_2SOCH_2(OM)CPh_2 \qquad (8)$$

$$Ph_2C(OM)CH_2SOCH_2(OM)CPh_2 \ \underset{\xleftarrow{\hspace{1cm}}}{\xrightarrow{\text{NH}_3}} \ Ph_2C(OM)CH_2SOCH_2M + Ph_2CO \qquad (9)$$

$$Ph_2C(OH)CH_2SOCH_3 + NaNH_2 \xrightleftharpoons{NH_3} Ph_2C\overset{ONa}{\underset{NH_2}{\diagup}} + CH_3SOCH_3 \qquad (10)$$
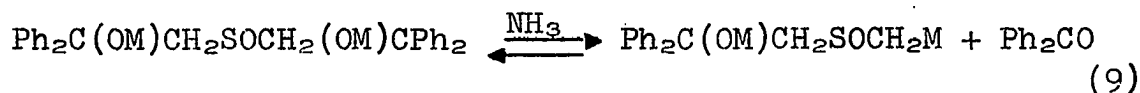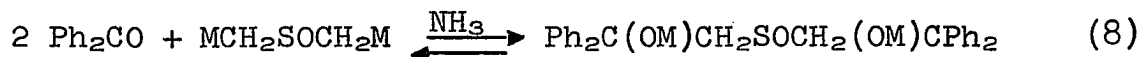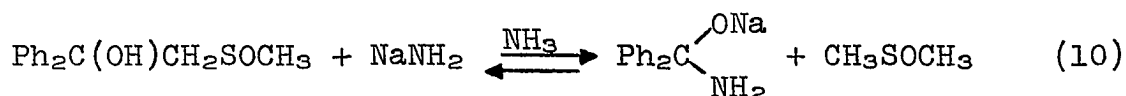
Reaction of the lithium dianion of dimethyl sulfoxide with aliphatic halides gave the 1,3-diadduct chain extension products in high yield (33). Further, preformed aliphatic-sulfinylmethide salts, Equation 11, reacted exclusively to yield the 1,3-diadduct, with no 1,1-diadduct observed.

$$2\ RX + LiCH_2SOCH_2Li \xrightarrow{THF} RCH_2SOCH_2R + 2\ LiX \qquad (11)$$

$$RCH_2SOCH_2Li + RX \xrightarrow{THF} RCH_2SOCH_2R + LiX \qquad (12)$$
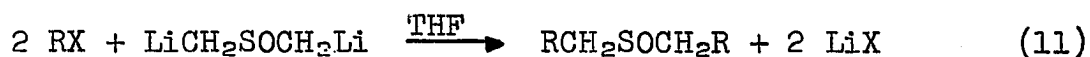
Surprisingly, under essentially identical reaction conditions for 1,3-dialkali salt formation of dimethyl sulfoxide, dimethyl sulfone failed to give evidence for 1,3-dianion formation (34). However, the 1,3-dianion of dibenzyl sulfone ($PhCH(M)SO_2CH(M)CPh$) has been prepared in liquid ammonia (35).

Various types of organic molecules can function as substrates for adduct formation with methylsulfinylcarbanion, Figure 1.

Adduct formation with sp^3 carbon is limited to two apparently isolated reports of nucleophilic displacement on alkyl halides (33, 36).

$$
\begin{array}{ccc}
\overset{\text{OH}}{\underset{|}{\text{RCHCHRCH}_2\text{SOCH}_3}} & \overset{\text{OH}}{\underset{|}{\text{R}_2\text{CCH}_2\text{SOCH}_3}} & \text{RCOCH}_2\text{SOCH}_3
\end{array}
$$
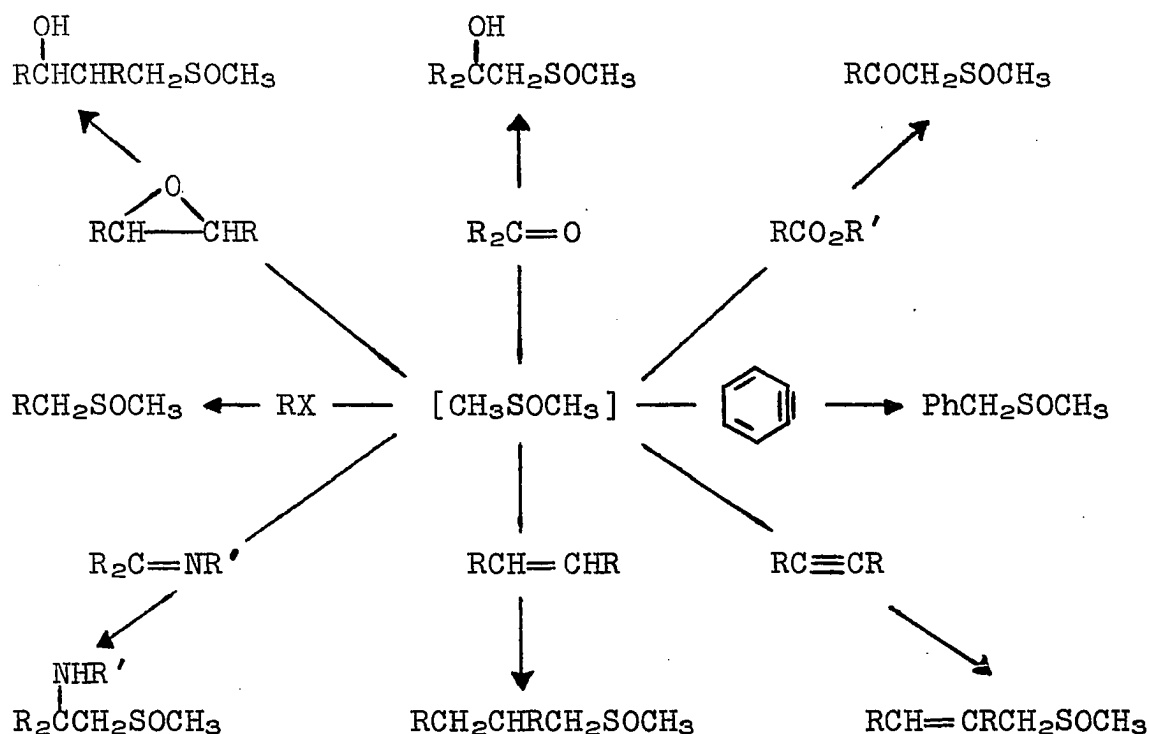
Figure 1. Condensation reactions of methylsulfinylcarbanion with organic substrates.

Examples of adduct formation with unsaturated carbon functions are numerous. Olefins (21, 37-39) add methyl-sulfinylcarbanion in particularly good yields for the case of aryl conjugated olefins. A specific procedure has been developed to prepare cyclopropane and propene derivatives by _in situ_ addition of methylsulfinylcarbanion to substituted styrene followed by γ-elimination of methylsulfenate anion (40). Mixtures of _cis_ and _trans_ monoadducts are obtained on

reaction with disubstituted acetylenes or 1,3-butadiynes, while unsubstituted acetylenes polymerize (41, 42). Addition to benzyne is known (19, 22). Methylation of polycyclic aromatics can occur in methylsulfinylcarbanion media (39, 43). Products apparently result from carbanion addition to the aromatic π-bond, followed by base-catalyzed elimination of methylsulfinate.

Additions of methylsulfinylcarbanion to the carbon-nitrogen multiple bond have been reported in the case of Schiff bases (22, 44), but condensations with the nitrile function are to date, absent from the literature. This study, however, has shown the reaction to be feasible.

As previously mentioned, the carbonyl function condenses with the methylsulfinylcarbanion to yield β-hydroxy sulfoxides. Both aromatic ketones (15, 19, 20, 21, 32, 33, 37) and aromatic aldehydes (19, 22, 45) form adducts with ease. Aliphatic carbonyls, particularly non-enolizable ketones, tend to undergo cleavage to carboxylic acids and alkanes (46). The formation of β-hydroxy sulfoxide is most facile with benzophenone. At room temperature, the adduct is formed in over 90% yield (37), Equation 2. However, at 80°C, Equation 13, the adduct undergoes in situ decomposition to yield diphenylacetaldehyde and 1,1-diphenylethylene (21, 37). Epoxides, in analogous fashion to carbonyl, condense with methylsulfinylcarbanion to yield δ-hydroxy sulfoxides (36,

47, 48).

$$Ph_2\overset{O^-}{\underset{}{C}}CH_2SOCH_3 \xrightarrow[\text{DMSO}]{80^\circ C} \begin{cases} \left[Ph_2\overset{\displaystyle \overset{CH_3}{\underset{}{O-S-O^-}}}{\underset{}{C}}—CH_2 \right] \longrightarrow Ph_2C{=\!=}CH_2 \qquad (13) \\ \\ [Ph_2C\overset{O}{\frown}CH_2] + CH_3SO^- \longrightarrow Ph_2CHCHO \end{cases}$$
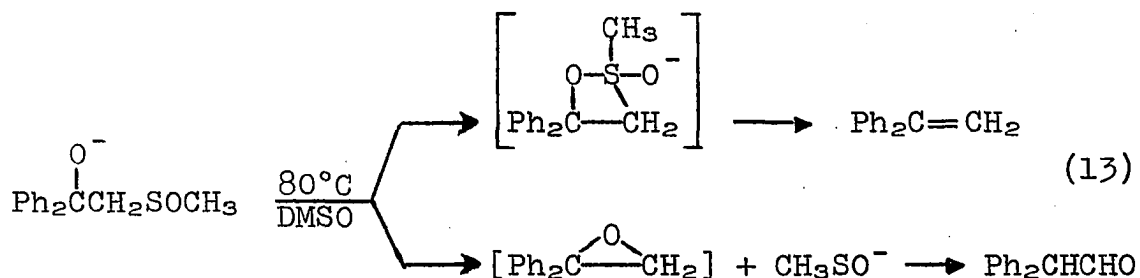
Although the incorporation of the methylsulfinylmethylene grouping (CH_3SOCH_2—) into the molecules mentioned above provides important synthetic intermediates, β-keto sulfoxides, Equation 14, from methylsulfinylcarbanion condensation with

$$RCO_2R' + CH_3SOCH_2^- \longrightarrow RCOCH_2SOCH_3 + R'O^- \qquad (14)$$

carboxylic esters provide the greatest utility. They consti-tute an entirely new class of compound, available only since 1963. The first example, ω-(methylsulfinyl)-p-methoxy-acetophenone (p-$CH_3OPhCOCH_2SOCH_3$), was prepared by manganese dioxide oxidation of the β-hydroxy sulfoxide adduct from methylsulfinylcarbanion addition to anisaldehyde (45). Esters of phenylsulfinylacetic acid ($PhSOCH_2CO_2R$) (49), which con-tain the carbonyl group beta to the sulfoxide function, have been known since 1909, but transformation of the esters to β-keto sulfoxides has not been affected. β-Keto sulfides and β-keto sulfones likewise have been known for two decades (50-52). However, direct oxidation of β-keto sulfide to β-keto

sulfoxide has not been reported to date. The major problem of over-oxidation of sulfoxide to the sulfone appears to be competitive with initial oxidation leading to sulfoxide. This observation is surprising in view of studies (53, 54) on aromatic sulfoxides with peroxy oxidants, which indicate by good sigma-rho correlation, that ease of oxidation increases with increase of electron density on sulfur. In the absence of other effects, however, the inductive effect of the carbonyl group in β-keto sulfoxides should decrease electron charge density at sulfur and retard over-oxidation. With this speculation in mind, a number of highly selective oxidizing reagents have recently been reported which appear to be promising for control of over-oxidation. Notably, the active halogen reagents, $\underline{t}$-butyl hypochlorite (55) and 1-chloro-benztriazole (56) are reported to offer clean oxidation to sulfoxide at low temperature, even in the presence of excess oxidant. Most promising, however, appears to be chloramine-β (57), Equation 15, which forms stable adducts with sulfides

$$PhSO_2\overset{\overset{\displaystyle Na}{|}}{N}Cl + R_2S \longrightarrow PhSO_2-N=SR_2 + NaCl \qquad (15)$$

$$PhSO_2-N=SR_2 + H_2O \longrightarrow PhSO_2NH_2 + R_2SO \qquad (16)$$
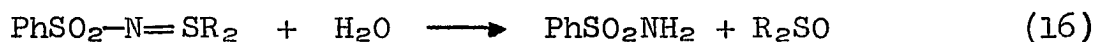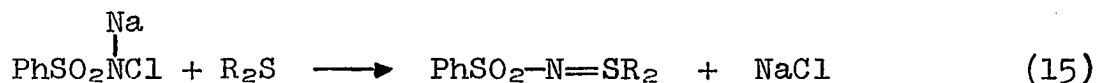
that readily hydrolyze to the sulfoxides.

The discovery (16) that the methylsulfinylcarbanion yields β-keto sulfoxides by ester condensation has inspired extensive research demonstrating the convenience and general
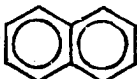
scope of the reaction, Equation 14. Original application was limited to reactions with aromatic esters (16, 22, 30). Optimum yields were obtained under conditions of equilibrium generation of the methylsulfinylcarbanion, with the exception of the p-toluates, which self-condensed under equilibrium conditions due to acidic aromatic methyl protons (58). Dimsylsodium condensation overcame this difficulty (1). The use of dimsylsodium has extended the reaction to numerous examples of condensation with aliphatic esters (59-62), including polyfunctional esters such as methyl 10-undecenoate (61) and esters of sugar acids (63). Under the proper reaction conditions, dibasic esters will react with methylsulfinylcarbanion and excess base to yield cyclized products (2, 64). An elegant application, Equations 17 and 18, is depicted for the conversion of diethylphthalate to 2-(methylsulfinyl)-1,3-indandione, an intermediate leading to ninhydrin (14). The

$$(17)$$

$$(18)$$
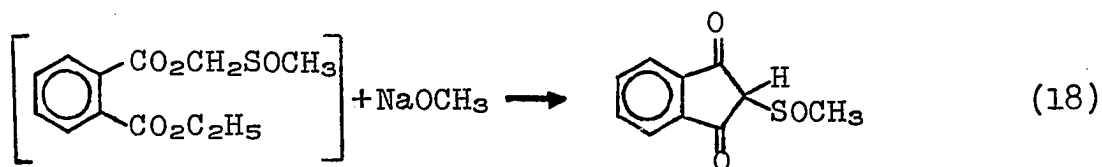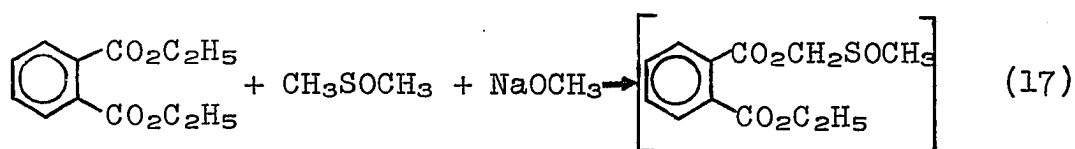
synthetic advantage of dimsyl carbanion condensations with esters is illustrated in Table 1 for isolated yields of β-keto

sulfoxides on a 50 mmole preparative scale by Professor Russell and co-workers (58, 60, 62).

Table 1. Yields of β-keto sulfoxides from methylsulfinyl-carbanion condensations with carboxylic esters (58, 60, 62)

$$RCO_2R' \; + \; CH_3SOCH_2^- \; \longrightarrow \; RCOCH_2SOCH_3 \; + \; R'O^-$$

R	% Yield
⬡	88
p-CH₃⬡	87
p-CH₃O⬡	95
p-Br⬡	79
α-⬡⬡	95
β-⬡⬡	91
⬡S	74
⬠	74
◻	44
▷	41

Previous studies of the synthetic utility of β-keto

sulfoxides have an immediate bearing on the present work. A

discussion of these results is imperative for placing the

present work in perspective. Furthermore, they will serve to

illustrate the chemistry of the bifunctional and isolated

moieties of the β-keto sulfoxides.

The conversion of β-keto sulfoxides to a variety of sulfur-

free products, containing one more carbon atom than the start-

ing ester employed for β-keto sulfoxide preparation, have been

described (1, 58, 64). Chart 1 lists seven of these sulfur-

free products for which practical transformations are illustra-

ted in Figure 2.

$$RCO_2R' \longrightarrow \left\{ \begin{array}{ll} RCOCH_3 & RCH(OH)CH_3 \\ RCOCH_2OH & RCH(OH)CH_2OH \\ RCOCHO & \\ RCOCO_2H & RCH(OH)CO_2H \end{array} \right.$$
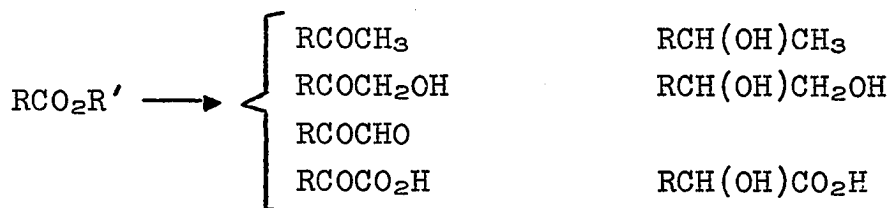
Chart 1. Sulfur-free products derived from β-keto sulfoxides
          prepared from carboxylic esters (58).

Figure 2 reveals six of the seven products listed in Chart

1 to be directly or indirectly derived from the Pummerer re-

arrangement (41, 65, 66) products of the β-keto sulfoxides,

the glyoxal hemimercaptals ($RCOCH(OH)SCH_3$). Tremendous syn-

thetic utility is provided by this rearrangement, since it

allows the sulfoxide moiety to function as a potential carbonyl

$$RCO_2R'$$

$$CH_3SOCH_2^-$$

$$\underset{CH_3}{\overset{OH}{RC}}-\underset{CH_3}{\overset{OH}{C}}-R \quad \leftarrow \quad Al,HgCl_2 \quad \text{———} \quad RCOCH_2SOCH_3 \quad \text{———} \quad Zn/HOAc \quad \rightarrow \quad RCOCH_3 \text{—} NaBH_4 \rightarrow R\overset{OH}{C}HCH_3$$

NaH

$$H_3O^+/DMSO$$

$$\overset{OH}{RCHCH_2OH} \leftarrow NaBH_4 \text{————} RCO\overset{OH}{C}HSCH_3 \text{———} SFS,Cu^{+2} \rightarrow RCOCH_2OH$$

$$Cu(OAc)_2$$

$$\overset{OH}{RCHCO_2H} \quad \leftarrow OH^-$$

$$RCOCHO\text{—}SFS \rightarrow RCO\overset{HO}{C}H \overset{OH}{C}HCOR$$

$$Br_2$$

$$RCO\overset{Br}{C}HSOCH_3 \text{———} H_3\overset{+}{O}/R'OH \rightarrow RCOCO_2R'$$

$$SFS \quad = \quad NaOSOCH_2OH$$
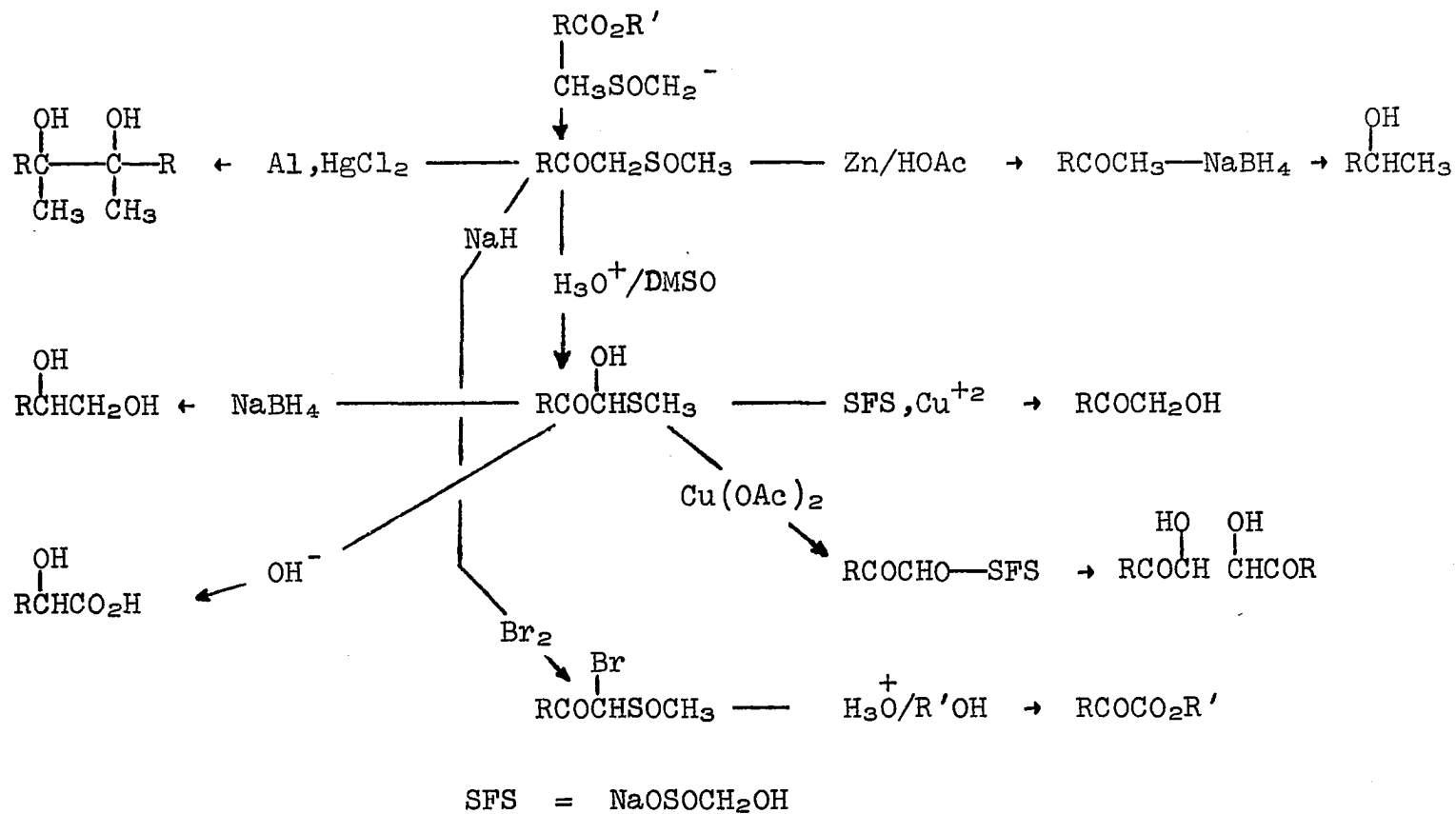
Figure 2. Transformations leading from β-keto sulfoxides to sulfur-free products (58).

protecting group.

The scope and mechanism of the Pummerer rearrangement have been reviewed (67-69). Sufficient for this survey is a brief discussion of the rearrangement mechanism and application of the reaction to β-keto sulfoxides. The "Pummerer reaction" is a general term for a class of reactions involving the reduction of a sulfonium sulfur with concommitant oxidation of the α-carbon, Equation 19. Numerous mechanisms have been proposed

$$\underset{\underset{+}{\overset{\overset{X}{|}}{R\overset{|}{S}CH_2R'}}}{} \longrightarrow \overset{\overset{X}{|}}{RS\overset{|}{C}HR'} + H^+ \qquad\qquad (19)$$
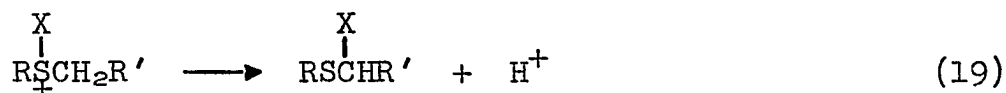
for this transformation, while the favored scheme (60) is illustrated in Figure 3 for the case of an oxysulfonium salt.
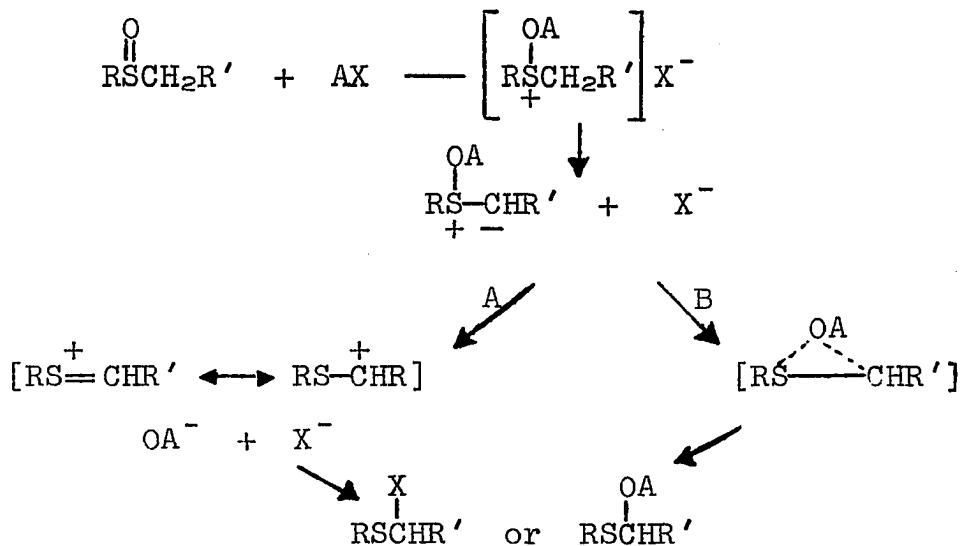
Figure 3. Mechanism of the ylide-intermediate Pummerer re-
arrangement.
   a: intermolecular or external nucleophile path.
   b: intramolecular path.

Nucleophilic attack by sulfoxide oxygen on an onium center

yields an oxysulfonium salt, which undergoes α-proton elimina-

tion to the ylide intermediate $(R\overset{+}{\underset{-}{S}}CHR')$. The ylide rearranges

to product by path A: dissociation to an α-sulfonium ion

$(R\overset{+}{S}=CHR')$, which is then attacked at the α-carbon by the oxy

anion (OH^-) or external nucleophile (X). Path B, ylide re-

arrangement by direct intramolecular transfer of OA^- to the

α-carbon, cannot be eliminated from consideration as an alterna-

tive to path A.

Conspicuously absent from Chart 1 is the α-hydroxy aldehyde

$(RCR'(OH)CHO)$ structure. Initial attempts to prepare α-hydroxy

aldehyde from either β-hydroxide sulfoxide $(RCH(OH)CH_2SOCH_3)$ or

the glyoxal hemimercaptal $(RCOCH(OH)SCH_3)$ were unsuccessful

(60). Glyoxal hemimercaptals undergo reduction with sodium

borohydride to yield diols (58). β-Keto sulfoxides could be

conveniently reduced to the β-hydroxy sulfoxides with sodium

borohydride (60). However, they proved to be quite resistant

to Pummerer rearrangement and forcing conditions with β-hydroxy-

β-phenethyl methylsulfoxide $(PhCH(OH)CH_2SOCH_3)$ produced either

ω-hydroxy acetophenone $(PhCOCH_2OH)$ or the dehydration product,

β-styryl methyl sulfoxide $(PhCH=CHSOCH_3)$ (60). Examples in

the literature, however, indicate that α-hydroxy aldehydes can

be prepared from α-keto mercaptals $(RCOCH(SR')_2)$ (70-72) or

α-keto acetals $(RCOCH(OR')_2)$ (73, 74). Glyoxal mercaptals (16)

can be indirectly prepared from the β-keto sulfoxides by acid-

catalyzed disproportionation of glyoxal hemimercaptals,

Equation 20, to the mercaptal and hydrate (75). Thus, the

$$2 \ \underset{\overset{|}{\text{OH}}}{\text{RCOCHSCH}_3} \ + \ \text{acid} \ \longrightarrow \ \text{RCOCH(SCH}_3)_2 \ + \ \text{RCOCH(OH)}_2 \quad (20)$$
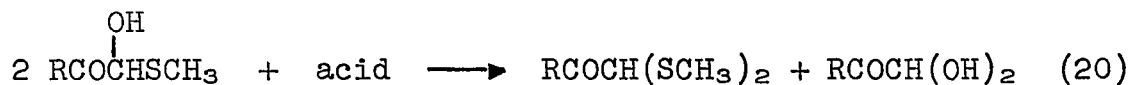
maximum yield of mercaptal from disproportionation is 50% of

the starting material. On the other hand, α-keto acetals

have been prepared directly from the β-keto sulfoxides, Equa-

tion 21, in high yield (76). However, reduction of α-keto

$$\text{RCOCH}_2\text{SOCH}_3 \ + \ \text{I}_2 + \text{R'OH} \longrightarrow \text{RCOCH(OR')}_2 \qquad (21)$$
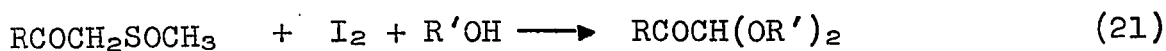
acetals and subsequent acid hydrolysis of the α-hydroxy ace-

tals has been shown to yield acid-catalyzed rearrangement

products rather than α-hydroxy aldehydes (77, 78). The pres-

ent study has been undertaken to overcome these difficulties

and provide a convenient conversion of β-keto sulfoxides to

α-hydroxy aldehydes.

In addition to synthetic advantages derived from the

Pummerer rearrangement of β-keto sulfoxide, the single step

reductive desulfurization with zinc, Figure 2, is an important

and highly convenient ketone synthesis (58). As an elegant

alternative for small scale reactions, a process using

amalgamated aluminum foil has been developed that cleans

sulfones and sulfanamides in addition to sulfoxides (22, 30,

79). The fact that reduction is facile for sulfones must be

due to the fundamental nature of the carbonyl group, rather than the sulfur moiety. Possible rationalization of the reaction would involve a ketyl $(R_2\overset{\bullet}{C}-\overset{-}{O})$ intermediate. It must

$$RCOCH_2X + e^- \longrightarrow R\overset{\bullet}{C}(O^-)CH_2X \longrightarrow RCOCH_2\cdot + X^- \qquad (22)$$
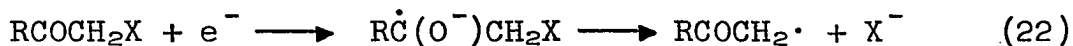
$$X = halogen, RS, RSO, RSO_2$$

be pointed out, however, that reductions related specifically to the sulfoxide moiety are numerous and of historical importance.

Clean reduction of the sulfoxide function without C-S bond cleavage can be affected by Lewis acid reagents capable of valence expansion, such as phosphines (80, 81) or borane derivatives (82, 83). Sodium borohydride, however, is a base and fails to coordinate with the electronegative sulfoxide oxygen (84), although a recent exception has been observed with the borohydride reduction of thianthrone to the sulfide (85). Lithium aluminum hydride (86, 87), as well as phenyllithium (31), will reduce aromatic sulfoxides to the sulfides. Grignard reagents have been studied as reducing agents for sulfoxides (88). However, the reaction does not appear to be general and can yield complex product mixtures (89). The most convenient reducing agent to date for sulfoxide to sulfide reduction appears to be sodium metabisulfite $(Na_2S_2O_5)$, originally reported to reduce methionine sulfoxide (90). No other applications were reported until a recent reinvestigation

by Professor Russell and Dr. Sabourin (2, 91). Their results, summarized in Table 2, show clean reduction of the sulfoxide function in the presence of various other functional groups.

Table 2. Sodium metabisulfite reduction of sulfoxides in aqueous media at 90°C (91)

$$R_2SO + Na_2S_2O_5 \longrightarrow R_2SO$$

Substrate	Product	% Yield
$PhCOCH_2SOCH_3$	$PhCOCH_2SCH_3$	52
$PhCH(OH)CH_2SOCH_3$	$PhCH(OH)CH_2SCH_3$	93
$PhCH(OCH_3)CH_2SOCH_3$	$PhCH(OCH_3)CH_2SCH_3$	80
$PhCH{=}CHSOCH_3$	$PhCH{=}CHSOCH_3$	66
$PhCH(OAc)CH_2SOCH_3$	$PhCH(OAc)CH_2SCH_3$	89

Reductive C-S bond cleavage is less common for sulfoxides than simple reduction to the sulfide. The exceptional case of β-keto sulfoxides has already been mentioned (22, 58). Other reducing agents, which function independently of the keto function, are W-2 Raney nickel (92) and an in situ generated catalyst from nickel chloride and sodium borohydride (93, 94). The latter catalyst has been shown by H. C. Brown to be nickel boride (Ni_2B), which can be prepared in varying states of activity (95, 96).

In comparison to sulfoxides, sulfones are highly resistant to reduction. However, reductions of sulfones to sulfides with zinc (86) (97) and lithium aluminum hydride are known (86). Reduction with C-S bond cleavage of sulfones is convenient only for β-keto sulfones (30, 79). Under rather vigorous conditions, W-2 Raney nickel (2, 98, 99) or sodium amalgam (100) are particularly effective reducing agents for sulfones which are not activated by a carbonyl group. Also, at high temperature and the pressure, molybdenum sulfide (MO_2S_3) catalysts reduce aromatic sulfones to hydrocarbons (101).

The synthetic utility of β-keto sulfoxides is considerably extended by the ease with which the α-carbon can be alkylated, Equation 23, 24.

$$RCOCH_2SOCH_3 + NaH \longrightarrow RCOCHSOCH_3^{-}Na^{+} + H_2 \tag{23}$$

$$RCOCHSOCH_3^{-}Na^{+} + R'X \longrightarrow RCOCHR'SOCH_3 + NaX \tag{24}$$
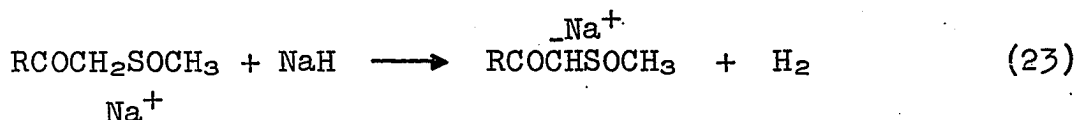
Sodium hydride in tetrahydrofuran readily yields the carbanion which nucleophilically displaces alkyl halides to give mono- or dialkylated β-keto sulfoxides in good yields (58, 59, 62). The carbanion has recently been used as a Michael nucleophile (61), Equation 25. The use of phenylsulfinyldihalomethide

$$RCOCHSOCH_3^{-}Na^{+} + CH_2{=}CHCO_2CH_3 \longrightarrow RCO\overset{SOCH_3}{\underset{|}{C}}HCH_2CH_2CO_2CH_3 \tag{25}$$

($PhSOCX_2^{-}$) in a Michael addition is also reported (102). The

alkylated β-keto sulfoxides can be desulfurized by the same techniques already discussed for the unalkylated derivatives to yield a variety of ketones (59), Equation 26, or α-di-ketones (62), Equation 27. Further, sulfoxides containing

$$RCOCR'R''SOCH_3 \xrightarrow{Al(\ Hg)} RCOCHR'R'' \qquad (26)$$

$$RCOCHR'SOCH_3 \xrightarrow{H_3O^+} RCOCOR' + HSCH_3 \qquad (27)$$

β-protons thermally eliminate methylsulfinic acid to yield olefins by an assumed radical mechanism (103). The assumption is supported by the reversible thermal radical rearrangement of sulfenates to sulfoxides (104). Numerous applications of this thermal elimination are reported for olefin synthesis (3). Particularly interesting are the thermolysis of β-hydroxy sulfoxides (60) to yield ketones, Equation 28, and β-keto sulfoxides (62) to yield α,β-unsaturated ketones, Equation 29, respectively.

$$\overset{OH}{RCHCHR'SOCH_3} \xrightarrow[\Delta]{} \overset{OH}{RC}{=}CHR' + CH_3SOH \longrightarrow RCOCH_2R' \qquad (28)$$

$$\overset{SOCH_3}{RCOCHCH_2R'} \xrightarrow[\Delta]{} RCOCH{=}CHR' + CH_3SOH \qquad (29)$$
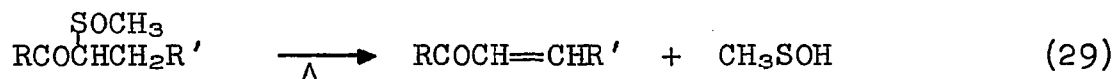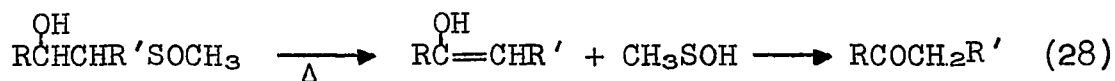
Little mention has been made to this point of the various sulfur-containing compounds, sulfides, sulfoxides and sulfones, directly available from β-keto sulfoxides. The variety of such products is too extensive for comprehensive review. As

a minimum effort, Chart 2 lists a number of sulfur derivatives obtained from β-keto sulfoxides by Professor Russell and co-workers (60, 64). Figure 4 summarizes these transformations.

$RCOCH_2SCH_3$ $RCOCH_2SO_2CH_3$

$RCH(OH)CH_2SCH_3$ $RCH(OH)CH_2SOCH_3$ $RCH(OH)CH_2SO_2CH_3$

$RCH(OCH_3)CH_2SCH_3$ $RCH(OCH_3)CH_2SOCH_3$ $RCH(OCH_3)CH_2SO_2CH_3$

$RCH_2CH_2SCH_3$ $RCH_2CH_2SOCH_3$ $RCH_2CH_2SO_2CH_3$

$RCH{=\!=}CHSCH_3$ $RCH{=\!=}CHSOCH_3$ $RCH{=\!=}CHSO_2CH_3$

$RCCl{=\!=}CHSCH_3$

$RC{\equiv}CSCH_3$
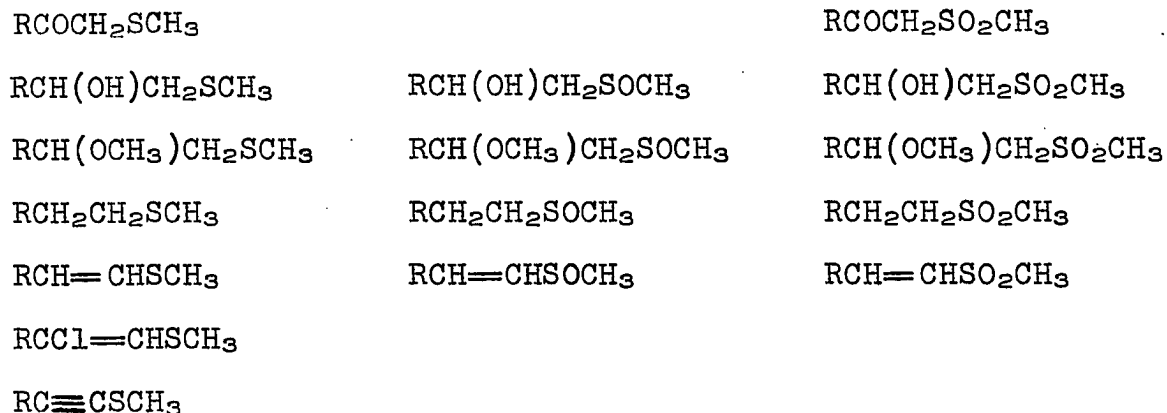
Chart 2. Sulfur-containing products derived from β-keto
          sulfoxides ($RCOCH_2SOCH_3$) (60, 64).

However, consideration of these transformations will be deferred to the discussion of results of the present work.

As a concluding historical note, two novel studies have recently been reported to exploit β-keto sulfoxides as synthetic intermediates. Both studies have postulated the reaction of β-keto sulfoxides through carbene intermediates. Hodson and Holt (105) prepared α-diazo-β-keto sulfoxides from the β-keto sulfoxide, Equation 30, and observed diazo decomposition to α-keto acid products, Equation 31.

RCOCH$_2$SCH$_3$ RCOCH$_2$SOCH$_3$ RCOCH$_2$SO$_2$CH$_3$

↑ MnO$_2$ MnO$_2$ ↕ NaBH$_4$ NaBH$_4$ ↕ MnO$_2$

RCH(OH)CH$_2$SCH$_3$ $\xrightarrow[\text{Na}_2\text{S}_2\text{O}_5]{\text{NaIO}_4}$ RCH(OH)CH$_2$SOCH$_3$ $\xrightarrow{\text{H}_2\text{O}_2}$ RCH(OH)CH$_2$SO$_2$CH$_3$

↓ B$^-$,MeI (H$^+$) ↓ B$^-$,MeI

(KHSO$_4$)

RCH(OMe)CH$_2$SCH$_3$ $\xrightarrow[\text{Na}_2\text{S}_2\text{O}_5]{\text{NaIO}_4}$ RCH(OMe)CH$_2$SCH$_3$ $\xrightarrow{\text{H}_2\text{O}_2}$ RCH(OMe)CH$_2$SO$_2$CH$_3$

↓ B$^-$,Δ H$^+$ or B$^-$

RCH=CHSCH$_3$ $\xrightarrow[\text{Na}_2\text{S}_2\text{O}_5]{\text{NaIO}_4}$ RCH=CHSOCH$_3$ $\xrightarrow{\text{H}_2\text{O}_2}$ RCH=CHSO$_2$CH$_3$

(SOCl$_2$)

↓ LAH

LAH

RCH$_2$CH$_2$SCH$_3$ $\xrightarrow{\text{NaIO}_4}$ RCH$_2$CH$_2$SOCH$_3$ $\xrightarrow{\text{H}_2\text{O}_2}$ RCH$_2$CH$_2$SO$_2$CH$_3$

RCCl=CHSCH$_3$ $\xrightarrow{\text{B}^-}$ RC≡CSCH$_3$

26

Figure 4. Sulfur containing intermediates derived from β-keto sulfoxides.

$$RCOCH_2SOCH_3 \ + \ TosN_3 \ \longrightarrow \ RCOC(N_2)SOCH_3 \ + \ TosNH_2 \qquad (30)$$

$$RCOC(N_2)SOCH_3 \ \longrightarrow \ RCOCOSCH_3 \ + \ N_2 \qquad (31)$$
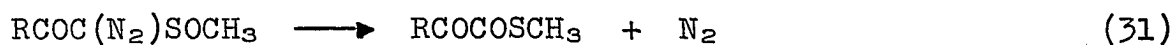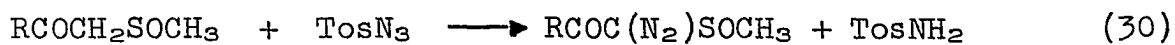
A carbene, benzoylmethylene, Equation 32, 33, has also been

$$PhCO\overline{C}HSOCH_3 \ \longrightarrow \ PhCOCH: \ + \ CH_3SO^- \ \xrightarrow{NO_2^-} \ PhCOCH{=}N^+\underset{O^-}{\overset{O^-}{\diagdown}} \ (32)$$

$$PhCOCH{=}N^+\underset{O^-}{\overset{O^-}{\diagdown}} \ \xrightarrow{HCl} \ PhCO\overset{Cl}{\underset{}{C}}H{-}NO \ \longleftrightarrow \ PhCO\overset{Cl}{\underset{}{C}}{=}N{\diagdown}_{OH} \qquad (33)$$
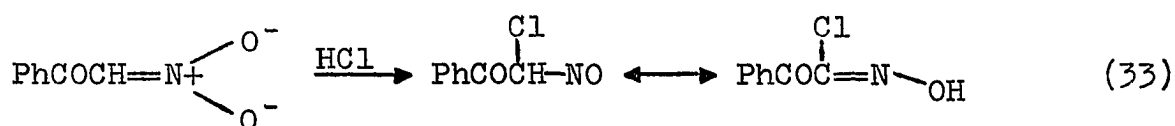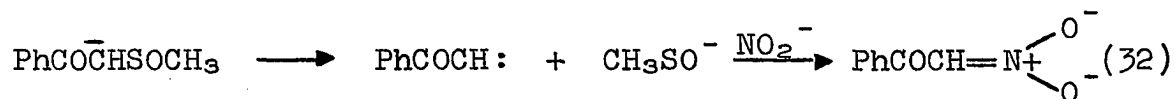
postulated as an intermediate for ω-(methylsulfinyl)aceto-
phenone exchange of nitrite for methylsulfinate anion (106).

RESULTS AND DISCUSSION

The β-keto sulfoxides, readily obtained by condensation of methylsulfinylcarbanion with carboxylic esters, have proven to be highly versatile synthetic intermediates (1, 2, 16, 22, 30, 58, 60, 62). The design of the present work was intended to further expand the scope of β-keto sulfoxide synthetic utility. ω-(Methylsulfinyl) acetophenone was chosen as the model substrate to fulfill the purpose of this study. Expediency led to this choice, since the β-keto sulfoxides are not commercially available as starting materials and ω-(methylsulfinyl)-acetophenone is conducive to preparation and purification on a large scale.

One point of clarification with respect to the title of this work is appropriate. The reader will discover that the majority of the reactions discussed in this text utilize the methylmercaptal of phenylglyoxal, directly derived from ω-(methylsulfinyl)acetophenone, as starting material. Thus, an informal alternative title may be proposed, "Chemistry of α-Keto Mercaptals". In view of this proposal, the context of this work to the overall synthetic utility of β-keto sulfoxides can be seen by referring to the Summary of this text.

Individual reactions in this study are categorized by assigning Roman numerals to a class of compounds and a lower case letter to designate derivatives within that class.

Condensations of the Methylsulfinylcarbanion

The methylsulfinylcarbanion ($CH_3SOCH_2^-$) reacts readily to form adducts with a variety of electrophilic centers, including alkyl halides (33, 36), olefins (21, 37-40), acetylenes (41, 42), benzyne (19, 22), carbonyls (15, 19-22, 32, 33, 37, 46), esters (16, 22, 30, 59-62) and Schiff bases (22, 43). Condensations with the nitrile function are absent from the literature, while the known reactions with epoxides (1, 2, 36, 47, 48) result in disappointingly low yields of δ-hydroxy sulfoxides. Experimentation was therefore undertaken to extend the condensation to the nitrite function and to optimize the preparation of δ-hydroxy sulfoxides.

Several attempts were previously made by Dr. G. J. Mikol (1) to obtain a product from the reaction of methylsulfinyl-carbanion, generated by equilibration with potassium t-butoxide, with benzonitrile. All attempts uniformly failed. Only dark-colored, resinous materials were isolated under varying conditions. A search of the literature subsequently revealed contradictory reports regarding the reactivity of the methyl sulfinylcarbanion toward the nitrile function.

Besides the failure of benzonitrile to yield condensation products, attempts to acylate or alkylate phenylacetonitrile carbanion in the presence of methylsulfinylcarbanion likewise yielded only resinous materials (28). However, no mention of these complications is made for a successful study affecting

the acylation of <u>para</u>-substituted phenylacetonitriles with esters when dimsylsodium was employed as base (107). The

$$p-XPhCH_2CN + RCO_2R' \xrightarrow[DMSO]{CH_3SOCH_2Na} (p-XPh\underline{C}HCN) \quad\quad (34)$$

with a COR group attached.
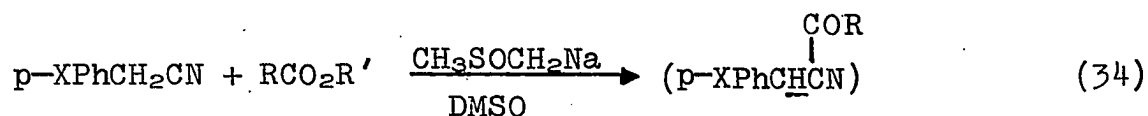
yields of α-acyl phenylacetonitriles were reported to be in excess of 80%, with no apparent complications from competitive ester condensation with dimsylsodium. The successful trans- formations were attributed to a very rapid and quantitative conversion of the nitrile to the α-cyanocarbanion by dimsyl- sodium proton abstraction, followed by immediate ester con- densation to the acylated product. Thus, complicating re- actions were avoided by rapid formation of product and its conversion to a stable enolate anion. On the basis of analo- gous mechanistic considerations, dimsylsodium has been shown to be an effective base to affect Dieckmann cyclization of 1,4-dinitriles directly to β-cyanoenamine nitriles in high yields (108).

$$\xrightarrow[DMSO]{CH_3SOCH_2Na} \quad\quad (35)$$
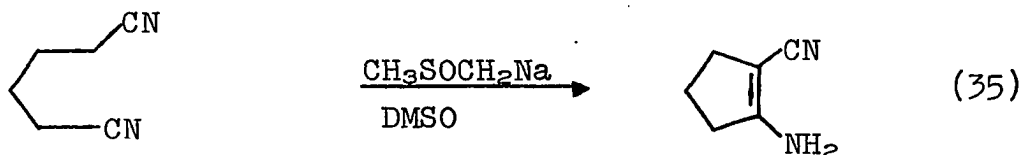
The latter two examples of successful nitrile substrate reactions in dimsylsodium solution suggest that the nucleo- philicity of dimsylsodium toward the cyano function of

aliphatic nitriles is insignificant relative to its role as a
proton abstracting base. This consideration does not present
itself in the case of benzonitrile. However, the previous
failure to affect benzonitrile condensation could have been
due to the lower reactivity of equilibrium generated methyl-
sulfinylcarbanion relative to dimsylsodium (23, 25). This
possibility was immediately discarded upon comparison of the
reaction results in the two base systems. The formation of a
blue color on addition of benzonitrile to either base system
was taken as evidence that the cyano function had reacted to
yield an imide-anion intermediate, Equation 36. The only

$$PhCN \ + \ CH_3SOCH_2^- \ \longrightarrow \ PhC(=\overline{N})CH_2SOCH_3 \qquad (36)$$
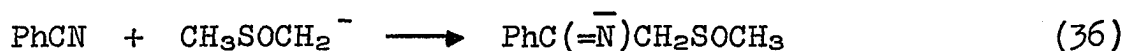
observed difference in the course of the two reactions was the
rate of polymerization. Addition of benzonitrile to a semi-
frozen slurry (0°C) of equilibrium generated potassium methyl-
sulfinylcarbanion in a nitrogen atmosphere resulted in the
development of a faint blue color which rapidly grew in in-
tensity. After 0.5 hrs the reaction was the texture of a
viscous black slurry. Addition of benzonitrile to dimsyl-
sodium immediately resulted in an intense blue color, which
persisted for several minutes during further nitrile addition.
The reaction at this point was prone to a sudden and violent
exothermic polymerization, yielding a black semi-solid residue.
Neither reaction yielded products other than polymeric resin.

Unavoidably, it was assumed that the polymerization was due to a very facile autoxidation of reaction intermediates, particularly in view of the well-known properties of dimethylsulfoxide as solvent to promote autoxidation in basic media (109). Thus, anticipation of a successful condensation was unsustained, unless the assumed imide anion intermediate (PhC($=\overline{N}$)CH$_2$SOCH$_3$) could in some fashion be stabilized toward decomposition.

A possible approach to stabilization of an imide anion was suggested from consideration of successful nitrile condensations with Grignard (110) or organolithium reagents (111). The facility of reaction in these cases can be considered to result in part from the stabilization of the "hard" base, imide anion intermediate, by the "hard" acid, metal ion, in accord with the principle of hard and soft acids and bases (112, 113). Furthermore, the lithium ion is known to strongly complex with the nitrile function and thereby increase the electrophilic reactivity of the carbon atom of the cyano group in condensation reactions. This fact has been demonstrated for the condensation of weakly nucleophilic phosphonium ylides with nitriles, which react only in the presence of lithium ions (114).

Attempts to prepare dimsyllithium by known literature procedures (22, 20) in order to avoid superfluous addition of lithium ion proved impractical. The conventional procedures

resulted in excessively decomposed dimsyllithium solutions.
Therefore, a 2:1 mole ratio of anhydrous lithium iodide was
added to a freshly prepared dimsylsodium solution and allowed
to equilibrate. Benzonitrile was then added dropwise, under
a nitrogen atmosphere, to the cooled slurry, 0°C, of dimsyl-
lithium. As previously observed, an intense blue color
developed. However, the decomposition of the reaction was slow
relative to the absence of lithium ion. The reaction was
neutralized and hydrolyzed 0.5 hrs after complete addition of
benzonitrile to yield 52% of ω-(methylsulfinyl)acetophenone (I).

$$PhCN + CH_3SOCH_2Li \longrightarrow [PhC(=NLi)CH_2SOCH_3] \qquad (37)$$

$$[PhC(=NLi)CH_2SOCH_3)] + H_3\overset{+}{O} \longrightarrow PhCOCH_2SOCH_3 + NH_3 \qquad (38)$$

I

The reaction of methylsulfinylcarbanion with styrene oxide,
Equation 39, to yield 3-(methylsulfinyl)-1-phenyl-propanol (II)

$$PhCH\overset{O}{\overbrace{\hspace{1cm}}}CH_2 + CH_3SOCH_2^- \longrightarrow PhCH(OH)CH_2CH_2SOCH_3 \qquad (39)$$
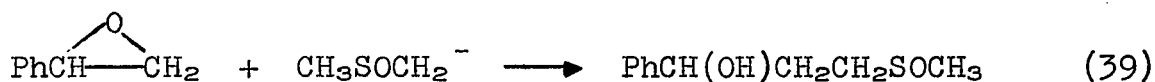
II

as a mixture of diastereomers has been previously described (1,
2). The chemistry of II was not explored in this or previous
studies, but on the basis of the known chemistry of sulfoxides,
it could serve as an intermediate for a series of useful com-
pounds: $PhCH(OH)CH_2X$ (X = H, CHO, CO_2H, CH_2SCH_3, $CH_2SO_2CH_3$),

$PhCH=CHCH_2X$ (X = H, SCH_3, $SOCH_3$, SO_2CH_3) and $PhCH(OH)CH=CH_2$.

Unfortunately, all attempts to isolate II in a reasonable state of purity resulted in low yields with the optimum yield of 36% on a 250 mmole reaction scale (2). A reinvestigation of the initial efforts revealed two major difficulties: extensive reaction decomposition during condensation, and product loss during aqueous workup. Although the reaction was run under a nitrogen atmosphere below room temperature, mixing of the reactants resulted in the rapid change of the reaction mixture to a dark viscous solution. Careful purification of starting materials failed to effect this observation. On aqueous work-up, considerable quantities of dimethylsulfide, in excess of the quantities observed for comparable ester condensation, were detected by its pungent odor. The dark decomposition products of the reaction were water soluble above pH ~4-5, while the δ-hydroxy sulfoxide (II) was extractable at this acidity with chloroform. At high acidity, pH ~ 1, the dark material could be extracted with ethyl acetate to yield a considerable quantity of resinous material. Thin layer chromatography indicated numerous trace components, with the bulk of the material comprising a highly polar residue, nearly immobile on elution with methanol. No attempt was made to characterize these products. The extensive decomposition may be related to the facility with which dimethyl sulfoxide oxidizes epoxides to α-hydroxy ketones (115). Only trace

amounts of radical initiators are required for effective oxidation under oxygen-free conditions.

Although II could be isolated free of major impurities by extraction above pH ~ 4-5, its high solubility in water required numerous batch extractions which resulted in extensive co-extraction of dimethyl sulfoxide. This posed a difficult purification problem, since attempts to distill II resulted only in polymerization and pyrolysis to a multi-product mixture. This difficulty was resolved by chromatographing the crude extraction residue on a silica gel column with 30% chloroform—70% hexane to separate dimethyl sulfoxide, followed by elution with more polar solvents to recover II. Isolation of the highly purified δ-hydroxy sulfoxide (II) on a preparative scale in 40 ~ 45% yields was thus possible in routine fashion.

As an alternative route to the preparation of II, an attempt was made to condense methylsulfinylcarbanion with phenacyl halides, Equation 40, to yield ω-(methylsulfinyl)propiophenone (III). However, addition of phenacyl halides to

$$PhCOCH_2X + CH_3SOCH_2^- \longrightarrow PhCOCH_2CH_2SOCH_3 \tag{40}$$

$$(X = Cl, Br) \qquad\qquad III$$
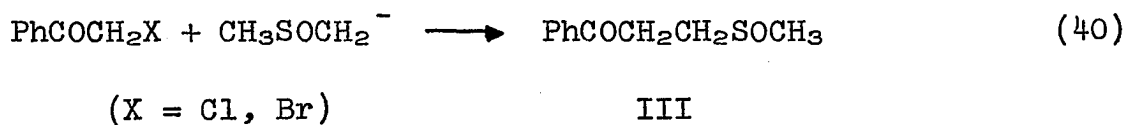
dimsylsodium under the usual reaction conditions resulted in immediate polymerization and eventual solidification of the reaction mixture. The bulk of the reaction product consisted

of resinous polymeric material, which could not be purified to yield a discrete product by chromatographic techniques. The only pure component isolated, other than traces of starting material, was ω-(methylsulfonyl)propiophenone (IIIa) (PhCOCH$_2$-CH$_2$SO$_2$CH$_3$). If all of the phenacyl halide were simultaneously introduced into the reaction, which is not advisable due to the exothermic nature of the reaction, IIIa could be isolated in excess of 30% yield. Considering the violent nature of the reaction, any rationalization for the formation of IIIa would be pure speculation.

Reactions of the ω-(Methylsulfinyl)acetophenone Anion

The conversion of ω-(methylsulfinyl)acetophenone (I) into its sodium salt, by reaction with sodium hydride in tetrahydrofuran, dimethyl sulfoxide, or dimethylformamide, has been previously described (58, 59). Due to the inductive effect of

$$PhCOCH_2SOCH_3 + NaH \xrightarrow[\text{or DMF}]{THF} [Ph CO\overline{C}HSOCH_3]Na^+ + H_2 \qquad (41)$$
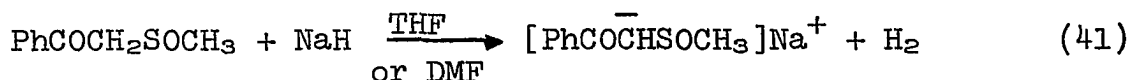
the carbonyl and sulfoxide functions, β-keto sulfoxides are readily converted to the enolate anion. This fact has allowed for the convenient α-carbon substitution of a variety of β-keto sulfoxides by selective electrophilic reagents, Equation 42,

$$Ph CO\overline{C}HSOCH_3 + R'X \longrightarrow RCOCHR'SOCH_3 + X^- \qquad (42)$$

(RX = alkylhalides, halogens, CH₃SOCl)
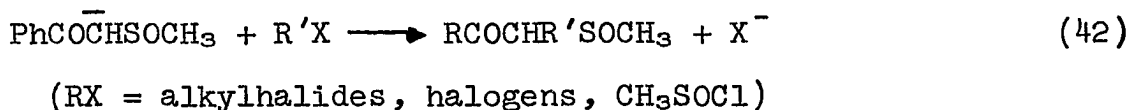
including alkyl halides (58, 59, 62), halogens (58, 60) and methylsulfinyl chloride (98). Methylation, with methyl iodide, occurs readily in tetrahydrofuran solution. However, ethylation (ethyl iodide) and benzylation (benzyl chloride), due to the lower reactivity of these halides (116), require highly polar dimethyl sulfoxide as co-solvent (58).

The a priori consideration of ethyl bromoacetate and ethyl acrylate as potential alkylating agents of β-keto sulfoxides was obvious to the objectives of the present study. These reagents are well known as nucleophilic acceptors in displacement and Michael condensation reactions, due to

electrophile activation by the carboxylate function. Further impetus was provided by the previously reported Michael condensation reactions of phenylsulfinyldihalomethide ($PhSOCX_2^-$) (102). Thus, by anticipating alkylation of I with ethyl bromoacetate and ethylacrylate, and also the possibility of α-carboxylating I, previous chemistry (58, 60) suggested the resulting α-substituted-β-keto sulfoxides as potential intermediates to the two, three and four carbon chain extension of carboxylic esters, Figure 5.

RCO_2Et

↓

$RCOCH_2SOCH_3$

XCO_2Et $BrCH_2CO_2Et$ $CH_2 = CHXCO_2Et$

↓   ↓   ↓

$RCOCH(SOCH_3)CO_2Et$ $RCOCH(SOCH_3)CH_2CO_2Et$ $RCOCH(SOCH_3)CH_2CH_2CO_2Et$

↓   ↓   ↓

$R(CH_2)_2CO_2Et$ $R(CH_2)_3CO_2Et$ $R(CH_2)_4CO_2Et$

$RCOCH_2CO_2Et$ $RCO(CH_2)_2CO_2Et$ $RCO(CH_2)_3CO_2Et$

                  $RCOCH=CHCO_2Et$ $RCOCH=CHCH_2CO_2Et$
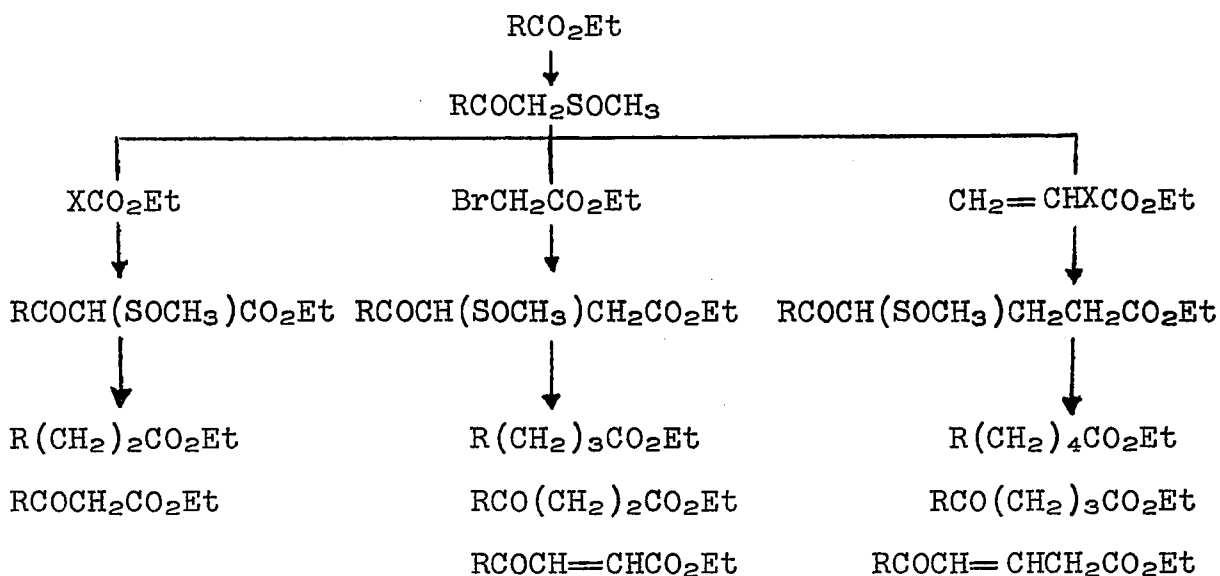
Figure 5. The proposed route for the two, three, and four carbon chain extensions of carboxylic esters through β-keto sulfoxide intermediates.

While the development of the proposal in Figure 5 was nearing completion, Nozaki, et al. (61) reported the condensation

of a number of aliphatic β-keto sulfoxides with ethyl bromo-acetate and methylacrylate, and implemented, in partial compliance with this work, an independent scheme for the chain extension of carboxylic esters. Thus, the independent result of the present work and those of Nozaki, et al., complement each other and demonstrate a general synthetic application of aliphatic and aromatic β-keto sulfoxides.

The addition of ethyl bromoacetate to the preformed salt of ω-(methylsulfinyl)acetophenone in tetrahydrofuran resulted in smooth C-alkylation, yielding ethyl β-(methylsulfinyl)-β-benzoylpropionate, (IV) as a mixture of diastereomers. No

$$PhCO\overline{C}HSOCH_3 + BrCH_2CO_2Et \longrightarrow PhCOCH(SOCH_3)CH_2CO_2Et + Br^- \quad (43)$$
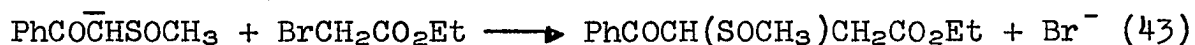
IV
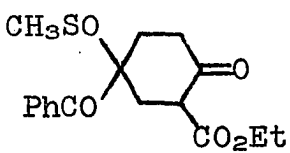
dialkylated or Dieckmann cyclized product, which could result from dialkylated product, was observed. This indicated a rapid alkylation and neutralization of the basic β-keto sulfoxide salt. Dimethylation of aliphatic sulfoxides with methyl iodide has been observed under these conditions, apparently due to slow mono-methylation (62). In a similar fashion to the preparation of IV, addition of ethyl acrylate to the salt of I in tetrahydrofuran yielded a diastereomeric mixture of ethyl δ-(methylsulfinyl)-δ-benzoylbutyrate (V). However, the reaction, Equation 44, also yielded the cyclo-hexanone derivative (VI). The formation of VI, as a mixture

of triastereomers, is due to further Michael condensation of
the initially formed mono-adduct to yield a diadduct, followed
by Dieckmann cyclization to the cyclohexanone (VI). The
driving force of the Dieckmann cyclization is the resulting
decreased basicity of the system by stable enolate anion
formation of VI. None of the Michael diadduct leading to
Dieckmann cyclization was isolated from the reaction. Since
Nozaki, et al. (61) reported no Dieckmann products from ali-
phatic β-keto sulfoxide Michael condensations in one to one
dimethylsulfoxide: tetrahydrofuran media, the condensation,
Equation 44, was repeated under these conditions. Results
under these conditions were entirely comparable to the reaction
in pure tetrahydrofuran; both V and VI were isolated.
Fortunately, formation of VI in the presence of V poses no
problem of purification. Preparative column chromatography
allows for convenient separation and purification of the two
components. Thus, VI can be isolated as the predominant
product when excess ethyl acrylate is employed in the con-
densation by virtue of the convenient purification technique.

On the basis of previously demonstrated chemistry of
β-keto sulfoxides (58, 60), adduct IV, V and VI were readily
transformed to sulfur-free products. These single step
transformations are summarized in Figure 6. Desulfurization
with zinc dust in acetic acid-ethanol (58) yielded the corres-
ponding γ- and δ-keto esters (IVa, Va and VIa). Under more

Table 3. Alkylation of ω-(methylsulfinyl)acetophenone anion with ethyl bromoacetate and ethyl acrylate

$$PhCO\overline{C}HSOCH_3 \longrightarrow \begin{array}{c} BrCH_2CO_2Et \\ or \\ CH{=}CHCO_2Et \end{array} \longrightarrow PhCOCH(SOCH_3)(CH_2)_nCO_2Et$$

$$(n = 1,2)$$

Alkylated Product	Alkylating agent/substrate	% Yield[a]
IV PhCOCH(SOCH₃)CH₂CO₂Et	1/1	61
V PhCOCH(SOCH₃)CH₂CH₂SO₂Et	1/1	75[b]
VI	2/1	60[c]

[a]The alkylations were performed on a 25 mmole scale.

[b]The yield of co-product VI was 4.8%.

[c]The yield of co-product V was 24.6%.

vigorous conditions, approaching those of a Clemmensen re-
duction (116), V and VI were induced to undergo desulfuriza-
tion and benzoyl carbonyl reduction to yield ethyl δ-phenyl-
valerate (Vb) and 2-carboxy-4-benzylcyclohexanone (VIb),
respectively. The alternative use of the Martin modification
of the Clemmensen reduction (117), which utilizes zinc amalgam
reducing agent in a toluene-aqueous hydrochloric acid two-phase
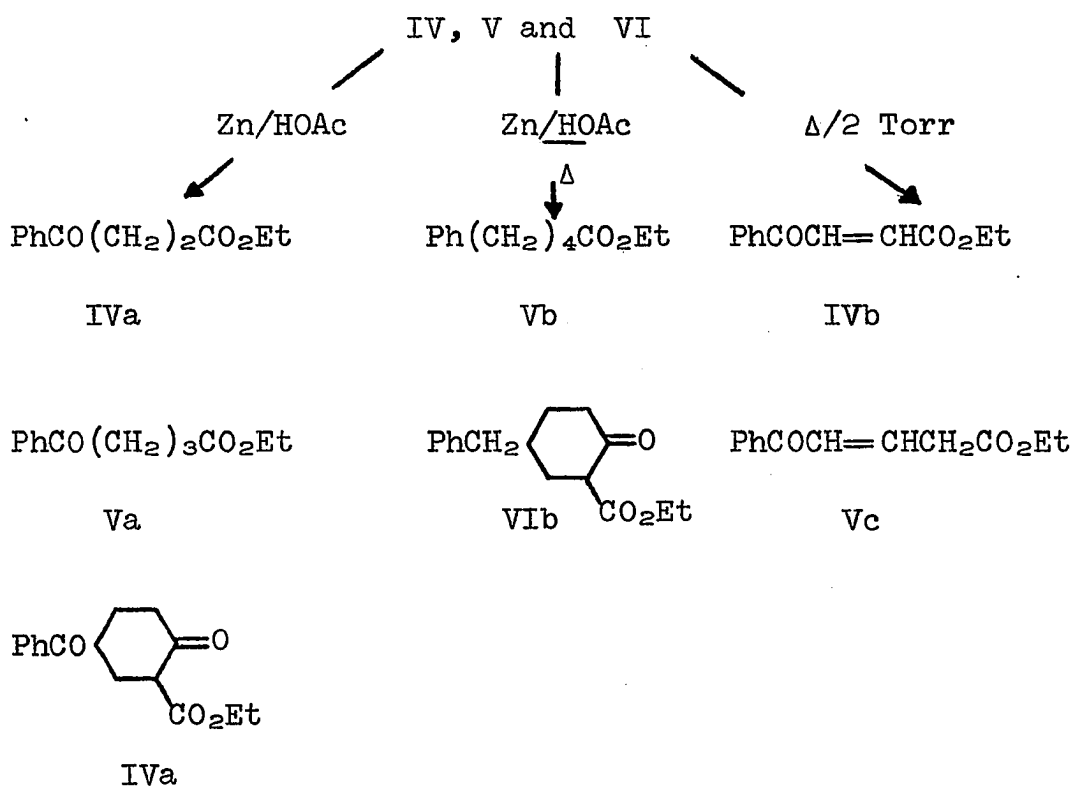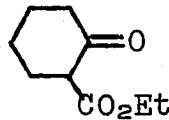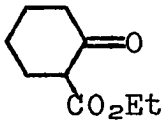
Figure 6. Transformation of adducts IV, V and VI to sulfur-free products.

solvent system, is recommended for slightly higher yields of benzoyl reduction product. A major advantage of this two-phase system is due to the occurrence of reduction at such high dilution that polymolecular reactions are inhibited. However, the aqueous conditions caused considerable ester hydrolysis and longer reaction periods are required than in the use of acetic acid solvent.

When IV and V were subjected to thermolysis, unsaturated keto esters were obtained. Thermolysis of IV proceeded at 120°/2 Torr with the elimination of methylsulfinic acid to yield ethyl β-benzoylacrylate (IVb), exclusively as the _trans_ isomer (J_{AB} vinyl = 19.2 Hz). On the other hand, the _cis_ isomer of ethyl 4-benzoyl-3-butenate (Vc) (J_{AB} vinyl = 9 Hz) was exclusively isolated on thermolysis of V and at 140°C/2 Torr. The stereospecificity of pyrolytic methylsulfinic acid elimination from sulfoxides is well established in spite of uncertainty as to the reaction mechanism, which is assumed to occur by a radical path (103, 118). At low temperature, _cis_-product has been shown to greatly predominate over _trans_-product. Conversely, at higher temperature, the stereospecificity of the reaction is lost and the more stable product, usually the _trans_-product, predominates. Attempts to pyrolyze VI afforded no olefinic products, only polymeric residue was formed.

In the initially proposed route for the chain extension of carboxylic esters, Figure 5, the possibility of a two carbon chain extension was envisioned by means of carboxylating the anion of ω-(methylsulfinyl)acetophenone. All attempts at C-carboxylation failed. No observable reaction occurred when dry carbon dioxide was passed through tetrahydrofuran, dimethylformamide or dimethyl sulfoxide solutions of the anion. Attempts to utilize chelation as a driving force to carboxylation, by the use of methyl magnesium carbonate ($Mg(OCO_2CH_3)_2$)

Table 4. The yields of sulfur-free product from the reduction
and pyrolysis of compounds IV, V, and VI

Product		Reaction Scale/mmoles	% Yield
IVa	PhCOCH$_2$CH$_2$CO$_2$Et	25.0	86
IVb	PhCOCH=CHCO$_2$Et	5.2	87
Va	PhCOCH$_2$CH$_2$CH$_2$CO$_2$Et	19.5	80
Vb	PhCH$_2$CH$_2$CH$_2$CH$_2$CO$_2$Et	10.0	54
Vc	PhCOCH=CHCH$_2$CO$_2$Et	3.9	52
VIa	PhCO⬡=O CO$_2$Et	12.0	91
VIb	PhCH$_2$⬡=O CO$_2$Et	5.0	41

as carboxylating agent, likewise failed (119). Addition of

methyl magnesium carbonate to a dimethylformamide solution of

I resulted in immediate evolution of carbon dioxide. After

neutralization and aqueous work-up, the β-keto sulfoxide (I)

was recovered unchanged. Apparently, sufficient stability is

derived by the magnesium ion through direct coordination with

the β-keto sulfoxide anion, Equation 45, such that coordination

with an in situ formed β-keto carboxylate moiety is by-passed,

Equation 46. Further, attempts to affect C-acylation included

$$\text{PhCO}\overline{\text{C}}\text{HSOCH}_3 + \text{Mg}(\text{CO}_3\text{CH}_3)_2 \longrightarrow \left[\begin{array}{c} \overset{+2}{\text{Mg}} \overset{\nearrow \text{OCH}_3}{\underset{\text{O}^-}{}} \\ {}^-\text{O} \qquad \text{O}^- \\ \text{PhC}{=}\text{CH}{-}\overset{+}{\text{S}}{-}\text{CH}_3 \end{array}\right] + 2\ \text{CO}_2 + \text{CH}_3\text{OH} \tag{45}$$

$$\xrightarrow{\,/\!/\,} \left[\begin{array}{c} \overset{+2}{\text{Mg}} \\ {}^-\text{O} \qquad \text{O}^- \\ \text{PhC}{=}\text{C}{-}\text{C}{=}\text{O} \\ \qquad \overset{|}{\text{SOCH}_3} \end{array}\right] + \quad \text{CO}_2 + \text{CH}_3\text{OH} \tag{46}$$

the addition of ethyl chloroformate to the sodium salt of I in a variety of solvents, or the reaction of I with a sodium hydride suspension in diethyl carbonate, a convenient method for the α-carboxylation of ketones (120). In all of these cases, only O-acylation resulted to yield ethyl-α-carboxy-β-(methylsulfinyl)styrene (VII) as a single isomer.

$$\text{PhCO}\overline{\text{C}}\text{HSOCH}_3 + \text{XCO}_2\text{Et} \longrightarrow \text{PhC}(\text{OCO}_2\text{Et}){=}\text{CHSOCH}_3 \tag{47}$$

$$(\text{X}^- = \text{Cl}^-,\ \text{EtO}^-)$$

Since β-keto sulfoxides are readily converted by means of the Pummerer reaction to α-dicarbonyl derivatives (58, 65, 67), numerous attempts have been made to acylate β-keto sulfoxides under basic conditions to the corresponding β-diacyl sulfoxides (2, 98). These in turn, would be potential intermediates to α-tricarbonyl derivatives by means of the Pummerer reaction.

To date, the only successful examples of β-keto sulfoxide C-acylation result from methylsulfinylcarbanion condensation and _in situ_ cyclization of aromatic 1,2 dibasic esters (14, 98). The driving force for acylation is due to rapid inter-molecular cyclization to the 2-(methylsulfinyl)-1,3-indane-dione, Equation 17 and 18.

Previous attempts to affect intermolecular acylation of ω-(methylsulfinyl)acetophenone sodium salt with acetic anhydride resulted in the formation of ω-acetoxy-ω-(methyl-sulfinyl)acetophenone (VIII) (98). This study has confirmed

$$PhCO\overline{C}HSOCH_3 \xrightarrow{(CH_3CO)_2O} [PhCOCH\underset{-}{\overset{OCOCH_3}{\underset{+}{-SCH_3}}}] \longrightarrow PhCOCH(OCOCH_3)SCH_3$$

$$VIII \qquad (48)$$
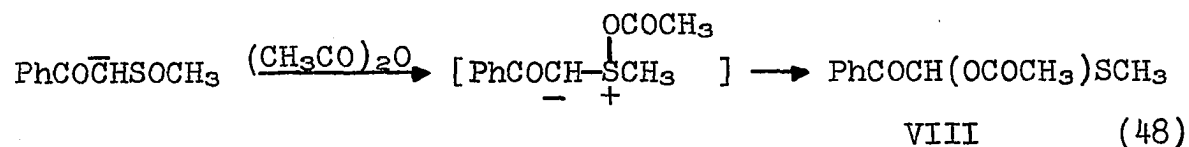
the formation of VIII by acylation with ethyl acetate under identical conditions. The transformation may be formulated as a modified Pummerer rearrangement proceeding through an acetoxy sulfonium ylide intermediate, Equation 48 (16, 98). This formulation is supported by the fact that α-mono-alkylated β-keto sulfoxides (RCOCHR'SOCH$_3$), which are not prone to under-go the Pummerer reaction (16, 58), yield only the O-acylated products (RC(OCOCH$_3$)=CR'SOCH$_3$) under the reaction conditions of Equation 48 (98).

During the course of the present study, further conclu-sions were drawn regarding the reaction between the sodium

salt of ω-(methylsulfinyl)acetophenone and acylating reagents. As already mentioned, reaction with acetic anhydride or ethyl acetate yielded the Pummerer rearrangement product (VIII). However, reaction with acetyl halides in tetrahydrofuran or dimethyl formamide produced the 0-acylated product α-acetoxy-β-(methylsulfinyl)styrene (IX). Although the analogous

$$PhCO\overline{C}HSOCH_3 + CH_3COX \rightarrow PhC(OCOCH_3)=CHSOCH_3 + X^- \qquad (49)$$

$$(X^- = Cl^-, F^-) \qquad\qquad IX$$
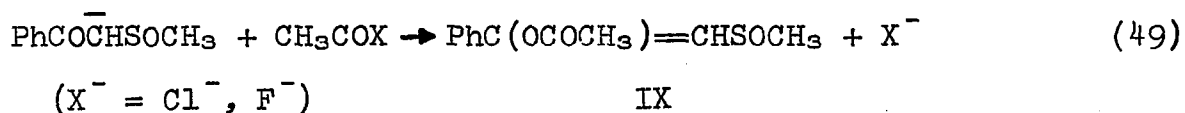
carbethoxy derivative (VII) is stable, IX was found to slowly rearrange in the neat to the Pummerer rearrangement product (VIII). Chromatographic purification to a high state of purity failed to deter the spontaneous course of the rearrangement. Furthermore, treatment of IX, as a saturated solution in tetrahydrofuran with a catalytic amount of sodium methoxide, resulted in rapid conversion to VIII. These observations, leading to the initial formation of VIII and IX as a function of acetylating reagents, can be rationalized in terms of the nucleophilicity of the gegen ion associated with the acetylating reagent (Figure 7). The attack on acetyl halides by the enolate anion of I can be considered an irreversible, kinetically controlled formation of IX. However, nucleophilic attack of acetic anhydride or ethyl acetate, leading to IX by Path A, may be considered reversible. Acetate or ethoxide are better

nucleophiles than chloride or fluoride ion (121). Furthermore, reversible attack by the oxy-ions on the carboxylate carbon of IX results in C-O bond cleavage and C-O bond formation of comparable energies, which is clearly not the case for halide attack. In the over-all scheme, Path B, ylide formation functions as a sink for the reaction by subsequent irreversible Pummerer rearrangement to VIII. The spontaneous rearrangement of pure IX into VIII, by Path C, could involve an intramolecular transformation of IX to the ylide intermediate. However, the possibility of trace acid or base catalyst-induced hydrolysis and intermolecular ylide reformation can not be excluded.
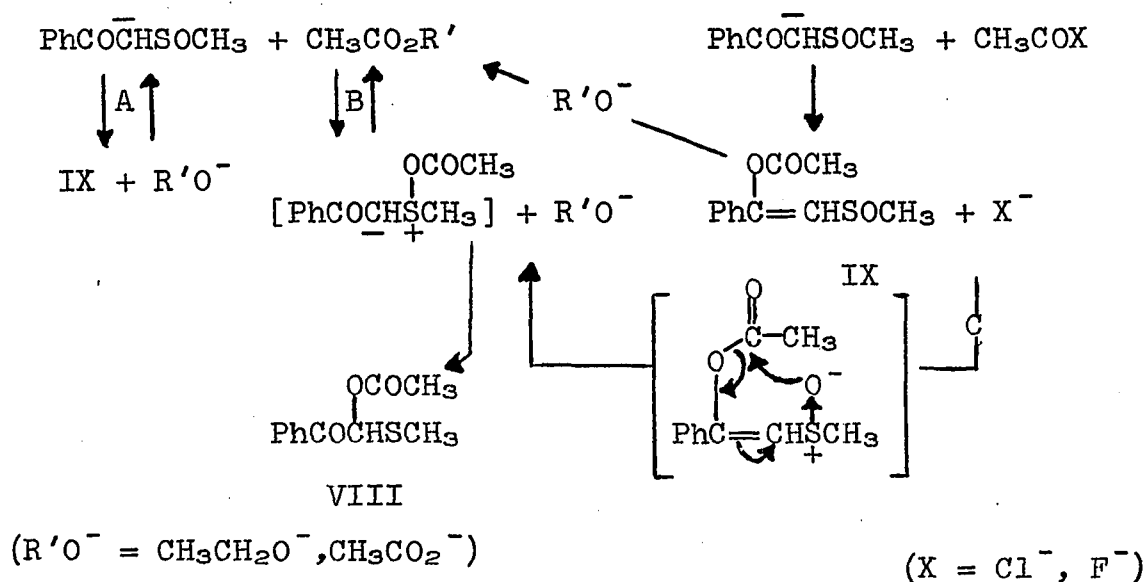
Figure 7. The possible reaction paths on acetylation of ω-(methylsulfinyl)acetophenone anion.

The failure to affect C-acylation by the sequence illustrated in Figure 7 prompted alternative attempts to secure a preparation of β-diacyl sulfoxide derivatives. Unfortunately, these efforts also failed to affect C-acylation of ω-(methylsulfinyl)acetophenone. However, as an aid to future research, they will be briefly summarized. Recently, the C-acylation of β-dicarbonyl has been achieved in elegant fashion by reaction of their C-thallium salts with acid fluorides (122). Attempts to prepare the thallium salt of ω-(methylsulfinyl)acetophenone, by methods applicable to β-dicarbonyls, uniformly failed. Likewise failure resulted in attempts to prepare the enamines of I, which were considered as potential intermediates to β-diacyl sulfoxides _via_ acylation. The reinvestigation of previous attempts (2) to acylate α-methylmercapto ketones ($RCOCH_2SCH_3$), directly available from β-keto sulfoxides (98), led to the original conclusion. Only O-acylation was observed, and enamine or thallium salt preparation could not be affected.

As a final approach to derive α-tricarbonyl derivatives from β-diacyl sulfoxides, Dr. E.T. Sabourin (2,98) had attempted the preparation of diacyl (methylsulfinyl) methanes (($RCO)_2CHSO$-CH_3) by the reaction of β-diketone enolate anions with methylsulfinyl chloride, Equation 50. With methylsulfonyl chloride

$$(RCO)_2\overline{C}H \ + \ CH_3SOCl \longrightarrow (RCO)_2CHSOCH_3 + Cl^- \qquad (50)$$
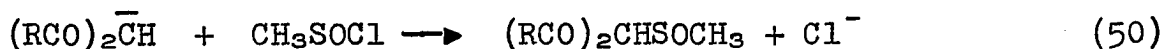
(CH$_3$SO$_2$Cl), the reaction proceeds normally to yield diacyl-
(methylsulfonyl)methane (50). However, addition of methyl-
sulfinyl chloride directly to the enolate anion solutions led
only to di-(methylsulfinyl)ation and disproportionation of the
intermediate (RCO)$_2$C(SOCH$_3$)$_2$ to the corresponding sulfone-
sulfide products, Equation 51. Since the postulated inter-
mediate, leading to di-(methylsulfinyl)ation, is the mono-

$$(RCO)_2\bar{CH} + CH_3SOCl \rightarrow [(RCO)_2C(SOCH_3)_2] \rightarrow (RCO)_2C(SCH_3)SO_2CH_3 \quad (51)$$

adduct and would have an anticipated pKa of less than 0 (14),
the resulting di(methylsulfinyl)ation, in the presence of
excess enolate anion base, was not surprising. Therefore, an
attempt was made in the present study to suppress the di-
(methylsulfinyl)ation by employing essentially neutral re-
action conditions. This was readily achieved by rapid inverse
addition of dibenzoylmethide in tetrahydrofuran to a 1.2
equivalent solution of methylsulfinyl chloride in tetrahydro-
furan. No attempt was made to isolate the methylsulfinyl

$$(PhCO)_2\bar{CH} \overset{\frown}{} (CH_3SOCl)THF \rightarrow [(PhCO)_2CHSOCH_3] \xrightarrow{H_3O^+} (PhCO)_2C\!\!\begin{array}{c} OH \\ OH \end{array} \quad (52)$$
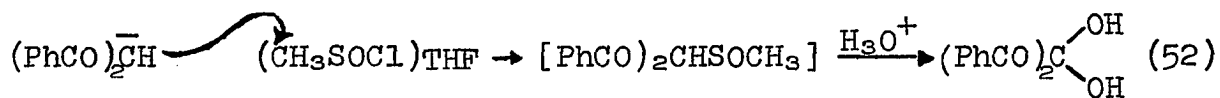
$$X$$

addition product. Immediately after mixing of reactants, the
reaction was poured into aqueous hydrochloric acid and sub-
jected to Pummerer rearrangement (14). On reaction work-up,

the hydrate of diphenyl triketone (X) was isolated in 58% yield.

In hindsight, the failure of ω-(methylsulfinyl)aceto-
phenone anion to undergo C-acylation is not surprising. The
extent of C- or O-acylation of a series of phenacylides
($\text{RCO}\overline{\text{C}}\text{HSOR}'$, $\text{RCO}\overline{\text{C}}\text{HSO}_2\text{R}'$, $\text{RCO}\overline{\text{C}}\text{HS}\overset{+}{\text{R}}_2'$) can be considered to reflect
the extent of delocalization of the carbanion charge density
by the electron sinks attached, the vacant 3d orbitals of
sulfur and the carbonyl group. Theory predicts that the anions
with the least pπ-dπ stabilization possess the most enolate
character and should undergo O-acylation (123). Furthermore,
resonance interaction of sulfoxide and sulfoxyrane 3d orbitals
is generally discounted on the basis of dipole studies (124,
125). The experimental observations appear to coincide with
theoretical implications. Both the anion of ω-(methylsulfonyl)-
acetophenone ($\text{PhCO}\overline{\text{C}}\text{HSO}_2\text{CH}_3$) (126) and the neutral phenacyli-
denedimethylsulfurane ($\text{PhCO}\overline{\text{C}}\text{H}\overset{+}{\text{S}}(\text{CH}_3)_2$) (127) are known to under-
go exclusive O-acylation with acyl halides. Since the anion
of ω-(methylsulfinyl)acetophenone would be expected to possess
intermediate pπ-dπ overlap with sulfur compared to the sulfonyl
and sulfurane derivatives, it is not surprising that only
O-alkylation has been observed.

α-Keto Mercaptal Formation from Hemimercaptal of

Phenylglyoxal and ω-(Methylsulfinyl)acetophenone

The conversion of β-keto sulfoxides to a variety of sulfur-
free compounds, involving one more carbon atom than the start-
ing ester employed for sulfoxide synthesis, was reviewed in
the Literature Survey of this text (58). Although the syn-
thetic utility of β-keto sulfoxides was extensively investi-
gated, Chart 1, the conversion of β-keto sulfoxides to
α-hydroxy aldehydes (RCR'(OH)CHO) was not realized. In view
of this, the present study was undertaken to render such
transformations feasible. Review of the literature indicated
that α-hydroxy aldehydes could be prepared from α-hydroxy mer-
captals (70-72) or in special cases from α-hydroxy acetals
(73, 74), both of which were readily available by Grignard or
hydride reduction of the keto derivatives. Thus, the immediate
objective was to devise a high yield conversion of β-keto
sulfoxides to α-keto mercaptals. A longer range objective was
to investigate the chemistry of the α-keto mercaptals.

The formation of stable mercaptals by acid-catalyzed addi-
tion of thiols to non-conjugated carbonyls is an old reaction,
Equation 53, known since 1885 (128). Recently the topic has

$$R_2CO + R'SH \xrightleftharpoons{H^+} [R_2C<^{OH}_{SR'}] + R'SH \xrightleftharpoons{H^+} R_2C<^{SR'}_{SR'} + H_2O \quad (53)$$
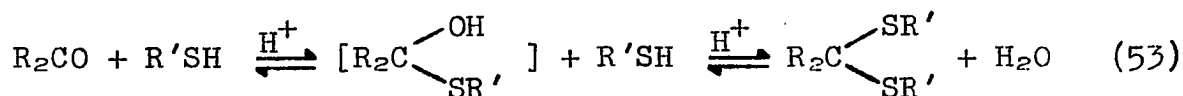
been reviewed (129). To date, however, only one practical
method has been reported for α-keto mercaptal synthesis under

acid-catalysis. This method, employing the dithiol reagent, 1,2-dimethyl-4,5-di(mercaptomethyl)benzene, Equation 54, was

$$PhCOCHO + \quad \overset{CH_3}{\underset{CH_3}{\bigcirc}}\overset{CH_2\ SH}{\underset{CH_2\ SH}{}} \xrightarrow{H^+} \quad PhCOCH \overset{S}{\underset{S}{\bigcirc}}\overset{CH_3}{\underset{CH_3}{}} \qquad (54)$$
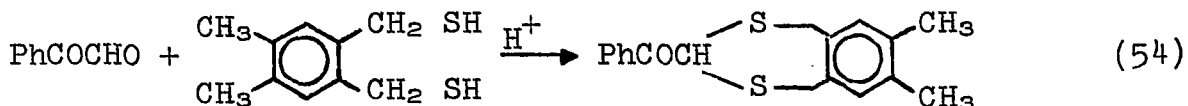
found to be suitable for the mono-mercaptal preparation of various α-dicarbonyl compounds (130). While no systematic studies are apparent in the literature, the use of less steri-cally hindered reagents inevitably resulted in the unsatis-factory formation of dimercaptal and polymer products (129, 131-133). In recent years, acid-catalyzed methods have been overlooked due to development of procedures which allow selective α-keto mercaptal preparation under neutral or basic conditions. Exchange of acetal alcohols by thiols under essentially neutral conditions has been moderately successful (134). Basic conditions allow for a more elegant approach. Trimethylene thiotosylate $(TosS-(CH_2)_3STos)$ readily converts active α-carbonyl methylene groups (135) or enamines (136) to α-keto mercaptals in the presence of excess base. Corey and Seeback (137) have devised a preparation of either α-hydroxy mercaptals or α-keto mercaptals by addition of 1,3-dithiane carbanions ($\overset{S}{\underset{S}{\diagup}}^-$) to carbonyls or carboxylic acid deriva-tives.

In spite of the lack of literature precedent, conversion of the methyl hemimercaptal of phenylglyoxal (XI), which is

directly available in high yield by Pummerer rearrangement of
ω-(methylsulfinyl)acetophenone (I), to the methylmercaptal of
phenylglyoxal (XII) under acid-catalyzed conditions was the
initial attempt of this study, Equation 55. The transformation

$$\underset{XI}{PhCO\overset{\overset{\displaystyle OH}{|}}{C}HSCH_3} + HSCH_3 \xrightarrow{H^+} \underset{XII}{PhCOCH(SCH_3)_2} + H_2O \tag{55}$$
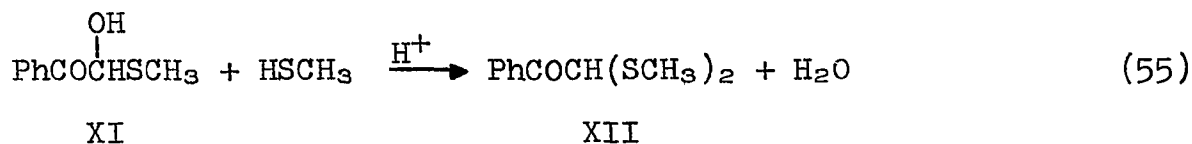
in Equation 55 would appear to be straightforward. However,
no practicality could be demonstrated for the reaction.
Yields, at best, approached the 50% expected for the known
disproportionation of the hemimercaptal, Equation 56 (16, 75).

$$2 \underset{XI}{PhCO\overset{\overset{\displaystyle OH}{|}}{C}HSCH_3} \xrightarrow{H^+} \underset{XII}{PhCOCH(SCH_3)_2} + \underset{XIII}{PhCOCH(OH)_2} \tag{56}$$
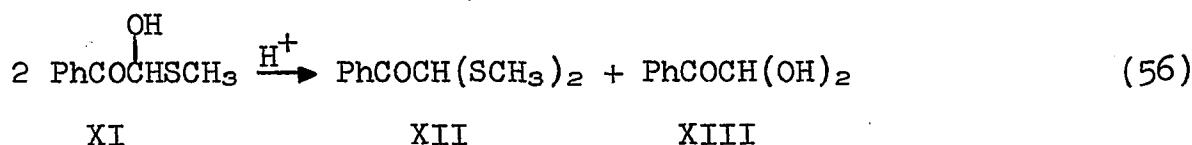
The overall results were actually more complex and yielded a
number of perplexing observations. When acid catalysts, such
as dry hydrogen chloride, boron trifluoride etherate, p-tolu-
ene sulfonic acid, or concentrated sulfuric acid, were em-
ployed with or without solvents in the presence of excess
extraneous mercaptan (other than methylmercaptan), no mer-
captan exchange products were formed. The sole disproportiona-
tion product was XII. On the other hand, 85% phosphoric acid
catalyst, under identical conditions, caused little dispro-
portionation and nearly quantitative exchange of methyl mer-
captan by extraneous mercaptan, Equation 57. This exchange

$$\text{PhCO}\overset{\overset{\text{OH}}{|}}{\text{C}}\text{HSCH}_3 + \text{HSR}' \xrightarrow[85\%]{\text{H}_3\text{PO}_4} \text{PhCO}\overset{\overset{\text{OH}}{|}}{\text{C}}\text{HSR}' + \text{HSCH}_3 \qquad (57)$$
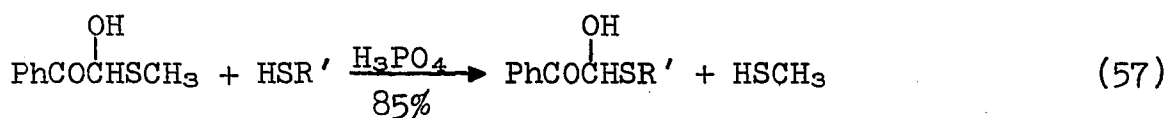
$(\text{HSR}' = \text{PhSH}, \text{PhCH}_2\text{SH}, \text{EtSH})$

phenomenon provides an ideal method for the preparation of various hemimercaptals of phenylglyoxal from the methyl derivative (XI). However, progressive dilution of the 85% phosphoric acid catalyst with water causes the disproportionation reaction, Equation 56, to proceed in a normal fashion. Moreover, 85% phosphoric acid functioned in identical fashion to the other acid catalysts mentioned when the extraneous exchange reagents employed were ethane dithiol or ethylene glycol. In these cases, the reaction products consisted predominantly of dimercaptal (XIV) or diacetal (XV) and polymers. Even when a deficiency of dithiol or glycol was employed, no α-keto mercaptal or acetal could be detected by thin layer chromatographic techniques. The observation of exclusive dimercaptal formation has also been reported for reactions of glyoxal (131).

The inability to affect the transformation in Equation 55 can, in part, be attributed to the fact that the hydrate of phenylglyoxal (XIII) does not readily form the hemimercaptal (XI), Equation 58. Treatment of an authentic sample of XIII

$$\underset{\text{XIII}}{\text{PhCOCH(OH)}_2} + \text{HSCH}_3 \xrightarrow[]{\text{H}^+} \underset{\text{XI}}{\text{PhCO}\overset{\overset{\text{OH}}{|}}{\text{C}}\text{HSCH}_3} + \text{H}_2\text{O} \qquad (58)$$
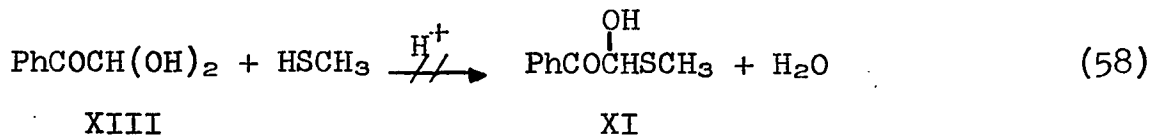
with a large excess of methylmercaptan in benzene, under dry
hydrogen chloride catalysis, produced only a trace of XI;
unreacted hydrate (XIII) was readily recovered. Under identi-
cal conditions, the hemihydrate of phenylglyoxal $((PhCOC\overset{OH}{\underset{H}{|}}-)_2O)$
formed XI in 59% yield, while anhydrous phenylglyoxal reacted
immediately and quantitatively with methylmercaptan even in
the absence of acid catalyst.

The failure of XIII to react readily with methylmercaptan
may be surprising in view of the average equilibrium constant
($K_{eq} \sim 20$) measured for mercaptan exchange of simple ketone
hydrates, Equation 59 (138). Unfortunately no values of K_{eq}

$$R_2C(OH)_2 + H^+ + HSR' \xrightleftharpoons{K_{eq}} R_2C(OH)SR' + H_2O + H^+ \tag{59}$$
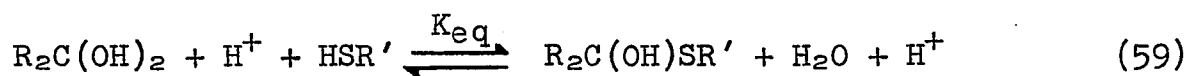
are available for α-keto hydrates. However, Lienhard and
Jenks (138, 139) have also demonstrated that hydrate to hemi-
mercaptal conversion involves prior dehydration to the free
carbonyl, rather than nucleophilic attack by mercaptan on
protonated hydrate ($R_2C(OH)O\overset{+}{H}_2$). Thus, a priori consideration
of the carbonyl electron-withdrawing inductive effect could
rationalize an increase in hydrate C-O bond strength and corres-
ponding decrease in tendency to dehydrate via a carbonium ion
intermediate to the free carbonyl. In fact, a primary requisite
for stable hydrate formation appears to be the absence of
electron-inducing or the presence of electron-withdrawing sub-
stitution on the host carbonyl function. Illustrative examples

include formaldehyde (138), chloral (140), and alloxan (141), whose stable hydrates can not be converted to mercaptals in appreciable yields under acid-catalyzed conditions. A consistent mechanistic rationalization must consider the unfavorable situation of carbonium ion formation alpha to strong electron-withdrawing functional groups, or alternatively, lack of carbonium ion stabilization by the available substitution.

Since practicality could not be achieved for the reaction in Equation 55, consideration was given to alternative routes to the α-keto mercaptal (XII). Weygand, et al. (70, 71) had previously reported the preparation of the ethyl mercaptal of phenylglyoxal by the series of reactions summarized in Equations 60-62. Clearly, the critical intermediate of the

$$PhCOCl + CH_2N_2 \longrightarrow PhCOCHN_2 + HCl \tag{60}$$

$$PhCOCHN_2 + EtSCl \longrightarrow PhCO\overset{Cl}{\underset{|}{C}}HSEt + N_2 \tag{61}$$

$$PhCO\overset{Cl}{\underset{|}{C}}HSEt + NaSEt \longrightarrow PhCOCH(SEt)_2 + NaCl \tag{62}$$
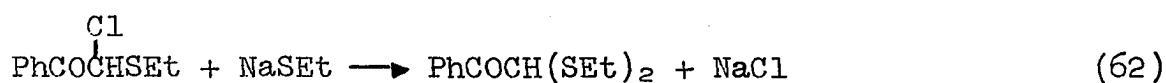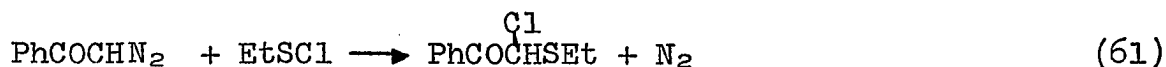
sequence is the α-chloro thioether , Equation 61. Therefore, the possibility of converting either XI or I to ω-chloro-ω-(methylmercapto)acetophenone, (PhCOCH(Cl)SCH$_3$) (XVI), was investigated. H.-D. Becker had demonstrated the preparation of an α-chloro thioether by reacting the methylhemimercaptal of ninhydrin with concentrated hydrochloric acid, Equation 63.

$$\text{(63)}$$
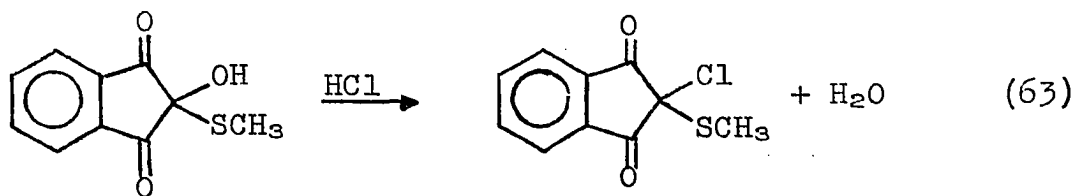
In this case, isolation of the product was possible due to its crystalline nature and high stability. On the other hand, XVI was expected to be an unstable oil by analogy to the ethyl-mercapto derivative (70). Moreover, the conditions employed for the ninhydrin reaction resulted only in the disproportiona-tion reaction of XI, Equation 55. The course of the dispro-portionation reaction could be altered, however, if pure methyl-mercaptan were employed as solvent at -24°C under dry hydrogen chloride catalysis. The procedure employed was analogous to that used for the preparation of α-chloro ethers; passage of dry hydrogen chloride into an anhydrous aldehyde-alcohol mixture at low temperature (142). Under the low temperature conditions, water of dehydration separates from solution as a dense immisible phase. The in situ formation of XVI, was con-firmed by NMR comparison of an ether-diluted reaction ali-quot to the spectra of an authentic sample, which was subse-quently prepared. On reaction work-up at room temperature, XVI underwent nucleophilic attack by mercaptan solvent to afford the mercaptal (XII) in 75% yield, Equations 64, 65. However, the major disadvantage of this procedure involves the

$$\text{PhCO}\overset{\overset{\text{OH}}{|}}{\text{CH}}\text{SCH}_3 + \text{HSCH}_3 \text{ (solvent)} \xrightarrow[-24°C]{\text{HCl}} [\text{PhCO}\overset{\overset{\text{Cl}}{|}}{\text{CH}}\text{SCH}_3] + \text{H}_2\text{O} \quad (6)$$

$$[\text{PhCO}\overset{\overset{\text{Cl}}{|}}{\text{CH}}\text{SCH}_3] + \text{HSCH}_3 \xrightarrow[20°C]{} \text{PhCOCH(SCH}_3)_2 + \text{HCl} \quad (65)$$
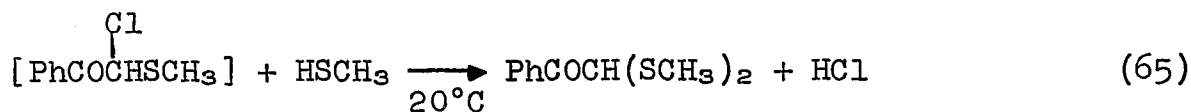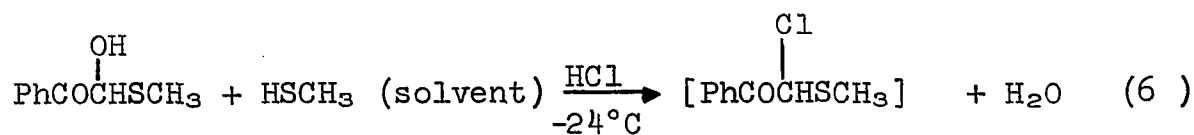
handling of large quantities of methylmercaptan.

The more convenient and desirable alternative to the pre-
paration of ω-chloro-ω-(methylmercapto)acetophenone (XVI) com-
pletely avoids the use of methylmercaptan. Bordwell and Pitt
(143) have demonstrated that sulfoxides readily undergo a
Pummerer type reaction with thionyl chloride to yield α-chloro
thioethers, Figure 8. Since the discovery of the reaction,
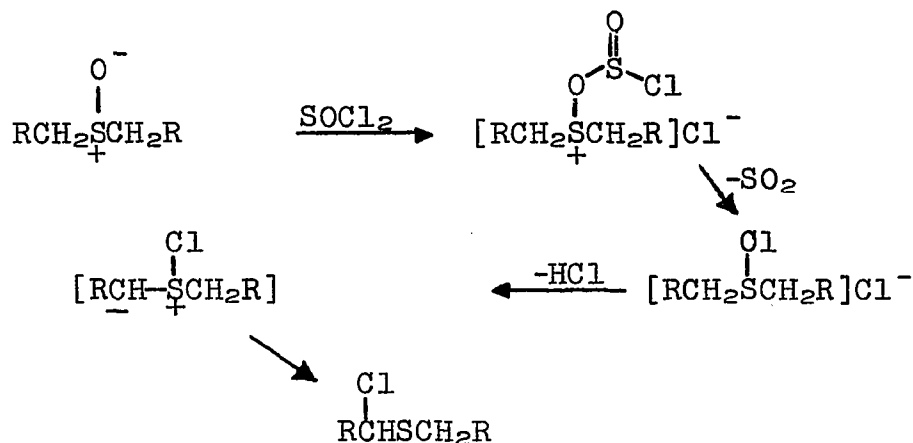
Figure 8. Pummerer type reaction of sulfoxides with thionyl
chloride.
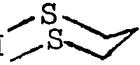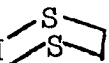
numerous examples of isolation and subsequently observed
Pummerer rearrangement of the chlorosulfonium salt

intermediates have been documented (67). ω-(Methylsulfinyl)-acetophenone (I) reacts likewise in very facile fashion. Drop-wise addition of thionyl chloride at 0°C to a methylene chloride solution of I results in the immediate formation of a white precipitate, presumably a sulfonium salt, which could not be isolated under the reaction conditions, but underwent rapid decomposition with the evolution of sulfur dioxide and hydrogen chloride. From the resulting reaction, XVI was isolated in nearly quantitative yield. The product could be purified by distillation, but proved unstable at room temperature. Storage for one month below -10°C, however, resulted in only minor decomposition of a purified sample.

For the purpose of preparing mercaptals, XVI need not be isolated. Moreover, sodium thiolates were not required as nucleophiles. Direct addition of methylmercaptan to the pre-formed methylene chloride solution of XVI yielded the methyl-mercaptal of phenyl glyoxal (XIII) on crystallization from 50% pentane -50% hexane in greater than 95% yield. In fact, this general procedure allows XVI to function as an ideal substrate for the preparation of a wide variety of α-keto mercaptals or acetals. Acetal formation is possible by displacement of methylmercaptan under vacuum evaporation with a large excess of anhydrous alcohol. Table 5 summarizes yields and products from the reactions of XVI with thiols and alcohols.

The successful conversion of I to XVI, and its utility as an intermediate to α-keto mercaptal synthesis, prompted an attempt

Table 5.   Preparation of α-keto mercaptals and acetals by
            reaction of XVI with thiols and alcohols

Product		Ratio of Reactants thiol or alcohol / XVI	Reaction Scale (mmoles)	% Yield
XIII	PhCOCH(SCH₃)₂	4	250	> 95
XVII	PhCOCH(SCH₃)SC₂H₅	1.2	25	84
XVIII	PhCOCH(S-S)⟍⟋	0.7	20[a]	51[b]
XIX	PhCOCH(S-S)⟍	0.7	20[a]	76[b]
XX	PhCOCH(OCH₃)₂	200	13	> 90

[a]XVI diluted to minimize polymolecular reactions with
methylene chloride to 0.1 M, normal [XVI] = 1 M.

[b]Yield based on thiol as limiting reagent.

to extend the reaction to mono-α-alkylated-β-keto sulfoxides,
Equation 66. The α-alkylated β-keto sulfoxides are known to

$$\text{PhCOCHR'SOCH}_3 \xrightarrow{\text{SOCl}_2} [\text{PhCO}\overset{\text{Cl}}{\underset{|}{\text{C}}}\text{R'SCH}_3] \xrightarrow{\text{HSCH}_3} \text{PhCOCR'(SCH}_3)_2$$
$$\text{XXI} \qquad\qquad (66)$$
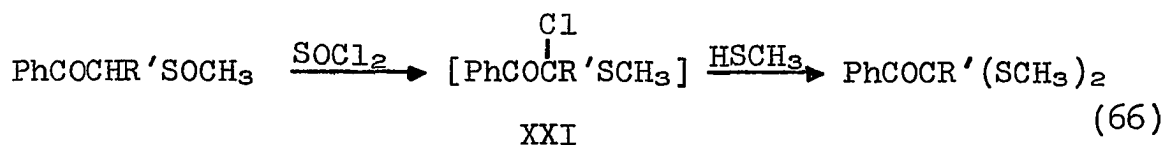
be resistant to Pummerer rearrangement under aqueous conditions
relative to the unsubstituted derivatives (58). If the

Pummerer type rearrangement with thionyl chloride proved more facile with the α-substituted-β-keto sulfoxides, XXI could also function as a convenient intermediate to α-diketones after aqueous hydrolysis.

Treatment of ω-(methyl)-ω-(methylsulfinyl)acetophenone (Ia) with thionyl chloride in identical fashion to I, resulted in the immediate and copious evolution of acid fumes. The crude reaction product was not isolated, but subjected to hydrolysis at room temperature for three hours. Distillation of this crude hydrolysis product yielded 1-phenyl-1,2-propane-dione in only 52% yield. The overall procedure offered no advantage over the normal acid-catalyzed Pummerer rearrangement and desulfurization of Ia (58).

When the reaction was repeated and the crude chlorinated intermediate (XXI) was treated with methyl mercaptan, no 1-phenyl-2,2-di(methylmercapto)propanone (PhCOC(SCH$_3$)$_2$CH$_3$) was isolated. Chromatographic separation yielded 1-phenyl-2-(methylmercapto)propanone (Ib) in 7.7% and 1-phenyl-2,3-di-(methylmercapto)propanone (XXIIa) in 83% yield, Equation 67.

$$\text{Ia} + \text{SOCl}_2 \longrightarrow \text{PhCOCH(SCH}_3\text{)CH}_3 + [\text{XXI}] \xrightarrow{\text{HSCH}_3}$$

$$\underset{\text{Ib}}{} \qquad\qquad \underset{\text{XXIIa}}{\text{PhCOCH(SCH}_3\text{)CH}_2\text{SCH}_3} \quad (67)$$
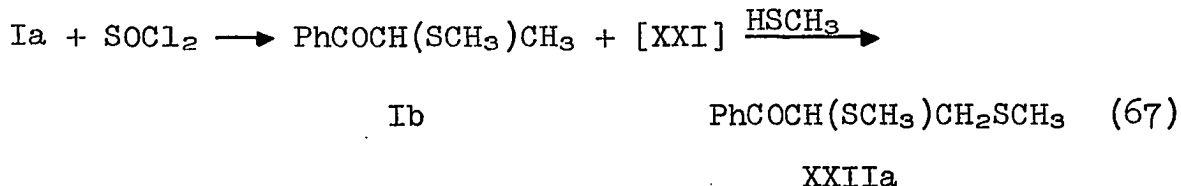
The reduction of sulfoxides (Ia) to sulfides (Ib) by thionyl chloride is a known reaction (144). Characterization of the

unexpected XXIIa was straightforward from its mass spectra ($\underline{m}/\underline{e}$ = 226) and its ABX (CH–CH$_2$) NMR pattern (J_{AX} = 8.1 Hz, J_{BX} = 6.9 Hz, J_{AB} = 13.5 Hz, δ_A = 3.26, δ_B = 2.876, δ_X = 4.416). Furthermore, XXIIa was prepared by an alternative route. Treatment of the methyl mercaptal of phenylglyoxal (XII) with diazomethane in the presence of boron trifluoride etherate catalyst afford XXIIa in 60% yield, Equation 68.

$$PhCOCH(SCH_3)_2 + N_2CH_2 \xrightarrow{BF_3} PhCOCH(SCH_3)CH_2SCH_3 + N_2 \qquad (68)$$

$$XII \qquad\qquad\qquad\qquad XIIa$$
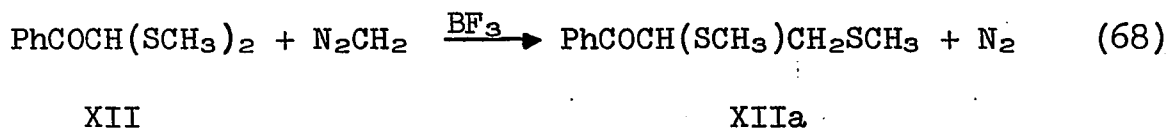
The reaction of diazo-compounds with mercaptals is a known reaction. Schönberg and Praefcke (145) have proposed the reaction to proceed by the step-wise sequence illustrated in Equations 69-70.

$$RCH(SR')_2 \xrightarrow{BF_3} [R\overset{+}{C}HSR']BF_3SR'^- + (N_2CHR'') \qquad (69)$$

$$\longrightarrow [RCH(SR')\overset{\overset{N_2^+}{|}}{-}CHR'']BF_3SR'^- \longrightarrow RCH(SR')CHR''SR' + N_2 \quad (70)$$
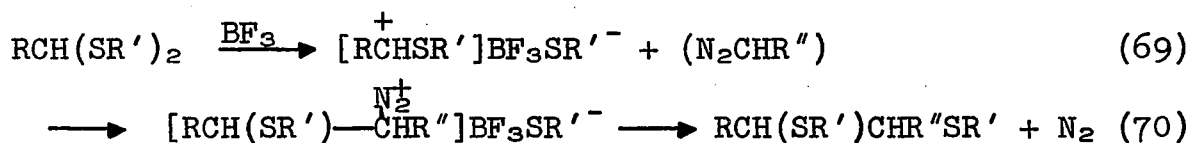
The formation of XXIIa was not surprising after careful consideration was given to the chlorinated intermediate. The crude chlorination reaction product could be isolated, but proved unstable to purification. Its NMR spectra, Figure 9, revealed a complex ABC (CH–CH$_2$) pattern, which in consideration with the mass spectral parent peak pattern ($\underline{m}/\underline{e}$ = 214, M + 2: relative intensity = 33%) was consistent with 1-phenyl-2-methyl-

Figure 9. Crude NMR spectra of reaction products from thionyl chloride treatment
of ω-(methyl)-ω-(methylsulfinyl)acetophenone (Ib), including ABC ex-
pansion, 100 Hz.
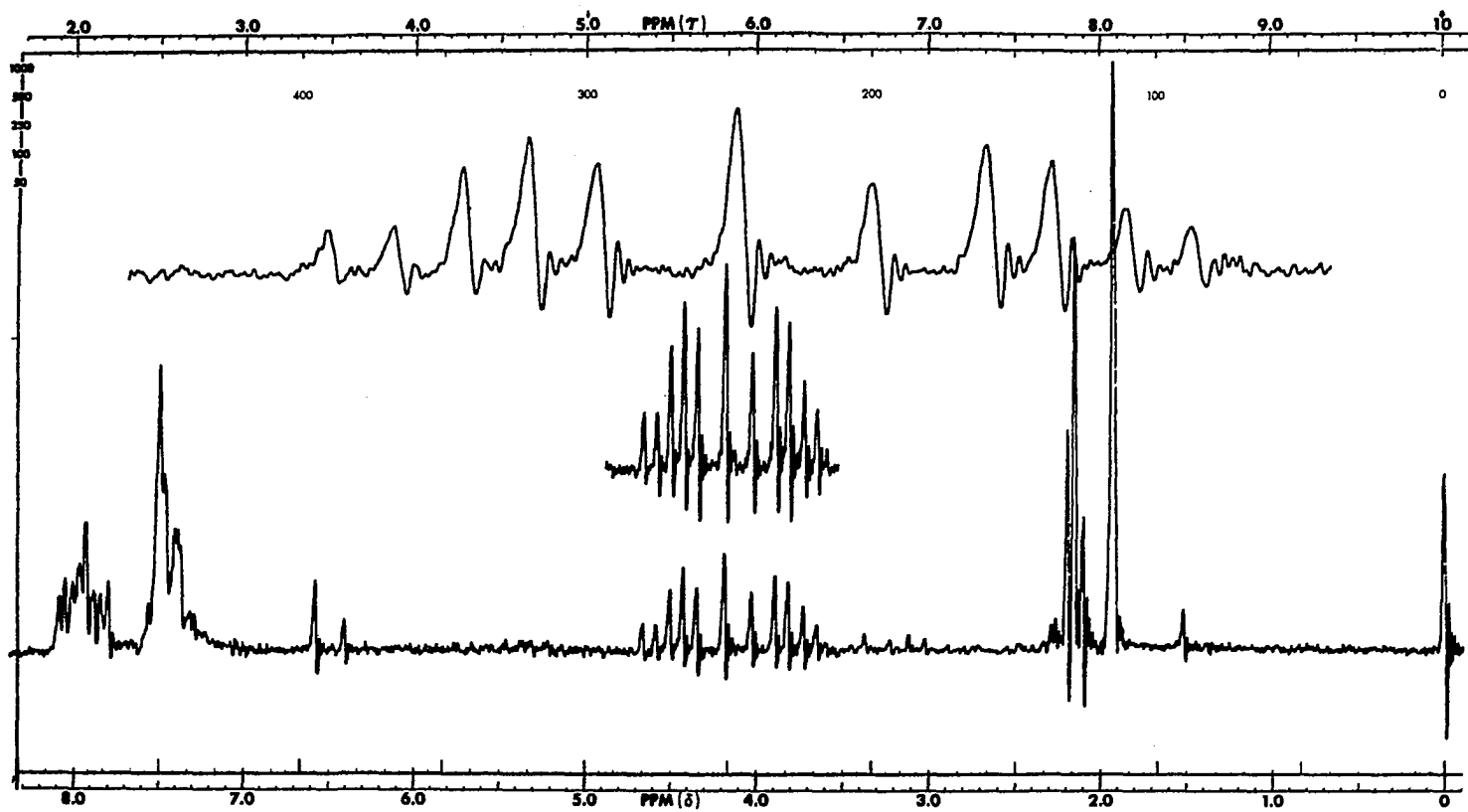
mercapto-3-chloropropanone (XXII) as the predominant product.

The presence of 1-phenyl-2-methylmercapto-2-chloropropanone

(XXI) can not be excluded or confirmed on the basis of the

observed NMR spectra. Abundant methyl proton resonance at

2.2δ could correspond to a mixture of Ib and XXI. However,

the formation of XXII can be rationalized, Figure 10, in terms

of a reaction mixture in equilibration by E_1 decomposition of

XXI to 1-phenyl-2-methylmercapto propenone (XXIa), followed by

conjugate readdition of hydrogen chloride to XXIa. Attempts to

prepare XXIa by tertiary amine base-catalyzed dehydrochlorina-

tion of XXII failed. Only resinous mixtures resulted, which

could not be separated by chromatographic techniques.

$$\text{PhCOCHSOCH}_3 \xrightarrow{\text{SOCl}_2} \overset{\text{Cl}}{\underset{\text{CH}_3}{\text{PhCOC-SCH}_3}} + SO_2 + HCl$$
$$\underset{\text{CH}_3}{|}$$

Ib   XXI

$$\underset{\text{CH}_2}{\overset{||}{\text{PhCOCSCH}_3}} \underset{\xrightarrow{\hspace{1cm}}}{\overset{-H^+}{\xleftarrow{\hspace{1cm}}}} [\overset{+}{\underset{\text{CH}_3}{\text{PhCOCSCH}_3}}]$$

XXIa

$$\overset{\text{OH}}{\underset{\text{CH}_2^+}{[\text{PhC}=\text{C-SCH}_3]}} \underset{\xleftarrow{\hspace{1cm}}}{\overset{Cl^-}{\xrightarrow{\hspace{1cm}}}} \overset{\text{H}}{\underset{\text{CH}_2Cl}{\text{PhCOCSCH}_3}}$$
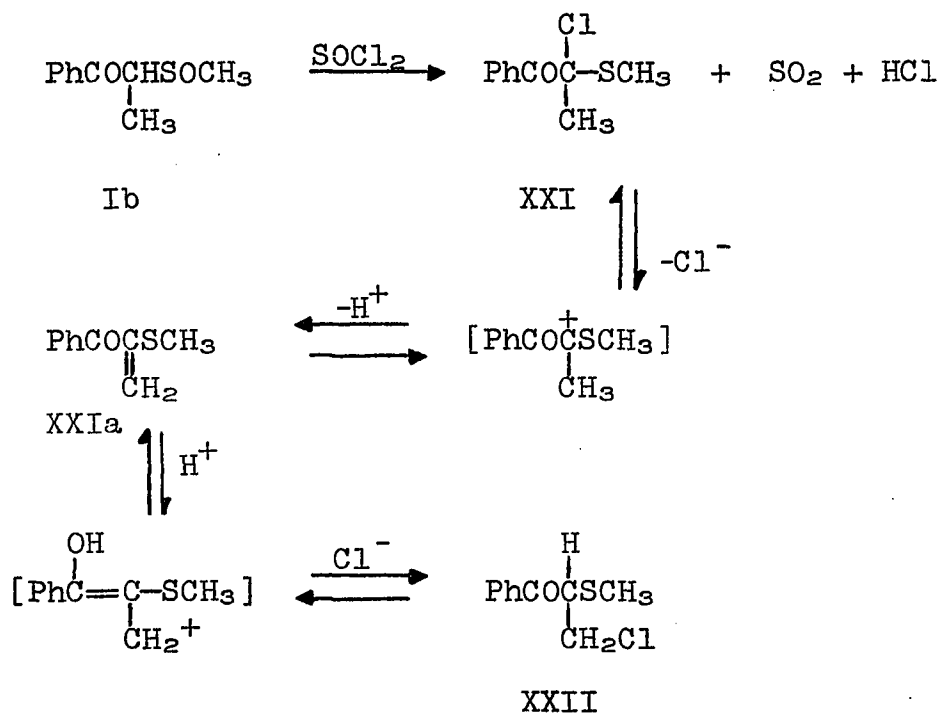
XXII

Figure 10. Proposed reaction path for the conversion of
ω-(methyl)-ω-(methylsulfinyl)acetophenone (Ib)
to 1-phenyl-2-methylmercapto-3-chloropropanone
(XXII).

Earlier in this section, mention was made of the bimole-
cular disproportionation of the hemimercaptal (XI), Equation
56. The bimolecular and acid-catalyzed nature of the dis-
proportionation was recognized by Böhme and Teltz (75). They
followed the disproportionation of formaldehyde hemimercaptals
by means of the chromotropic acid-formaldehyde color reaction.
Subsequent examples of hemimercaptal disproportionations have
appeared in the literature (146-149).

During the course of the present study, it was observed
that the disproportionation phenomenon is common to a number
of β-keto-α-substituted thioethers. These compounds include
α-chloro thioether (XVII), α-acetoxy thioether (VIII) and the
mixed mercaptal, ω-(methoxy)-ω-(methylmercapto)acetophenone
(XXIII). In fact, XXIII could only be isolated in an impure
state, due to its facile disproportionation. XXIII was pre-
pared by reaction of XVI with sodium methoxide in ether,
followed by water extraction of the resulting sodium chloride
at pH > 7. The isolated organic residue was nevertheless con-
taminated by the acetal (XX) and mercaptal (XII) disproportiona-
tion products. It should be interposed at this point, that the
facile disproportionation of XXIII provides the rationale for
the unusual products observed on reaction of ω-(methylsulfinyl)-
acetophenone (I) with diazomethane. The reaction proceeds only
in the presence of a Lewis acid catalyst, and yields an equal
molar mixture of XX and XII. Equations 71-72 summarize the

reaction route, involving a Pummerer rearrangement to yield
XXIII, followed by disproportionation. Figures 11 and 12

$$2PhCOCH_2SOCH_3 + CH_2N_2 \xrightarrow{\text{BF}_3} 2[PhCOCH\overset{\overset{\displaystyle OCH_3}{|}}{=}\underset{+}{S}CH_3]] + 2\ N_2 \qquad (71)$$

$$\longrightarrow 2\ \underset{\text{XXIII}}{PhCOCH(OCH_3)SCH_3} \xrightarrow{\text{BF}_3} XX + XII \qquad (72)$$
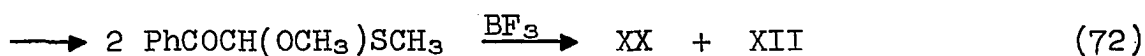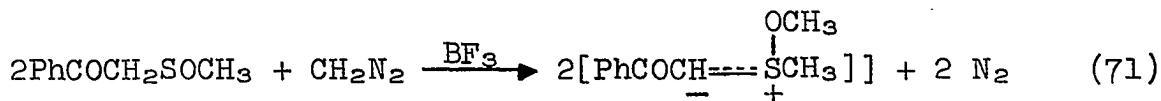
illustrated consecutive NMR scans of the disproportionation
reaction of compounds XI, XVI, VIII and XXIII under boron tri-
fluoride etherate catalysis in d-chloroform. The progress of
the disproportionation can be observed by the increase in the
relative intensity of the methine proton resonance (5.32δ) of
the methylmercaptal of phenylglyoxal (XII), a common dispro-
portionation product of all the reactants. Unfortunately, the
disproportionation rates of the substrates are either very
rapid or very slow and NMR techniques proved impractical for
absolute rate measurements. The relative disproportionation
aptitudes   appear to be as follows: $PhCOCH(OCH_3)SCH_3 \geq PhCOCH$-
$(OH)SCH_3 >>> PhCOCH(OAc)SCH_3 > PhCOCH(Cl)SCH_3$.

At present the mechanism of this disproportionation is un-
resolved. Pearson and Songstad (112) have pointed out that the
hemimercaptal disproportionation is consistent with the "symbi-
osis" stabilizing effect (hard or soft ligands tend to flock
together with mutual exclusion of each other) resulting when
like ligands combine with a mutual acceptor atom. However, no

Figure 11. Consecutive NMR scans for the boron trifluoride etherate-catalyzed disproportionation into ω,ω-di(methylmercapto)acetophenone (XII) of the:

A, methyl hemimercaptal of phenylglyoxal (XI);

B, ω-acetoxy-ω-(methylmercapto)acetophenone (VIII);

C, ω-chloro-ω-(methylmercapto)acetophenone (XVI).

t = 20 hrs amp: 2.5
t = 12 hrs amp: 2.5
t = 2.5 hrs amp: 2.5
t = .5 min amp: 2.5
t = 0 min   amp: 2.5

C

t = 12 hrs amp: 1.25
t = 8 hrs   amp: 1.25
t = 3 hrs   amp: 1.25
t = .5 min amp: 1.25
t = 0 min   amp: 1.25

B

t = 4 min amp: 5.0
t = .5 min amp: 2.5
t = 0 min amp: 2.5

A
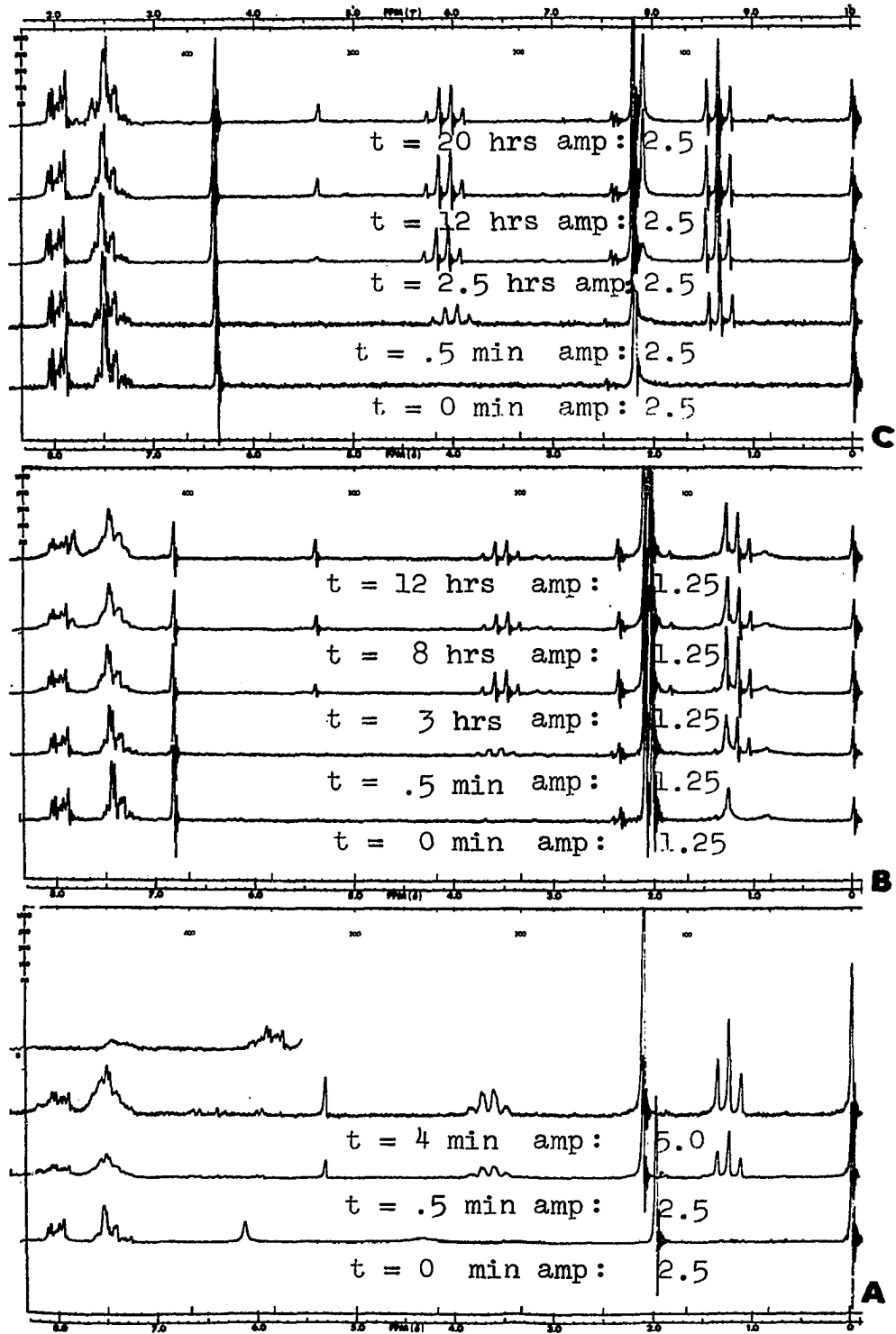
Figure 12. Starting material and product NMR spectrum for
the boron trifluoride etherate-catalyzed dis-
proportionation of ω-methoxy-ω-(methylmercapto)-
acetophenone (XXIII) into the methyl mercaptal
(XII) and methyl acetal of phenylglyoxal (XX).

t = 0 min amp : 6.3

t = 0.5 min amp : 6.3
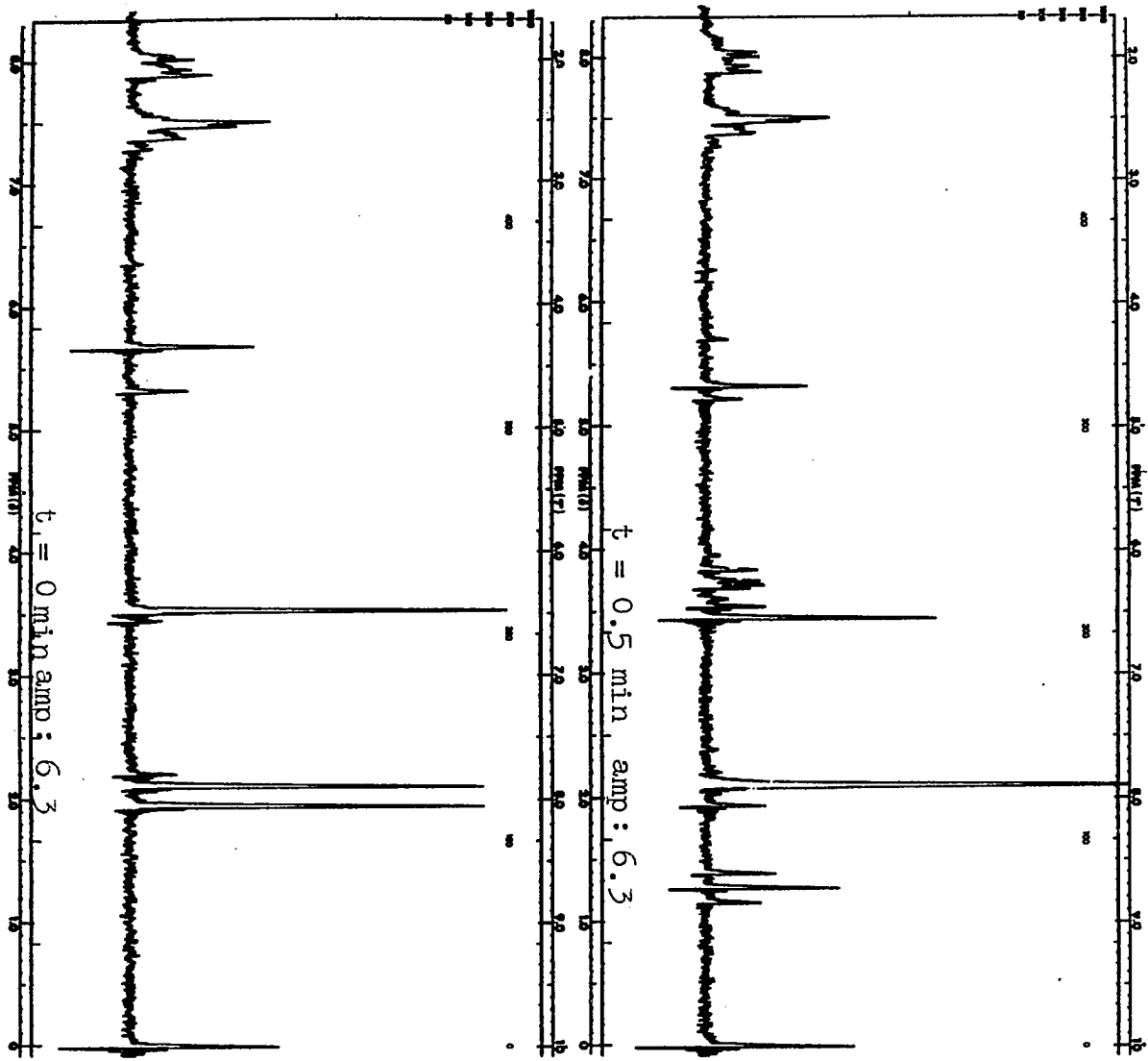
thermodynamic data is available for the hemimercaptal case.
Without undue emphasis, a reasonable mechanistic representa-
tion for the bimolecular disproportionation could envision a
four-centered transition-state with concerted ligand migra-
tion, Figure 13. A mechanism of analogous representation has

$$
\begin{array}{c}
\text{BF}_3 \\
\vdots \\
\text{HO} \quad \delta^- \\
\end{array}
$$

PhCO—CH $\delta+$ ⟶ $\delta+$ CH—COPh ⟶

SCH$_3$ SCH$_3$

δ^-

BF$_3$

PhCOCH(SCH$_3$)$_2$

+

PhCOCH(OH)$_2$
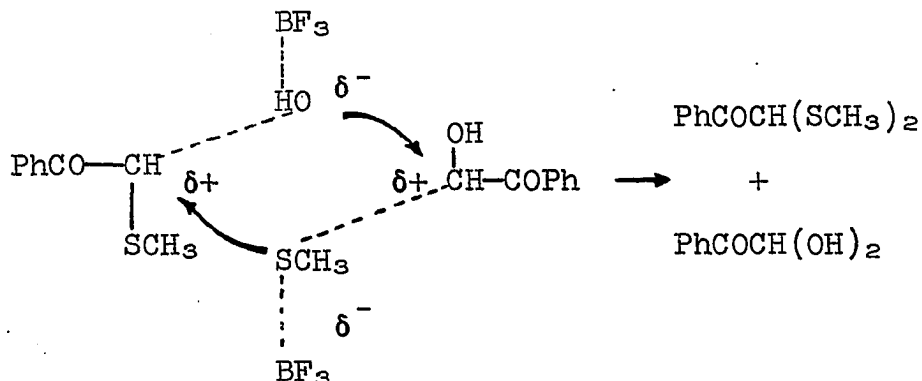
Figure 13. Proposed four-centered transition-state dispro-
portionation mechanism of hemimercaptal dispropor-
tionation.

been proposed for the disproportionation of unsymmetrically
substituted alkylsilanes (150). The point in common for the
silane and the very different α-keto hemimercaptal systems is
that neither the silicon atom of the silane, nor a carbon
atom **alpha** to a carbonyl would be conducive to siliconium or
carbonium ion formation. Thus, intervention of a concerted
four-centered disproportionation would provide a pathway to
by-pass the energetically unfavorable formation of the onium
ions.

Preparation of β-Hydroxy Mercaptals and

Conversion to α-Hydroxy Aldehydes

Investigation of the step-wise sequence, Equation 73, for

$$PhCOCH(SCH_3)_2 \longrightarrow Ph\overset{\overset{\displaystyle OH}{|}}{C}RCH(SCH_3)_2 \longrightarrow Ph\overset{\overset{\displaystyle OH}{|}}{C}RCHO \qquad (73)$$

XII   XXIV   XXV
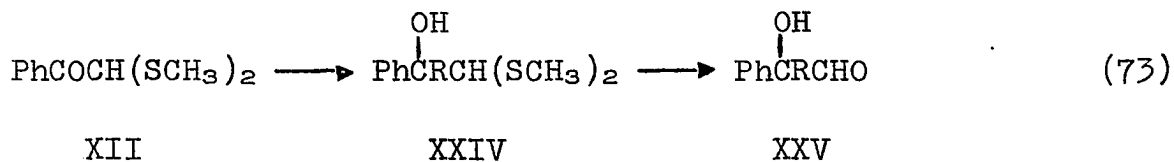
the transformation of the readily available methylmercaptal of phenylglyoxal to α-hydroxy aldehydes was undertaken on a preparative scale.

Sodium borohydride reduced XII in aqueous ethanolic solvent to yield 1-phenyl-2,2-di(methylmercapto)ethanol (XXIVa) in a high state of purity. Compound XII underwent normal addition reactions with methyl, ethyl and phenyl Grignard reagents. Ethyl Grignard led to the formation of traces of XXIVa, which was the predominate product on reaction of isopropyl and t-butyl Grignard, due to reduction of the carbonyl (XII). Table 6 summarizes some pertinent results for α-hydroxy mercaptal formation.

The conversion of α-hydroxy acetals to α-hydroxy aldehydes is a difficult process. Acid catalysis is required to affect acetal hydrolysis. Since the reaction is reversible, the alcohol must be removed if the hydrolysis is to go to completion. Moreover, acid-catalyzed rearrangement of the α-hydroxy aldehyde to the isomeric α-hydroxy ketones, Equation 74, readily occurs (77, 78). On the other hand, α-hydroxy

$$\underset{\underset{R_2C-CH(OR')_2}{\overset{OH}{|}}}{} \xrightleftharpoons{\ H_3O^+\ } \underset{\underset{R_2C-CHO}{\overset{OH}{|}}}{} + 2\,HOR' \xrightarrow{\ H^+\ } \underset{\underset{RCOCHR}{\overset{OH}{|}}}{} \qquad (74)$$

Table 6. Formation of α-hydroxy mercaptals

$$\underset{XII}{PhCOCH(SCH_3)_2} \longrightarrow \underset{XXIV}{\overset{\overset{OH}{|}}{PhCRCH(SCH_3)_2}}$$

Product XXIV		% Yield Procedure A[a]	% Yield Procedure B[b]	Boiling Pt. (%)
XXIVa	$\overset{OH}{\underset{}{PhCHCH(SCH_3)_2}}$	98	88	78-80/0.2 torr
XXIVb	$\underset{CH_3}{\overset{OH}{PhC-CH(SCH_3)_2}}$	93	68	130-133/0.7 torr
XXIVc	$\underset{C_2H_5}{\overset{OH}{PhC-CH(SCH_3)_2}}$	85	70	137-138/0.7 torr
XXIVd	$\overset{OH}{Ph_2C-CH(SCH_3)_2}$	85	65	155-158/0.7 torr

[a]50 Mmole scale, product isolated by column chromatography.

[b]50 Mmole scale, product isolated by vacuum distillation.

mercaptals offer the possibility of the hydrolysis going to completion because of the oxidation of the liberated mercaptan (70-72, 151, 152), or because of the precipitation of the

released mercaptan as a heavy metal mercaptide (71, 152).

Brominolysis of α-hydroxy mercaptals results in the consumption of up to six moles of bromine, due to further oxidation of the initially formed disulfide. The concomitant release of twelve moles of hydrogen bromide and resulting acidity of the reaction media was initially reported to produce the rearrangement products of the α-hydroxy aldehydes (72). Similar results were reported for the brominolysis of α-hydroxy acetals (77, 78). However, Weygand and Bestmann (71) reported that the ethylmercaptal of mandelaldehyde (PhCH(OH)CH(SEt)$_2$) underwent brominolysis in aqueous media to yield mandelaldehyde without formation of acid-catalyzed rearrangement product. A reinvestigation of this brominolysis (71) was carried out with XXIVa in the present study. All attempts to isolate mandelaldehyde (XXVa) failed; only the acid-catalyzed rearrangement product, ω-hydroxyacetophenone (XXVI) was isolated. Furthermore, the tendency of XXVa to rearrange under acid-catalysis was demonstrated by treatment of an authentic sample of mandelaldehyde dimer with 48% hydrobromic acid in benzene at room temperature. Compound XXVI was rapidly and quantitatively formed. The rearrangement may be considered to involve a mechanism analogous to the Pinacol rearrangement, Figure 14. In identical fashion to XXVa, benzilaldehyde dimer (XXVd) rapidly rearranged to benzoin, an observation which was also previously reported (153).

XXVa (dimer) ⇌ XXVa (monomer)

$\uparrow\downarrow$ H$^+$

OH   HO OH
 | | |
PhC–CH₂OH   ⟵ H⁻O⟵ PhCHCH   Ph⁻
 +   +
$$Ph\overset{OH}{\underset{+}{C}}-CH_2OH \xleftarrow{\ H^-O\ } Ph\overset{HO\ OH}{\underset{+}{CHCH}} \quad Ph^-$$

$\downarrow$ -H$^+$

PhCOCH₂OH

XXVI
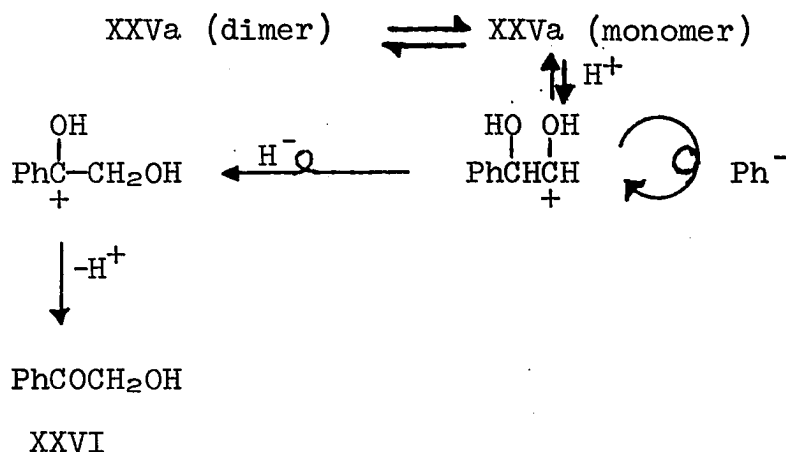
Figure 14. Proposed mechanism for the acid-catalyzed rearrange-
          ment of mandelaldehyde to ω-hydroxy acetophenone.

In view of the tendency of α-hydroxy aldehydes to undergo
acid-catalyzed rearrangement to the α-hydroxy ketones, con-
sideration was given to α-hydroxy mercaptal hydrolysis under
acid-free conditions. Hydrolysis under essentially neutral
conditions has been reported with the use of an equal-molar
mixture of cadmium carbonate and mercuric chloride in refluxing
acetone (77). However,a test of this procedure on a preparative
scale revealed that a long reaction period was required and
product separation from the heavy metal mercaptides was diffi-
cult.

A more satisfactory procedure was developed in the present
study. This procedure was based on the known smooth trans-
formation of β-keto sulfoxides to α-keto acetals on iodine

treatment of the sulfoxides in alcohol media (76). The initial step of the reaction undoubtedly involves a Pummerer rearrangement, which, in the presence of alcohol as an external nucleophile, yields the mixed acetal as the Pummerer product, Equation 75. Due to generation of hydrogen iodide from reaction with

$$RCOCH_2SOCH_3 + R'OH \xrightarrow{H^+} RCOCHSCH_3 + H_2O \qquad (75)$$
$$\overset{OR'}{|}$$

$$\xrightarrow{I_2} \xrightarrow{R'OH} RCOCH(OR')_2 + 2\ HI + CH_3SSCH_3 \qquad (76)$$

trace impurities and subsequent oxidation of bivalent sulfur intermediates, the Pummerer rearrangement is auto-catalytic. In addition to the mixed acetal, the α-keto mercaptal is formed during the course of the reaction by the acid-catalyzed disproportionation of the mixed acetal to the acetal and the mercaptal. In fact, the methyl mercaptal of phenylglyoxal could be readily converted to the methyl acetal (XX) by iodine hydrolysis in methanol. Furthermore, acid-catalysis was not required. The reaction proceeded equally well in the presence of a five-fold excess of sodium bicarbonate suspended in methanol.

The use of sodium bicarbonate to neutralize hydrogen iodide produced during hydrolysis proved ideal when extended to the hydrolysis of the α-hydroxy mercaptals. Treatment of the mercaptals with an equal-molar mixture of iodine and sodium bicarbonate in a 1:1 dioxane-water solvent afforded the α-hydroxy

aldehydes (XXXVa-d) in excellent yields. The use of one or two mole equivalents of sodium bicarbonate did not prove to be critical in this solvent media. However, when less than one mole equivalent of base was used, the acidity of the reaction was not sufficiently suppressed to prevent the acid-catalyzed rearrangement of the α-hydroxy aldehydes. On the other hand, an excess of bicarbonate (3:1 bicarbonate-iodine mole ratio) resulted in the formation of ω-hydroxyacetophenone (XXVI) on hydrolysis of XXIVa. A possible rationalization for this apparent base-catalyzed rearrangement will be presented in the following section of this thesis.

The iodine hydrolysis of α-hydroxy mercaptals appears to involve a 1:1 stoichiometry, Equation 77, particularly if the

$$Ph\overset{\overset{\displaystyle OH}{|}}{C}RCH(SCH_3)_2 + I_2 + 2\ NaHCO_3 \longrightarrow Ph\overset{\overset{\displaystyle OH}{|}}{C}RCHO + 2\ NaI +$$

$$CH_3SSCH_3 + CO_2 \quad (77)$$
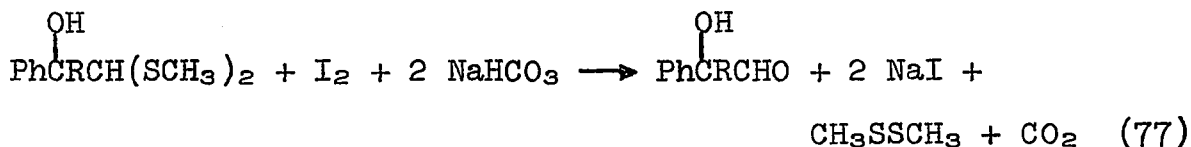
reaction is modified to utilize a two-phase ether-water solvent and a 2:1 sodium bicarbonate-iodine mole ratio. However, this modification is not convenient for large scale reactions due to a very rapid reaction with violent effervescence. This requires periodic addition of iodine in small portions. In the homogeneous dioxane-water solvent, the reaction is slower, apparently due to lower iodine soluability, and proceeds smooth-ly. However, overoxidation of the initially formed methyl

disulfide in the more polar homogeneous media was more competi-
tive, and the use of two moles of iodine slightly increased
the yields of the α-hydroxy aldehydes. The yields of the
α-hydroxy aldehydes (XXVa-d) and the state of aggregation
observed for the isolated products are summarized in Table 7.

Table 7.   Preparation of α-hydroxy aldehydes by the iodine
oxidative hydrolysis of α-hydroxy mercaptals

Product (XXV:R=) (PhCR(OH)CHO)		% Yield[a]	Isolated form (°C)	Mol. Wt.[b]
XXVa	H	88	mp 135-138°	265 (dimer)
XXVb	CH₃	94	mp <27°	300 (dimer)
			bp 116-120°/ 0.7 torr	(monomer[c])
XXVc	C₂H₅	80	bp 65-68°/ 0.7 torr	172 (mono- mer[c])
XXVd	C₆H₅	94	mp 164-166°	706 (dimer)

[a]Isolated yields on preparative scale from 2 moles of
iodine per mole of hydroxy mercaptal in dioxane-water solvent.

[b]In tetrahydrofuran by thermoelectric osmometry; Spang
Micro Analytical Laboratory, Ann Arbor, Michigan.

[c]Confirmed by NMR and acid-catalyzed conversion to dimer
or polymer.

Weygand and Bestman (71) had previously reported that mandelaldehyde (XXVa), prepared by brominolysis of its mercaptal, was isolated as the monomeric form on the basis of carbonyl infrared absorption. However, in this study no evidence for the monomeric form was observed. The crude preparation of XXVa contained no aldehydic proton resonance in the NMR, and the purified material was free of carbonyl infrared absorption. This difference between the results of the present work and the results reported by Weygand and Bestmann, and also the report in previous studies that the "α-hydroxy aldehyde" structure can exist in the form of a cyclic dimer (154, 155), Equation 78, demanded a closer examination of the isolated products (XXVa-d).

$$
\underset{\underset{\text{PhCRCHO}}{\overset{\overset{\text{OH}}{|}}{}}}{} \rightleftarrows
\;\;
\begin{array}{c}\text{HO} \\ \text{Ph(R)}\end{array}\!
\begin{array}{c}\text{(R)Ph}\\ \text{OH}\end{array}
\;\;\rightleftarrows\;\;
\text{O}-\!\!\left(\;\text{PhCR}\!-\!\overset{\overset{\text{OH}}{|}}{\text{CH}}\!-\!\text{O}\right)_{n}
\qquad (78)
$$
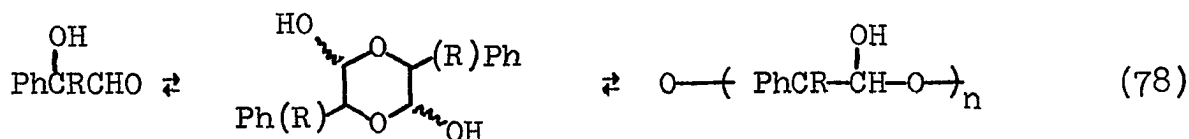
When XXVa and XXVd were analyzed by NMR, the spectra were consistent with diastereomeric mixtures of 1,4-dioxanes and compared favorably with respect to the hemiacetal methine proton chemical shifts (XXVa $-CH\!\!<^O_O$ δ~5.4, XXVd $-CH\!\!<^O_O$ δ~5.9) of an authentic sample (Aldrich) of glycolaldehyde dimer ($-CH\!\!<^O_O$ δ~6.3). Degassed and sealed samples of pure XXVa and XXVd were also investigated by variable temperature NMR in d_6-DMSO and a trace of acid catalyst. At the maximum

temperature attained, 165°C, very low intensity resonances were observed in the 9.5 ppm (δ) region, which could be attributed to the aldehyde protons of the monomers of XXVa and XXVd. However, on cooling to ambient temperature, the downfield resonances disappeared, while the spectral resolution was steady over the whole temperature range investigated. This observation is consistent with the equilibrium represented in Equation 78, (ring opening of dimer to polymer or cleavage to monomer) but appears to favor the ring-closed structure.

Mass spectra recorded by direct sample inlet (Atlas CH-4 spectrometer) gave a weak peak for the dimer ($\underline{m}/\underline{e}$ = 272) of XXVa. However, the dimer of XXVd gave no peaks with higher mass than the monomer ($\underline{m}/\underline{e}$ = 212) at the lowest available ionization potential, 16 ev. Atrolactaldehyde (XXVb) and 2-phenyl-2-ethylglycolaldehyde (XXVc) could be isolated in monomeric form, as confirmed by their NMR aldehyde proton resonances (s, 9.43δ and s, 9.50δ, respectively). Upon standing, or more rapidly on trace acid-catalysis, XXVb dimerized to the 1,4-dioxane, which gave a mass spectrum with a parent peak of $\underline{m}/\underline{e}$ = 300. Both the stable dimer and monomer of XXVb have been previously reported (156, 157). The monomer of XXVc failed under all conditions to form a stable dimeric structure; instead an unstable open-chained polymer was formed. Its molecular weight, Table 7, of 174 (monomer = 164) suggests that on dissolution in tetrahydrofuran, the predominant form is

monomeric. In summary, the "α-hydroxy aldehyde" structure can exist in all three forms represented in Equation 78, and the formation of the 1,4-dioxane dimer form is sensitive to minor substitution changes between similar derivatives.

Formation of Semidione Radical Anions from
α,α-Disubstituted α-Hydroxy Aldehydes

The α-hydroxy aldehydes (XXVa-d) described in the proceeding section were further studied by electron spin resonance (esr) technique in order to clarify a surprising observation in a previous esr study. Rieger and Fraenkel (158) had observed a radical signal by esr spectroscopy upon electrolytic reduction of acetophenone at high irreversible potentials in dimethyl formamide solution. Professor Russell and co-workers (159) subsequently provided the correct structural interpretation of the radical, which corresponded to 1-phenylpropane-1,2-semidione (PhC(O$^-$)=C($\dot{\text{O}}$)CH$_3$), and proposed a mechanism, Figure 15, to explain this surprising result. Alternatively to the scheme in Figure 15, one could imagine the formation of an α-hydroxy aldehyde intermediate that undergoes rearrangement in basic solution, Equation 79, 80. The dianions derived from ketones are known to be very effective nucleophiles and

$$\text{PhC}\overset{=}{\text{O}}\text{CH}_3 + \text{DMF} \rightarrow (\text{CH}_3)_2\text{N}^- + \text{Ph}\overset{\text{O}^-}{\underset{\text{CH}_3}{\overset{|}{\text{C}}}}-\overset{\text{O}}{\overset{||}{\text{C}}}_{\text{H}} \tag{79}$$

$$\longrightarrow \text{CH}_3\overset{\text{O}}{\overset{||}{\text{C}}}-\overset{\text{O}^-}{\overset{|}{\text{C}}}\text{HPh} \overset{-\text{H}^+}{\rightleftharpoons} \text{CH}_3\overset{\text{O}^-}{\overset{|}{\text{C}}}=\overset{\text{O}^-}{\overset{|}{\text{C}}}\text{Ph} \overset{-\text{e}^-}{\rightleftharpoons} \text{PhC}\overset{\text{O}^-}{\overset{|}{=}}\overset{\text{O}\cdot}{\overset{|}{\text{C}}}\text{CH}_3 \tag{80}$$

PhCOCH₃ $\xrightarrow{+e^-}$ [PhĊOCH₃] $\xrightarrow{+e^-}$ [PhC̈OCH₃]

(schematic)
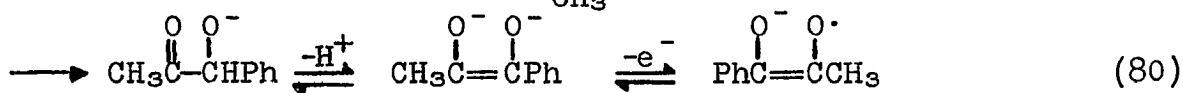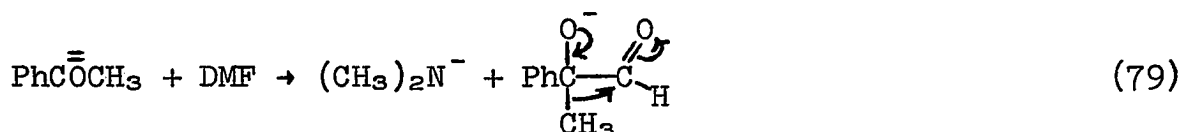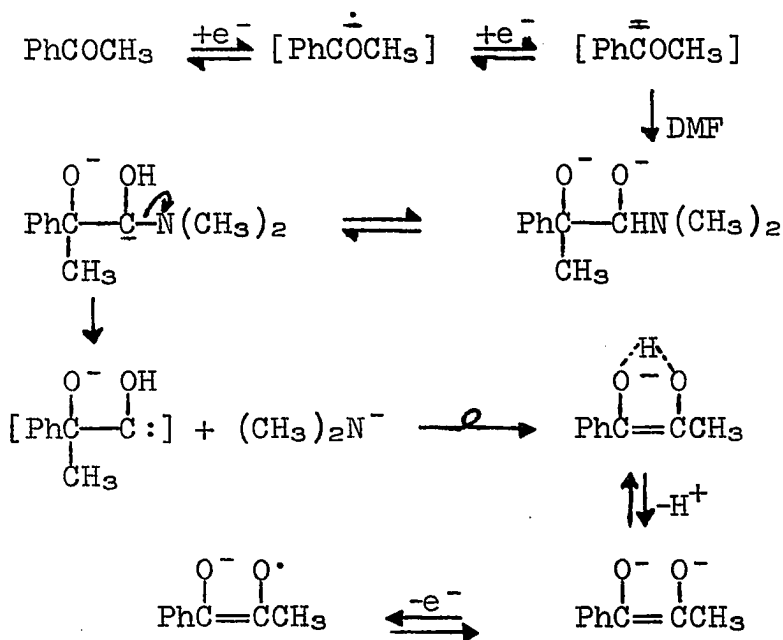
Figure 15. Proposed mechanism for the formation of 1-phenyl-
propane-1,2-semidione on electrolysis of aceto-
phenone in dimethyl formamide solution (158, 159).

form adducts on attack of various electrophilic centers, in
particular carbonyl functions (160). In the present study, it
was observed that the reaction of benzophenone dianion (161)
with dimethyl formamide or ethyl formate proceeds to yield the
glycerol (XXVII), a product highly suggestive of an α-hydroxy
aldehyde intermediate, Equations 81, 82.

$$2 \; Ph_2\ddot{C}O + DMF \rightarrow (CH_3)_2N^- + [Ph_2\overset{O^-}{\underset{|}{C}}-CHO] + Ph_2\ddot{C}O \tag{81}$$

$$\longrightarrow Ph_2\overset{^-O}{\underset{|}{C}}-\overset{O^-}{\underset{|}{C}}H-\overset{O^-}{\underset{|}{C}}Ph_2 \xrightarrow{H^+} Ph_2\overset{HO}{\underset{|}{C}}-\overset{OH}{\underset{|}{C}}H-\overset{OH}{\underset{|}{C}}Ph_2 \tag{82}$$
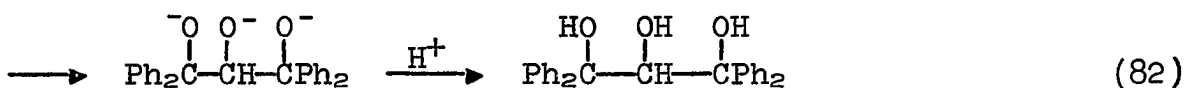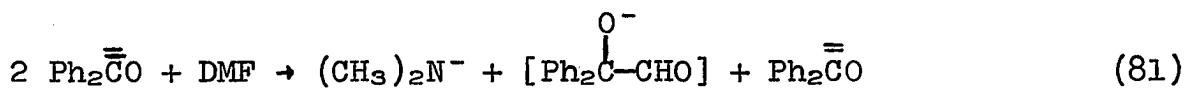
XXVII

The possibility of converting α-hydroxy aldehydes (XXVa-d) to semidiones was studied in deoxygenated dimethyl sulfoxide solutions, conditions which result in endiol dianion oxidation in the presence of base (109). When the monomeric forms of XXVb and XXVc were mixed with a potassium t-butoxide-DMSO solution, no semidione formation was observed, even on addition of a trace of oxygen. However, the dimeric (1,4-dioxane) forms of XXVa, XXVb and XXVd, or the polymeric form of XXVc did react in the presence of potassium t-butoxide-DMSO to yield the re-arranged semidiones (PhC($\bar{O}$)=C($\dot{O}$)R), which were readily detected by esr spectroscopy. When sodium methoxide was employed as the base in DMSO, the semidiones were observed in higher concentration relative to the potassium t-butoxide base system. Further-more, the monomers (XXVb and XXVc) also yielded well-resolved semidione signals with sodium methoxide-DMSO.

The results with sodium methoxide were unexpected. For the disproportionation of α-hydroxy ketones to semidiones, the stronger base, potassium t-butoxide, has been observed to give higher yields of semidiones (109, 162). Moreover, the reducing properties of the methoxide ion can probably be discounted in the present experiments, since the conversion of the α-hydroxy aldehydes to the semidiones involves oxidation. However, by a priori consideration, the methoxide ion is a better nucleophile than t-butoxide, and it seems likely that the present observa-tions reflect this nucleophilicity. This consideration would offer little support for the base-catalyzed rearrangement of the

α-hydroxy aldehydes illustrated in Equation 79. However, modification of the scheme in Figure 15 offers convenient explanation. In the case of the monomeric aldehydes, the methoxide ion can add to the carbonyl function to form the oxy-anion of a hemiacetal (PhCR—CHOCH₃), an intermediate analogous to the dimethyl amide adduct (PhC(CH₃)CHN(CH₃)₂) postulated in Figure 15. The methoxy adduct can then undergo rearrangement as illustrated in Figure 16.
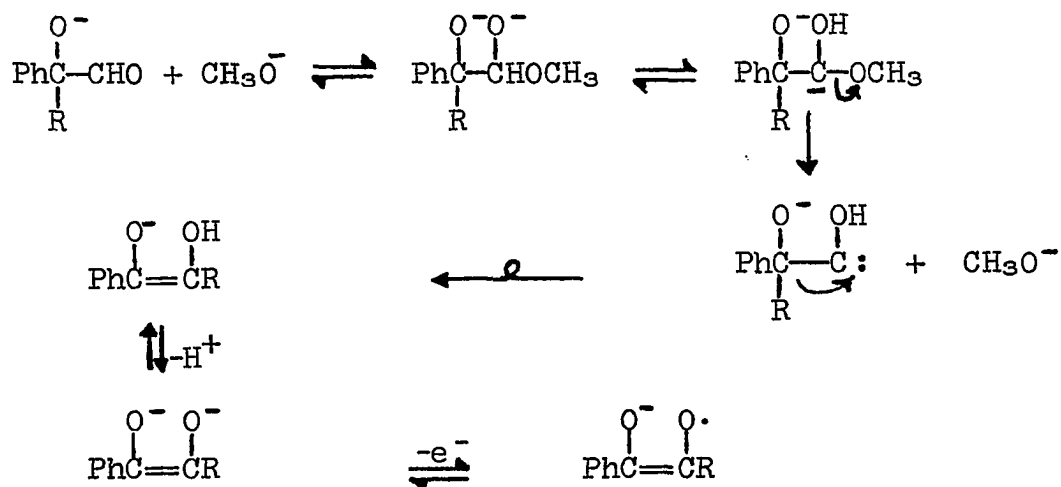
Figure 16. Proposed mechanism for the methoxide nucleophile-catalyzed rearrangement and oxidation of monomeric α-hydroxy aldehydes to semidiones.

In the case of the dimeric form of the α-hydroxy aldehydes, the 2,5-dihydroxy-1,4-dioxane structure already contains the hemiacetal moiety, and only base-catalysis is necessary for rearrangement, Figure 17. Likewise, the polymeric form of XXVe is accounted for by the scheme in Figure 17. Furthermore, the scheme provides a rationale for the higher concentration of

Ph(R) ⌐O⌐ OH

HO ⌐O⌐ (R)Ph

↓ B⁻

Ph(R) ⌐O⌐ O⁻   Ph(R) ⌐O⌐ ⁻OH   Ph(R) ⁻O C OH
⇌   ⇌
⁻O ⌐O⌐ (R)Ph   ⁻O ⌐O⌐ (R)Ph   ⁻O O (R)Ph

↓

O⁻   O⁻ OH   O⁻O⁻   OH
‖   ‖ | ‖ ‖ |
PhC—CHO + PhC=CR   ⟵   PhC—CH—O—C=CR
| | |
R   ↑↓ -H⁺   R   Ph

          ↑↓ -e⁻

          O⁻ O·
          ‖ |
          PhC= C—R
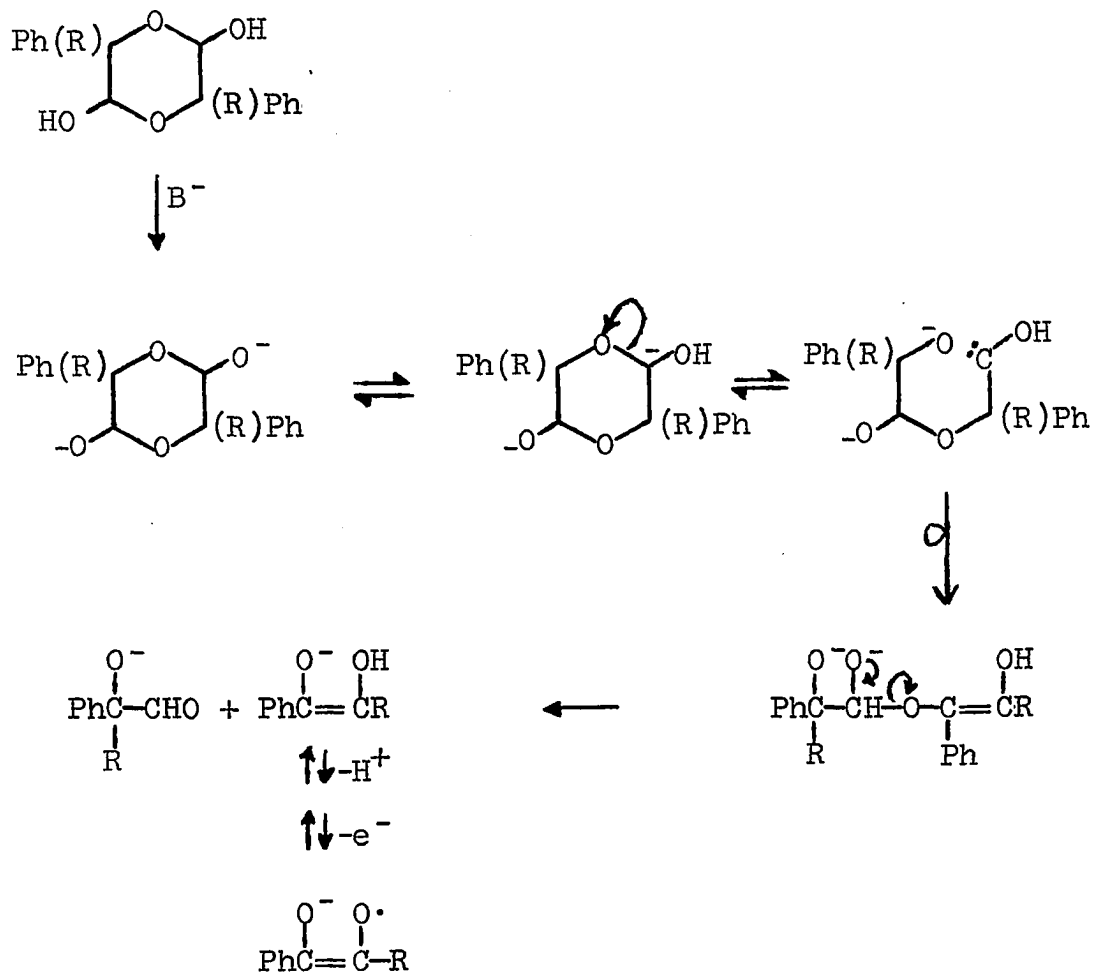
Figure 17.   Proposed mechanism for the base catalyzed rearrange-
             ment of dimeric α-hydroxy aldehydes. to semidiones.

semidiones formed with sodium methoxide base.   On base-catalyzed

decomposition of the dimeric structure, one mole of monomeric

aldehyde is liberated and can undergo methoxide nucleophile-

catalyzed rearrangement by the scheme in Figure 16.   In the

presence of the poor t-butoxide nucleophile, the liberated

monomer is unconsumed.

← 10 GAUSS →
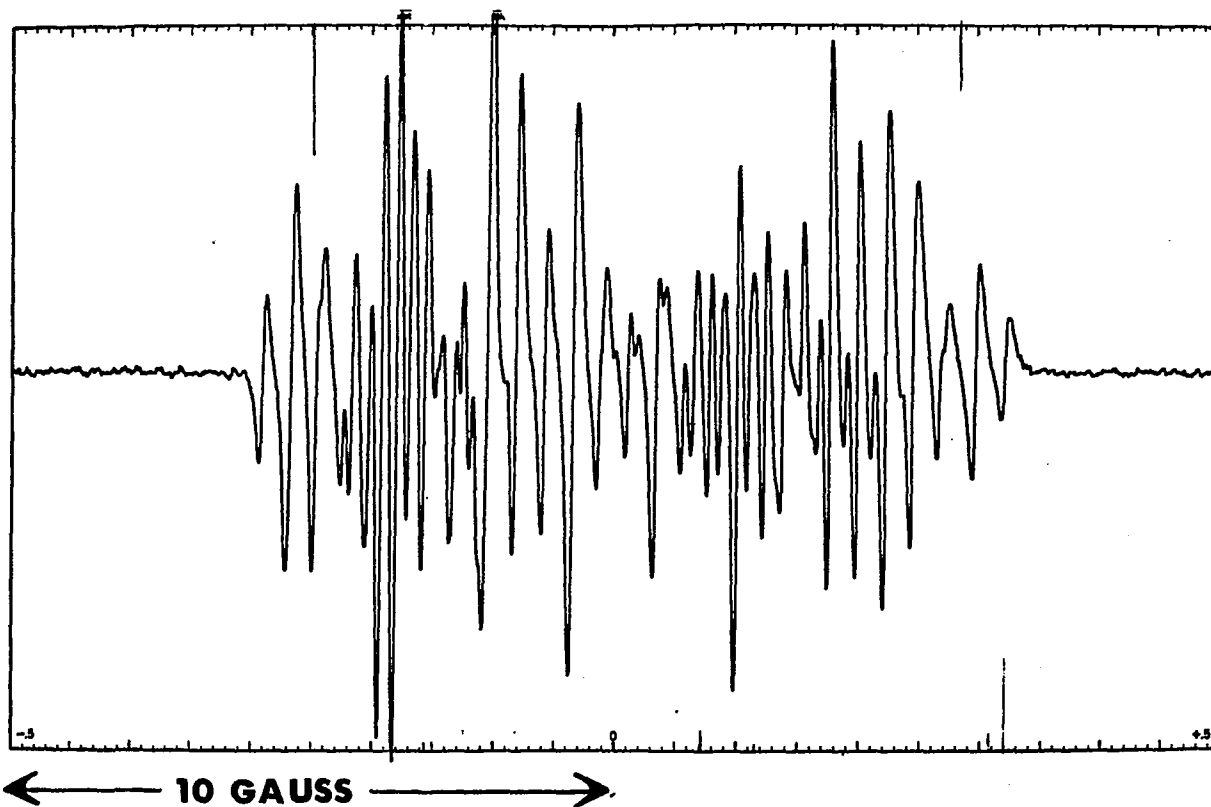
Figure 18. First-derivative ESR spectrum of phenylglyoxal radical anion generated from mandelaldehyde (XXVa) dimer by reaction in potassium $\underline{t}$-butoxide-DMSO solution and absence of air.

The spectra in the present work were recorded on a Varian E-3 spectrometer using deoxygenated solutions in an inverted U-type mixing cell previously described (162). The use of α-hydroxy aldehydes provides a novel route to the formation of semidiones in high yields, with good resolution of the esr spectra. Particularly good resolution was noted in the spectrum of phenylglyoxal radical anion prepared from dimeric XXVa, Figure 18. The hyperfine splitting constants in DMSO solution were in excellent agreement with those previously reported for phenylglyoxal semidione (163, 164), 1-phenyl-propane-1,2-semidione (159), 1-phenyl butane-1,2-semidione (159), and benzil radical anion (165).

<div align="center">

Reactions of the Enolate Anion of the Methyl

Mercaptal of Phenylglyoxal

</div>

Since the α-keto mercaptals were readily available by a two-step synthesis, both proceeding in over 80% yield from an aromatic carboxylic ester, an investigation of some of the other chemistry of these substances was undertaken. Already described were the reactions of mercaptals with diazo compounds, which resulted in carbene insertion into the mercaptal C-S bond to yield carbon chain-extended α,β-di(mercapto) products. The design of further work was to affect C-alkylation and C-acylation of the mercaptal carbon with retention of the mercaptal moiety in the reaction products. This synthetic

approach has been realized for sulfur-stabilized, but uncon-jugated, 1,3-dithiane carbanion (137). The conceivable ex-tension of the reaction to α-keto mercaptal carbanion would yield α-keto-α-alkyl or α-keto-α-acyl substituted mercaptals, synthetically useful intermediates for varied carbonyl com-pounds (α-tricarbonyls) not directly available from β-keto sulfoxides. Since the methyl mercaptal of phenylglyoxal (XII) was the most convenient mercaptal to prepare, it was exploited as the model system.

The enolate anion (VIIa) of the methyl mercaptal of phenyl-glyoxal could be prepared in a variety of ways. Treatment of XII with sodium hydride, under a nitrogen atmosphere in tetra-hydrofuran, proved to be the most convenient method for the smooth and rapid generation of the sodium enolate, Equation 83.

$$PhCOCH(SCH_3)_2 + NaH \xrightarrow{THF} PhC(O^-){=}C(SCH_3)_2 + H_2 \qquad (83)$$
$$Na^+$$

XII   XIIa
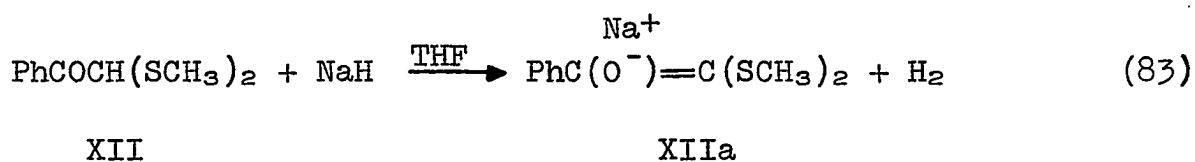
The reaction also proceeds slowly, but to completion, in ether or hydrocarbon solvents. Homogeneous solutions of XIIa were prepared in concentrations up to 4 molar in tetrahydrofuran, while in ether or hexane solvent, concentrations in excess of 0.5 molar resulted in suspensions of XIIa. The corresponding lithium enolate of XIIa was prepared by mercaptal treatment with t-butyllithium in ether or lithium hydride in tetrahydro-furan and a trace of ethanol promoter. No difference in

reactivity between the sodium and lithium enolates could be detected during the course of this study. Since sodium hydride was the more convenient base to handle, the sodium enolate was utilized in all cases of the following discussion.

The reactions of the enolate anion (XIIa) with various electrophiles are summarized in Figure 19. Treatment of XIIa with methyl sulfate resulted in O-methylation and the isolation

$$XII \quad + \quad NaH$$

$$\downarrow$$

$$\underset{XXVIII}{\overset{OCH_3}{\underset{}{PhC=C(SCH_3)_2}}} \leftarrow (CH_3)_2SO_4 - \underset{XIIa}{\overset{O^-}{\underset{}{PhC=C(SCH_3)_2}}} - NBS \rightarrow PhCOC(SCH_3)_2N\overset{CO}{\underset{CO}{\diagdown}}]$$

$$\underset{XXIX}{\overset{OCOR}{\underset{}{PhC=C(SCH_3)_2}}} \overset{RCOX}{\longleftarrow} \underset{}{\overset{}{CH_3SCl}} \downarrow \qquad Br_2 \searrow$$

RCOX   CH₃SCl   Br₂

$$\underset{XXX}{PhCOC(SCH_3)_3} \qquad \underset{XXXI}{[PhCOCBr(SCH_3)_2]}$$
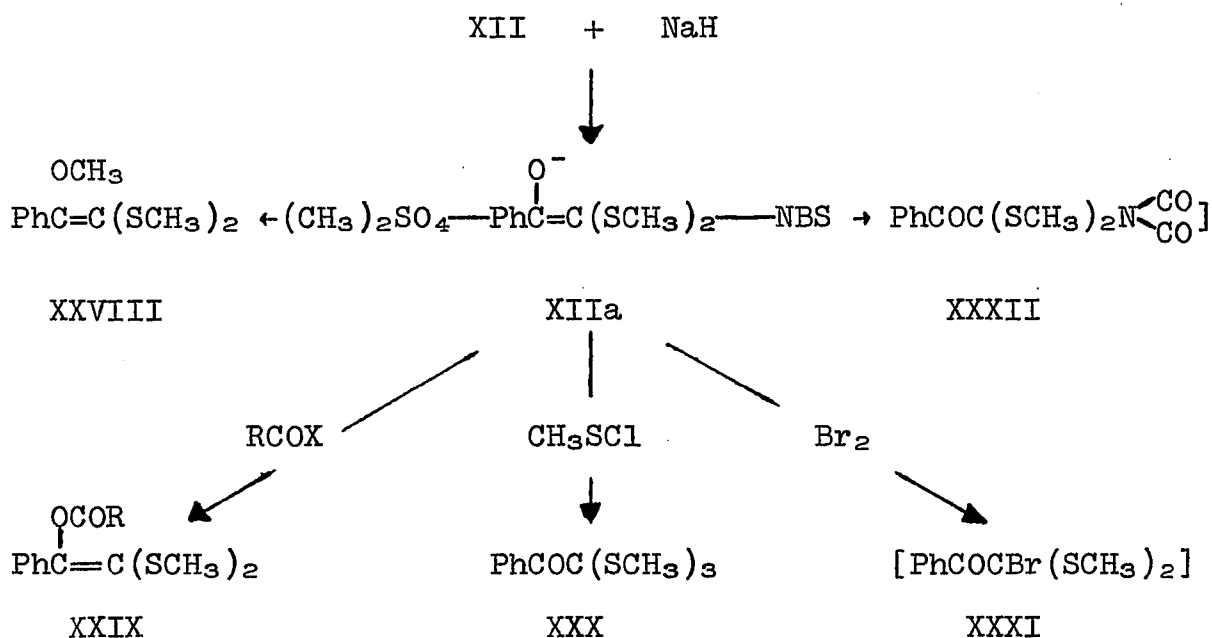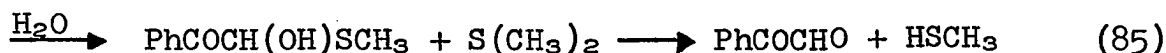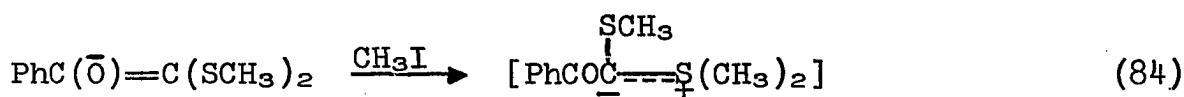
Figure 19. Reactions of the enolate anion of phenylglyoxal methyl mercaptal with electrophilic reagents.

of β,β-dimethylmercapto-α-methoxy styrene (XXVIII) in 85% yield. The analogous reaction with alkyl iodides produced iodine-contaminated oil residues containing multiple products. Only O-alkylated product (XXVIII) (53%) and phenylglyoxal (26%) could

be isolated in a pure state from the residue. Numerous minor polar components and polymer could not be separated by column chromatographic techniques. The composite NMR spectra of these components were consistent with S-methyl chemical shifts of sulfoxides (2.5-2.6δ) and sulfones (3.3-3.5δ). The overall variety of the reaction products suggests the partial (competitive with O-alkylation) formation and hydrolysis of an intermediate sulfonium ylide, Equations 84, 85.

$$PhC(\bar{O})=C(SCH_3)_2 \xrightarrow{CH_3I} [PhCO\underset{\underline{\quad}}{C}\overset{SCH_3}{=\!=\!=}\overset{+}{S}(CH_3)_2] \qquad (84)$$

$$\xrightarrow{H_2O} PhCOCH(OH)SCH_3 + S(CH_3)_2 \longrightarrow PhCOCHO + HSCH_3 \qquad (85)$$

Treatment of the enolate anion (XIIa) with acyl halides or esters resulted exclusively in O-acylation. The O-benzoylated (XXIXa) and O-acetylated (XXIXb) products were isolated in excellent yields and a high state of purity from reaction with the corresponding acyl chlorides. Identical products were isolated in lower yields from the corresponding acyl fluorides or ester reagents, but no C-acylations of the sodium or lithium enolates were observed. Attempts were also made to affect C-acylation by alternative means analogous to those previously described for the acylation of the ω-(methylsulfinyl)acetophenone carbanion. Preparation of an enamine of the methyl mercaptal of phenylglyoxal was unsuccessful. Likewise, a stable thallium salt (122) of XII could not be prepared. Reaction of

XII with methyl magnesium carbonate (119) resulted in rapid evolution of carbon dioxide. However, on neutralization of the reaction, starting material (XII) was quantitatively recovered.

Reaction of the enolate anion (XIIa) with methane-sulfenyl chloride (166) afforded ω,ω,ω-tri(methylmercapto)acetophenone (XXX) in 71% yield. The preparation of unconjugated ortho-thioesters has been previously reported by treatment of acyl chlorides with excess mercaptan and zinc chloride catalyst (167). The acidic conditions complicate isolation of the acid-sensitive orthothioesters. In the present study, XXX proved to be sensitive to both acid and base. However, a neutral solution results on reaction of XIIa with methanesulfenyl chloride and XXX was isolated without difficulty. When XXX was suspended in an aqueous acid media, it readily reverted to starting mercaptal (XII), and methane-sulfinic acid anhydride was isolated as the hydrolysis by-product, Equation 86. Treatment of XXX

$$\text{PhCOC(SCH}_3)_3 \xrightarrow{\text{H}_3\overset{+}{\text{O}}} [\text{Ph}\overset{|}{\underset{\overset{+}{\text{SCH}_3}}{\text{C}}}-\text{C(SCH}_3)_2] \xrightarrow{\text{H}_2\text{O}} \text{Ph}\overset{\text{OH}}{\underset{}{\text{C}}}=\text{C(SCH}_3)_2 + \text{HOSCH}_3$$

XXX   XII   (86)
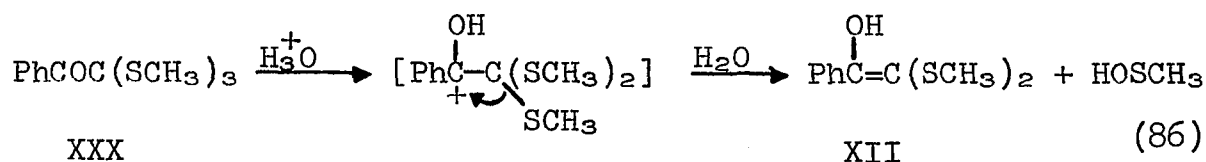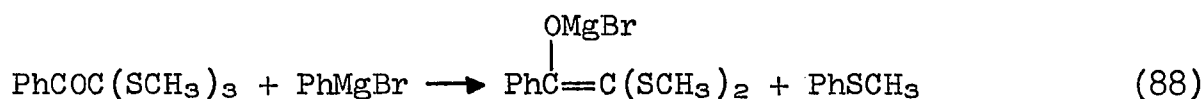
with strong aqueous base produced identical results, Equation 87. The nucleophilic displacement on sulfur of the conjugated

$$\text{PhCOC(SCH}_3)_3 + \text{OH}^- \longrightarrow \text{Ph}\overset{\text{O}^-}{\underset{}{\text{C}}}=\text{C(SCH}_3)_2 + \text{HOSCH}_3 \qquad (87)$$
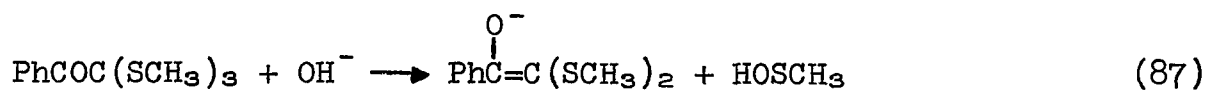
orthothioester, as depicted in Equation 87, was confirmed by

reaction of XXX with Grignard or organolithium reagents. No

reduction of the benzoyl carbonyl resulted; instead the mag-

nesium or lithium enolates of XII and the organometallic-

methylmercapto adducts were formed. Thioanisole was nearly

quantitatively recovered from the reaction of XXX with phenyl

Grignard, Equation 88. However, ω, ω, ω-tri(methylmercapto)aceto-

phenone (XXX) could be reduced in excellent yield (>95%) with

$$PhCOC(SCH_3)_3 + PhMgBr \longrightarrow Ph\overset{\overset{\displaystyle OMgBr}{\displaystyle |}}{C}{=}C(SCH_3)_2 + PhSCH_3 \qquad (88)$$

non-nucleophilic sodium borohydride in ethanolic media to methyl

orthotrithiomandelate (XXXIII).

The orthothioesters (XXX) and (XXXIII) proved to be excellent

intermediates for the preparation of partially or completely

desulfurized products by means of iodine oxidative hydrolysis.

Figure 20 summarizes these transformations. The heterogeneous

ether-water-bicarbonate procedure developed for the hydrolysis

of α-hydroxy aldehydes (XXIVa-d) was satisfactory for the prep-

aration of S-methyl phenylthioglyoxylate (XXXIV) and phenyl-

glyoxalic acid (XXXV). However, S-methylthiomandelate (XXXVII)

was too labile to complete hydrolysis with iodine, apparently

due to neighboring group assistance by the α-hydroxy function

(168). Even when a deficiency of iodine was employed, only

mandelic acid (XXXVIII) could be isolated. However, selectivity

and termination of the hydrolysis at the S-methyl thioester

(XXXVII) moiety was achieved by the use of air as oxidant. The

PhCOC(SCH₃)₃ $\xrightarrow{\text{I}_2,\text{Et}_2\text{O}}$ PhCOCOSCH₃
XXXIV   95%

PhCOC(SCH₃)₃ $\xrightarrow{\text{H}_2\text{O}}$

PhCOC(SCH₃)₃ —3/2 I₂,H₂O—→ PhCOCO₂H
XXX   XXXV   >95%

3/2 I₂EtOH → PhCOCO₂Et
XXXVI   69%

$\dfrac{\text{NaBH}_4}{\text{EtOH}}$

PhCH(OH)C(SCH₃)₃ $\xrightarrow{\text{O}_2,\text{H}_3{}^+\text{O}}$ PhCH(OH)COSCH₃
XXXVII   72%

PhCH(OH)C(SCH₃)₃—3/2 I₂,H₂O—→ PhCH(OH)CO₂H
XXXIII >95%   XXXVIII   >95%

3/2 I₂,EtOH → PhCH(OH)CO₂Et
XXXIX   59%
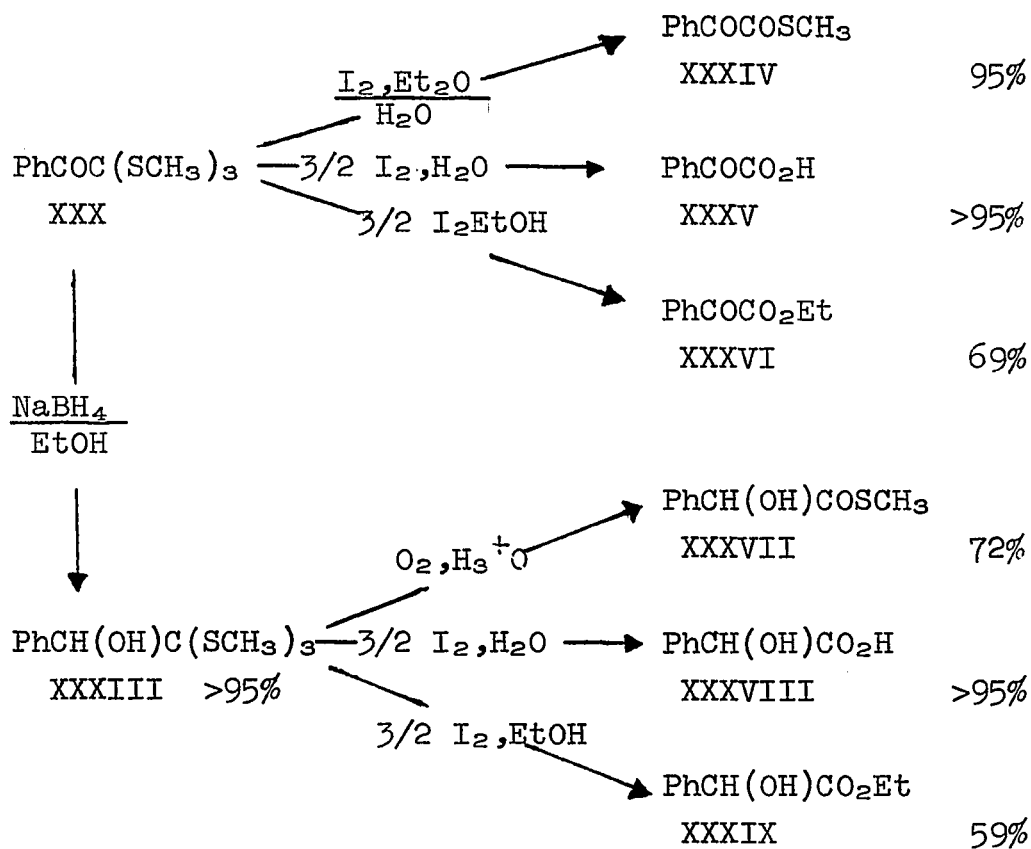
Figure 20. Summary of routes and yields for the oxidative
           hydrolysis of orthothioesters (XXX) and (XXXIII).

procedure involved the passage of air through an aqueous sus-
pension of XXXIII in the presence of ammonium chloride buffered-
acid catalyst. Iodine hydrolysis of XXX and XXXIII in alcohol
media yielded the ethyl ester derivatives (XXXVI) and (XXXIX).
The preparation of the ethyl glycolate (XXXVI) required the use
of excess bicarbonate to neutralize hydrogen iodide by-product,
which otherwise catalyzed the conversion of XXXVI to its diethyl

ketal. Bicarbonate in situ neutralization was not required for the preparation of XXXIX, but its use appears to increase the rate of hydrolysis and eliminates the final neutralization on reaction work-up.

Prior to the successful reaction of XIIa with methanesulfenyl-chloride, attempts were made to prepare XXX from ω-bromo-ω-(methylsulfinyl)acetophenone (58). Conceivably, the treatment of the α-bromo sulfoxide with thionyl chloride would yield ω-bromo-ω-chloro-ω-(methylmercapto)acetophenone, which by an analogous reaction scheme to the preparation of the methyl mercaptal of phenylglyoxal (XII), would yield XXX, Equation 89.

$$\text{PhCOCH(Br)SOCH}_3 \xrightarrow{\text{SOCl}_2} \overset{\overset{\text{Cl}}{|}}{\text{PhCOC}}\text{(Br)SCH}_3 \xrightarrow{\text{HSCH}_3} \text{PhCOC(SCH}_3)_3 \quad (89)$$

$$\text{XXX}$$
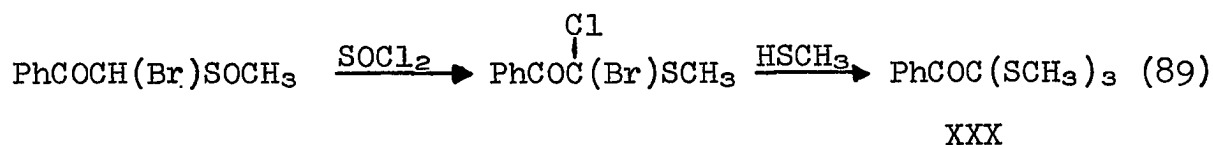
A test of this scheme led to the formation of some ω-bromo-ω-chloro-ω-(methylmercapto)acetophenone. However, considerable conversion to ω-chloro-ω(methylmercapto)acetophenone (XVII) also resulted. The loss of bromine apparently involves a modification of the Pummerer reaction (67), Equations 90, 91.

$$\text{PhCOCH(Br)SOCH}_3 \xrightarrow{\text{SOCl}_2} [\overset{\overset{\text{Br}}{|}}{\text{PhCOCH}}\text{---}\overset{\overset{\text{Cl}}{|}}{\underset{+}{\text{SCH}_3}}]\text{Cl}^- + \text{SO}_2 \quad (90)$$

$$\xrightarrow{\text{-BrCl}} [\text{PhCOCH}\text{---}\overset{\overset{\text{Cl}}{|}}{\underset{+}{\text{SCH}_3}}] \xrightarrow{\ell} \text{PhCOCH(Cl)SCH}_3 \quad (91)$$
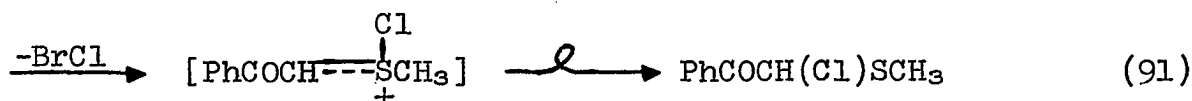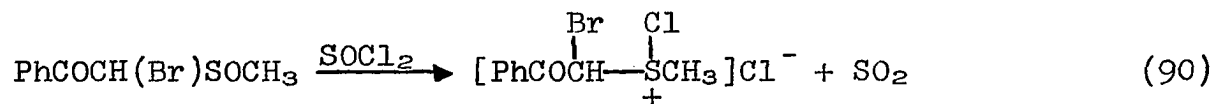
The bromination of XIIa was anticipated to yield ω-bromo-ω,ω-di(methylmercapto)acetophenone (XXXI). However, if XXXI

were indeed formed, it proved too unstable to isolate. Instead the reaction product was characterized to be an 86% yield of cis- and trans-1,2-dibenzoyl-1,2-di(methylmercapto)ethylene (XL), Equations 92, 93. The preparation of XL was also

$$PhC(O^-)\!=\!C(SCH_3)_2 \xrightarrow{\text{Br}_2} [XXXI] \xrightarrow{\text{XIIa}} [PhCOC(SCH_3)_2\!\!-\!] + Br^- \tag{92}$$
$$\text{XIIa}$$

$$\xrightarrow{\text{Br}_2} PhCOC(SCH_3)\!=\!C(SCH_3)COPh + 2\ CH_3SBr \tag{93}$$
$$\text{XL}$$
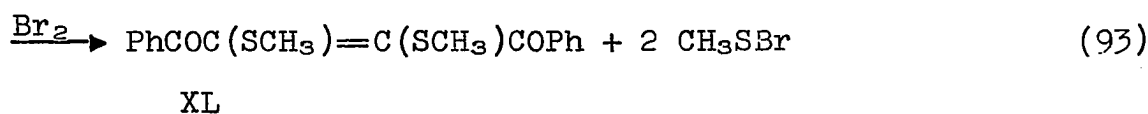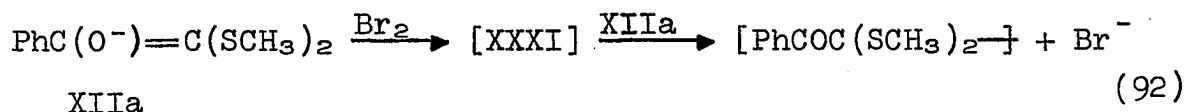
affected by pyrolysis of ω-chloro-ω-(methylmercapto)aceto-phenone (XVI) at 190° in the liquid phase, Equations 94, 95.

$$\overset{\overset{\displaystyle Cl}{\displaystyle |}}{PhCOCHSCH_3} \xrightarrow[\Delta]{} [PhC(O^-)\!=\!C(Cl)SCH_3]H^+ \tag{94}$$
$$\text{XVI}$$

$$\xrightarrow{\text{XVI}} PhCOC(SCH_3)\overset{\overset{\displaystyle Cl}{\displaystyle |}}{\underset{\underset{\displaystyle H}{\displaystyle |}}{C}}(SCH_3)COPh \xrightarrow{-HCl} XL \tag{95}$$
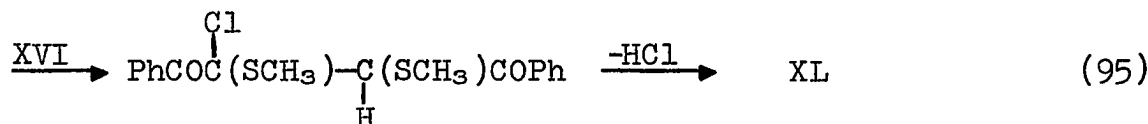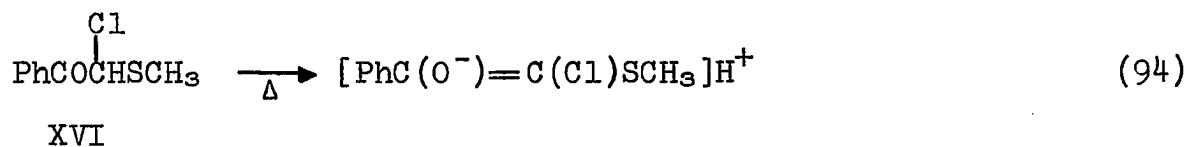
The scheme illustrated in Equations 92, 93 is consistent with the known coupling reactions resulting from direct bromina-tion of conjugated carbanions (169). However, on treatment of XIIa with one-half mole equivalent of bromine, the α-dimercaptal coupled intermediate [(PhCOC(SCH_3)_2—}_2 was not isolated; but XL and an equal quantity of ω,ω,ω-tri(methylmercapto)aceto-phenone (XXX) were formed. The formation of XXX in this

experiment is consistent with the by-product formation of methane-
sulfenyl bromide and its reaction with excess XIIa. However,
the results also imply that desulfurization of the α-dimercaptal
intermediate is competitive with bromination of XIIa, which is
totally unexpected. An alternative mechanism may well be pro-
posed to involve disproportionation of the initially formed
ω-bromo-ω,ω-di(methylmercapto)acetophenone to a phenacylcarbene
and methylsulfenyl bromide, with subsequent carbene coupling to
yield XL, Equation 96. The fact that no cyclopropane derivative

$$\underset{XXXI}{[PhCO\overset{\overset{\displaystyle Br}{|}}{C}(SCH_3)_2]} \longrightarrow [PhCO\overset{\cdots}{C}SCH_3] + CH_3SBr \longrightarrow XL \qquad (96)$$
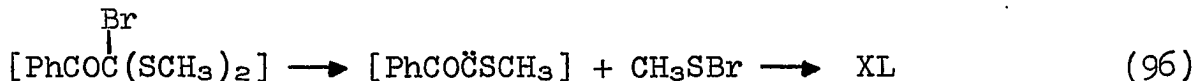
was observed among the reaction products does not eliminate the
possibility of a carbene mechanism. Serratosa and Quintana
(170) have demonstrated that phenacylcarbenes possess very low
nucleophilicity and rarely yield cyclopropane derivatives in the
presence of olefins.

Although no conclusive observations in support of a carbene
mechanism were made, the stoichiometry of the scheme for carbanion
coupling, Equations 92, 93, is not supported by further experi-
mentation, while the scheme in Equation 96 is compatible.
Immediate hydrolysis of the reaction after bromination of XIIa
resulted in S-methyl phenylthioglyoxylate (XXXIV) in excess of
60% yield. This indicates that bromination of the enolate anion
is more facile than enolate attack on the ω-bromo-ω,ω-di(methyl-

mercapto)acetophenone (XXXI) leading to XL. Furthermore, when N-bromosuccinimide is the brominating agent, no coupling and subsequent formation of XL results. The succinimide anion is the dominant nucleophile in the reaction media and displaces bromine from XXXI. ω,ω-Di(methylmercapto)-ω-succiniminoaceto-phenone (XXXII) was isolated in 88% yield.

Dehydration Studies of β-Hydroxy Mercaptals

Previous sections of this study have described the preparation of a number of β-hydroxy sulfides. These compounds, enumerated in Chart 3, were further examined in expectation of preparing ketene thioacetals when subjected to dehydration. The ketene mercaptals were of interest as potential precursors to phenylacetic acid derivatives upon their acid-catalyzed hydration.

$$\overset{OH}{\underset{|}{PhCR}}\text{-CH(SCH}_3)_2 \qquad\qquad \overset{OH}{\underset{|}{PhCH}}\text{-C(SCH}_3)_3$$

XXIVa-e   XXXIII

a, R = H
b, R = CH₃ $\overset{OH}{\underset{|}{PhCH}}\text{-CH(R)SCH}_3$
c, R = C₂H₅
d, R = C₆H₅   XLIa,b
e, R = D
                              a, R = H
                              b, R = CH₃
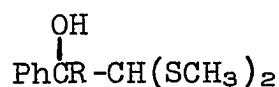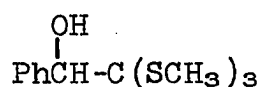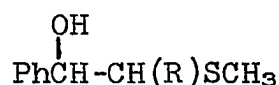
Chart 3. β-Hydroxy sulfides utilized for dehydration studies.

The dehydration of XLIa under acid-catalyzed conditions to yield β-(methylmercapto) styrene (XLII) has been previously described (60). In a similar fashion, dehydration of β-hydroxy-m-dithianes has been reported as a route to ketene thioacetal derivatives (137), Equation 97. The elimination of mercaptan

$$R_1R_2C(OH)CH\overset{S}{\underset{S}{\diagdown}}\overset{H^+}{\longrightarrow} R_1R_2C=C\overset{S}{\underset{S}{\diagdown}} + H_2O \qquad (97)$$
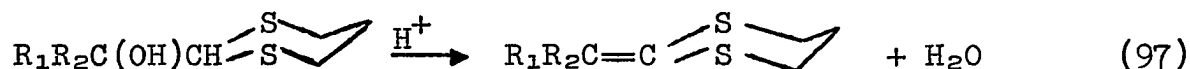
under acid-catalysis to form orthothioacetic esters has also been reported as a route to ketene thioacetals (167). Recently Arens (171) and Bestman (172) have independently reported an elegant synthesis of ketene thioacetals by treatment of dithioesters with strong base and subsequent S-alkylation of the resonance stabilized anions, Equation 98, 99.

$$R_1R_2CH-\overset{\overset{S}{\|}}{C}\diagdown_{SR_3} \xrightarrow{\text{ B}^-} [R_1R_2\overset{-}{C}-\overset{\overset{S}{\|}}{C}\diagdown_{SCH_3} \longleftrightarrow R_1R_2C{=}C\diagup^{S^-}_{\diagdown SR_3}] \qquad (98)$$

$$\xrightarrow{\text{ RX}} R_1R_2C{=}C\diagup^{SR}_{\diagdown SR_3} \qquad (99)$$
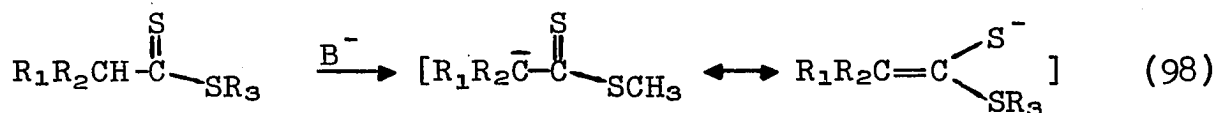
In this fashion both symmetrical ($R{=}R_3$) and unsymmetrical ($R{\neq}R_3$) S-alkylated derivatives were prepared. Arens, et al. (167) also demonstrated that ketene thioacetals could be prepared under very vigorous conditions by base-catalyzed elimination of mer-captan from α-(mercapto) thioacetals, Equation 100.

$$RCH(SEt)CH(SEt)_2 + \underline{t}\text{-BuOK} \xrightarrow[\Delta]{} RCH{=}C(SEt)_2 \qquad (100)$$

The initial attempt to affect XXIVa-d dehydration to ketene thioacetals was the apparent straight-forward method of acid-catalysis under azeotroping conditions employed for β-hydroxy-m-dithiane dehydration (137). However, when the α-hydroxy mer-captals (XXIVa-d) were so treated, the 2°-benzylic alcohol (XXIVa) underwent dehydration and rearrangement, Equation 101,

$$PhCH(OH)-CH(SCH_3)_2 \xrightarrow{H^+} PhC(SCH_3)=CHSCH_3 + H_2O \qquad (101)$$

    XXIVa   XLIIIa
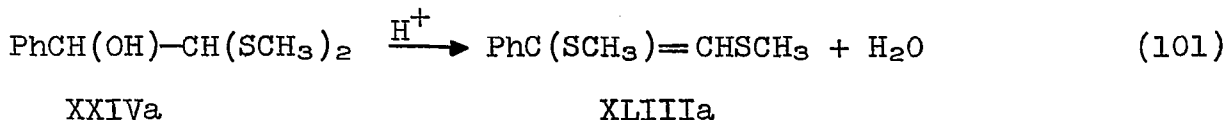
while the 3°-benzyl alcohol (XXIVb-d) dehydrated and eliminated the elements of methanesulfinic acid to yield β-styrenyl sulfides (XLIIIb-d), Equation 102.

$$PhCR(OH)-CH(SCH_3)_2 \xrightarrow{H^+} PhC(R)=C(SCH_3)_2 + CH_3SOH \qquad (102)$$

    XXIVb-d   XLIIIb-d
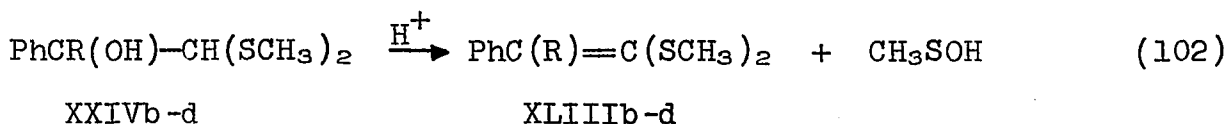
Further investigation revealed the tendency of 2°-benzylic alcohols <u>alpha</u> to the mercaptal function, XXIVa and XXXIII, to dehydrate and rearrange under neutral or basic conditions in solution and pyrolysis conditions in the neat, in addition to the acid-catalyzed conditions. Thus, the alkoxide anion of XXIVa, readily prepared by reaction with sodium hydride in tetrahydrofuran, reacted with tosyl or thionyl chloride under essentially neutral conditions to afford α,β-di(methylmercapto)-styrene (XLIIIa) in 75 ~ 80% yields. Comparable results were obtained by reaction of XXIVa with the same reagents in pyridine. Moreover, the benzyl-deuterio analogue (XXIVe) of XXIVa underwent dehydration and rearrangement with complete loss of deuterium, as confirmed by the NMR and mass spectrum of the resulting α,β-di(methylmercapto)styrene, Equation 103. Heating

$$PhCD(OH)-CH(SCH_3)_2 \xrightarrow{NaH} \xrightarrow{SOCl_2} PhC(SCH_3)=CHSCH_3 \qquad (103)$$

    XXIVe   XLIIIa
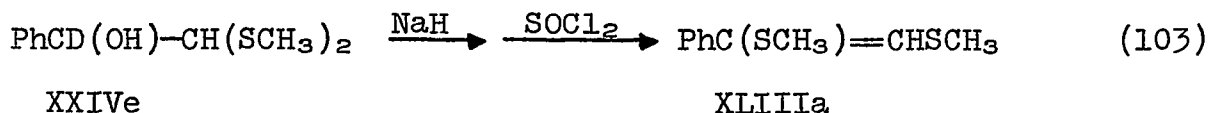
of XXIVa in Pyrex glassware at 80°C for 48 hours produced a 99% yield of XLIIIa as a mixture of <u>cis</u> and <u>trans</u> isomers that could be completely isomerized to the <u>trans</u> isomer by treatment with mineral acids. During the course of XXIVa pyrolysis, the reaction passed from a mobile liquid phase to a highly viscous, colorless residue, which on further heating yielded the non-viscous liquid styrene (XLIIIa). The crude NMR of this viscous intermediate phase, Figure 21, appeared to be consistent with a diastereomeric mixture of epimers of either the rearranged 2-phenyl-1,2-di(methylmercapto)ethanol ($PhCH(SCH_3)CH(OH)SCH_3$) or the mercaptohemihydrate dimer ($[PhCH(SCH_3)CH(SCH_3)]_2O$). On standing at room temperature, the intermediate phase underwent slow conversion to a 30:70 mixture of starting material (XXIVa) and styrene (XLIIIa). Moreover, attempts to prepare a pure sample of the intermediate phase by chromatography on silica gel or neutral alumina resulted in the surprising, quantitative reversion to starting alcohol (XXIVa). When thermolysis of the 2°-benzyl alcohol, methyl orthotrithiomandelate (XXXIII), was carried out under conditions similar to the reaction of XXIVa at 50° or 80°C under a nitrogen atmosphere for 48 hours, a complex product mixture resulted from which α,β,β-tri(methylmercapto)-styrene (XLV) was isolated in only 16% yield. Other monomeric products isolated from the reaction included traces of benzaldehyde, benzoic acid, 1,1,2,2-tetraphenylglycol, and 22% of S-methyl-α-(methylmercapto)phenylthioacetate (LIII). Treatment

of XXXIII with tosyl or thionyl chloride in pyridine likewise
yielded complex reaction mixtures with low conversion to XLV.
However, when XXXIII was converted to its sodium alcoholate,
with sodium hydride in tetrahydrofuran, and treated with thionyl
chloride, α,β,β-tri(methylmercapto)styrene was produced in 81%
yield, Equation 104. Furthermore, the stable benzoate ester
(XLVI) was prepared by XXXIII alcoholate anion reaction with
benzoyl chloride and subsequently vacuum pyrolyzed at 170°C/0.3
Torr to yield 73.8% of XLV, Equation 105.

$$PhCH(OH)C(SCH_3)_3 \xrightarrow{NaH} \xrightarrow{SOCl_2} PhC(SCH_3)=C(SCH_3)_2 \qquad (104)$$

XXXIII   XLV

$$\overset{\displaystyle OCOPh}{PhCH}-C(SCH_3)_3 \xrightarrow[0.3\ Torr]{170°C} PhC(SCH_3)=C(SCH_3)_2 + PhCO_2H \qquad (105)$$

XLVI   XLV
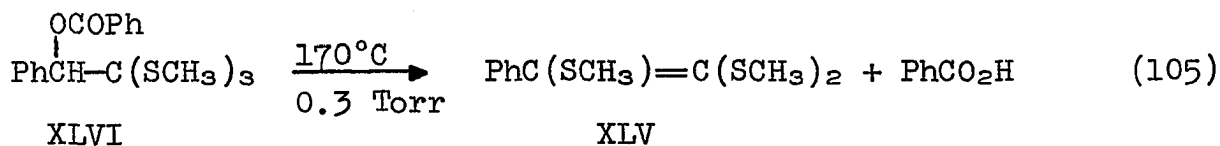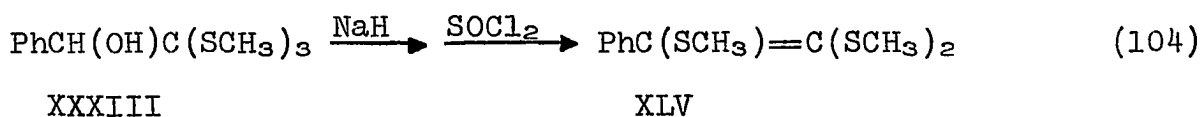
Rearrangements, similar to those in Equations 101, 103, 104,
105, have been previously observed for α-halothioacetals (173-
175) and interpreted in terms of episulfonium ion intermediates
(168), Equations 106, 107. A similar interpretation was

$$RCHBr-CR'(SEt)_2 \rightleftarrows [RCH\overset{\overset{\displaystyle Et}{|}}{\underset{+}{S}}CR'SEt]Br^- \rightleftarrows RCH(SEt)-CR'(Br)SEt$$

$$(106)$$

$$[RCH\overset{\overset{\displaystyle Et}{|}}{\underset{+}{S}}CRSEt] \rightleftarrows [RCH-\overset{\overset{\displaystyle SEt}{|}}{C}RSEt] \xrightarrow{-H^+} RC(SEt)=CR'SEt \qquad (107)$$
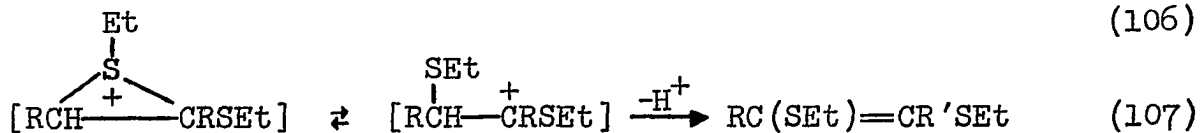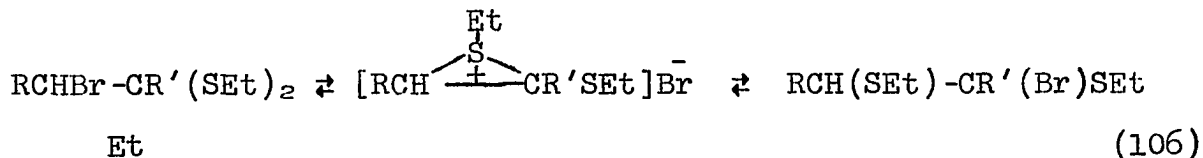
suggested for the formation of α,β-dimercapto olefins during
attempts to mercaptalize α-hydroxy ketones under acid-catalysis
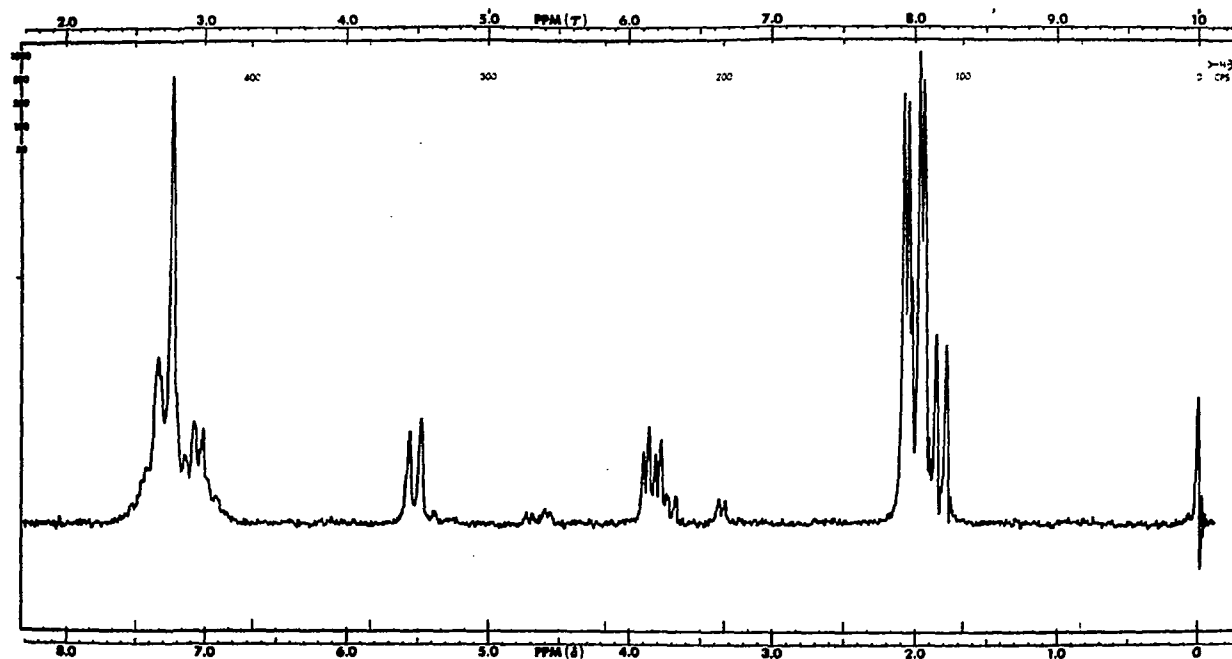
Figure 21. Crude NMR spectrum of the viscous intermediate phase formed during the thermolysis of 1-phenyl-2,2-di(methylmercapto)ethanol (XXIVa) in Pyrex. The spectrum is consistent with a diastereomeric mixture of epimers of rearranged alcohol (PhCH(SCH₃)CH(OH)SCH₃).

(139). Presumably, α-hydroxy mercaptal intermediates were formed, but could not be isolated due to their dehydration and rearrangement under the reaction conditions, Equations 108, 109.

$$\overset{OH}{\underset{|}{RCHCOR}} + 2\ HSR' \xrightarrow{H^+} [\overset{OH}{\underset{|}{RCHC(SR')_2R}}] + H_2O \qquad (108)$$

$$\xrightarrow{H^+} [RCH\!\!\overset{\overset{\displaystyle R'}{\overset{\displaystyle S}{\diagup\!\!\overset{+}{\diagup}\!\backslash}}}{-\!\!-\!\!}CRSR'] + H_2O \xrightarrow{-H^+} RC(SR')=CRSR' \qquad (109)$$
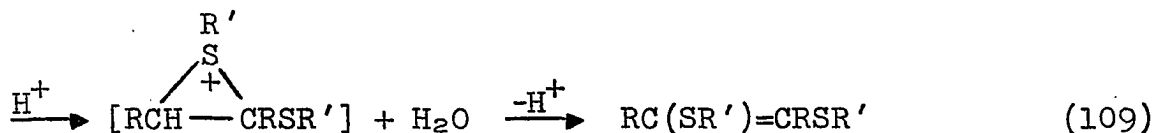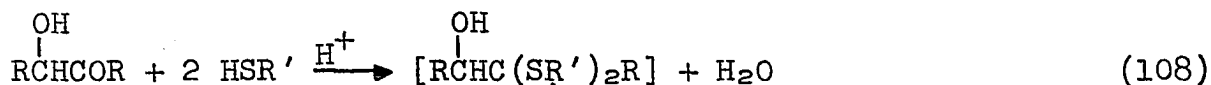
In the present study, the results observed for 2°-alcohols (XXIVa) and (XXXIII) can likewise be rationalized by a scheme involving episulfonium ion intermediates. Thus, the 2°-alcoholate adducts of tosyl or thionyl chloride undergo "E_1-type" decomposition under neutral conditions, assisted by methylmercapto neighboring-group participation (168), which leads to episulfonium ion formation, Figure 22.

XXIVa or XXXIII

↓ NaH

↓ YCl

R = H, D

R'= H, SCH$_3$

OY⁻ = Tos⁻, ClSO$_2$⁻
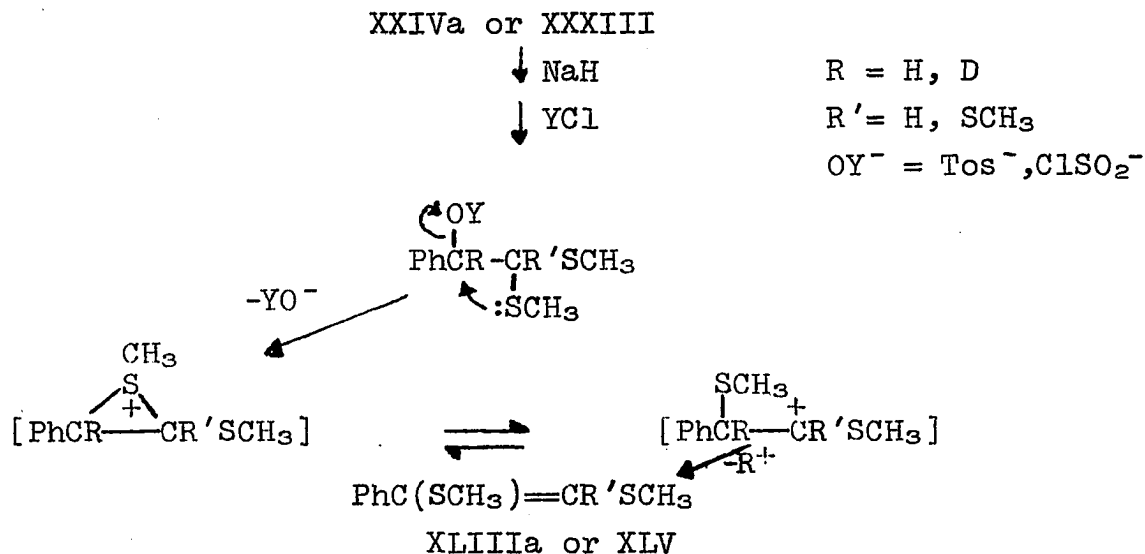
Figure 22. Proposed scheme for the "E_1-type" elimination and rearrangement of *in situ* generated tosyl or thionyl chloride adducts of 2°-alcohols XXIVa and XXXIII.

In strongly acidic media, the scheme illustrated in Figure 22 is complicated by acid-catalyzed cleavage of the mercapto function, which can become the predominant reaction (176, 177). This is particularly true in the case of orthothioesters, as previously described in this work for the hydrolysis of methyl orthotrithiomandelate (XXXIII) into S-methyl thiomandelate (XXXVII). Thus, treatment of XXIVa with thionyl chloride in methylene chloride gave 40% of α-chloro-β-(methylmercapto)-styrene. This product was not detected when the in situ generated hydrogen chloride was neutralized by pyridine solvent. Treatment of 1-phenyl-2-(methylmercapto)propanol (XLIb) with hydrogen bromide in benzene produced 15% of β-methylstyrene oxide and 60% of the dehydration product, β-methyl-β-(methyl-mercapto)styrene (XLVII). However, treatment of 1-phenyl-2-(methylmercapto)styrene (XLIa) with acidic reagents resulted in exclusive dehydration. This apparently is due to lack of steric assistance and instability of primary relative to benzyl carbonium ion formation upon XLIa mercapto protonation and potential cleavage. All of these results are conveniently rationalized by competition between acid-catalyzed dehydration and mercapto cleavage, Figure 23.

The reactions of the 3°-benzylic alcohols adjacent to the thioacetal function (XXXIVb-d) were also investigated under neutral and basic conditions in addition to acid-catalyzed conditions, Equation 102. In identical fashion to the 2°-benzylic alcohols, the alkoxide ions of XXIVb-d were treated

with tosyl, benzoil, acetyl, and thionyl chloride to afford

excellent yields (70 ~ 90%) of the α-substituted-β-(methyl-

mercapto)styrenes (XLIIIb-d). All attempts to isolate the

A: XXXIII $\xrightarrow[\text{H}_2\text{O}]{\text{HCl}}$ [PhCH–C(SCH₃)₂] $\xrightarrow{\text{–HSCH}_3}$ [PhCH–C(SCH₃)₂]⁺

$\xrightarrow{\text{H}_2\text{O}}$ $\xrightarrow{\text{–H}^+}$ $\xrightarrow{\text{HSCH}_3}$ PhCH–COSCH₃

XXXVIII

B: XXIVa $\xrightarrow[\text{CH}_2\text{Cl}_2]{\text{SOCl}_2}$ [PhCH–CH(SCH₃)₂] + SO₂ + HCl

$\xrightarrow{\text{HCl}}$ [PhCH–CHSCH₃] $\xrightarrow{\text{–HSCH}_3}$ [PhCH–CHSCH₃]⁺

$\xrightarrow{\text{–H}^+}$ PhC=CHSCH₃

XLIV

C: XLIb $\xrightarrow[\text{ØH}]{\text{HBr}}$ PhCH–CSCH₃ $\xrightarrow{\text{–HSCH}_3}$ PhCH–CHCH₃

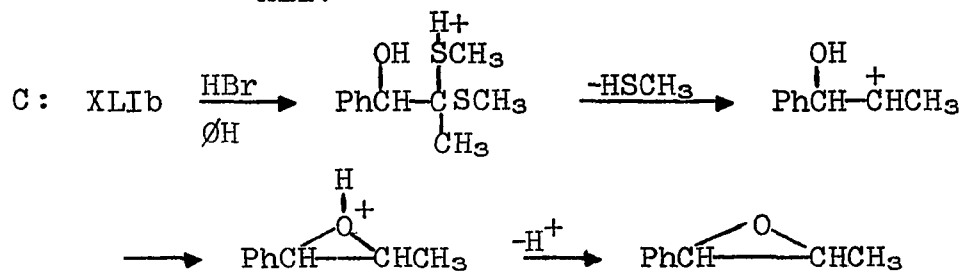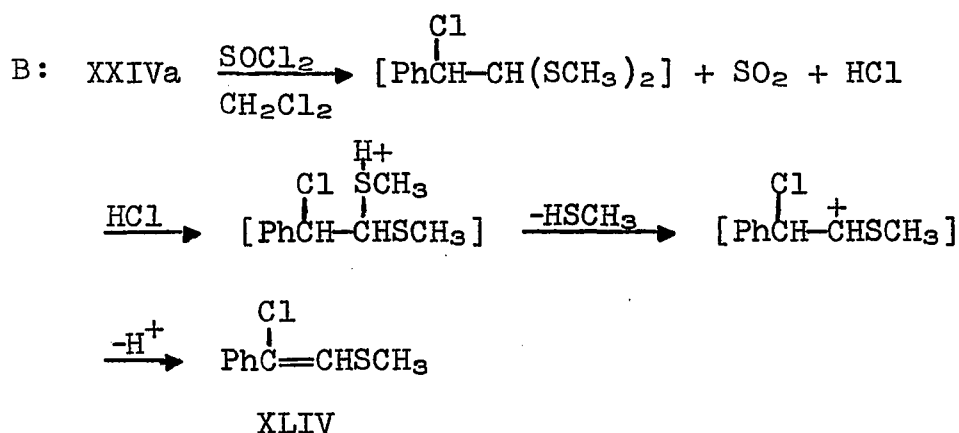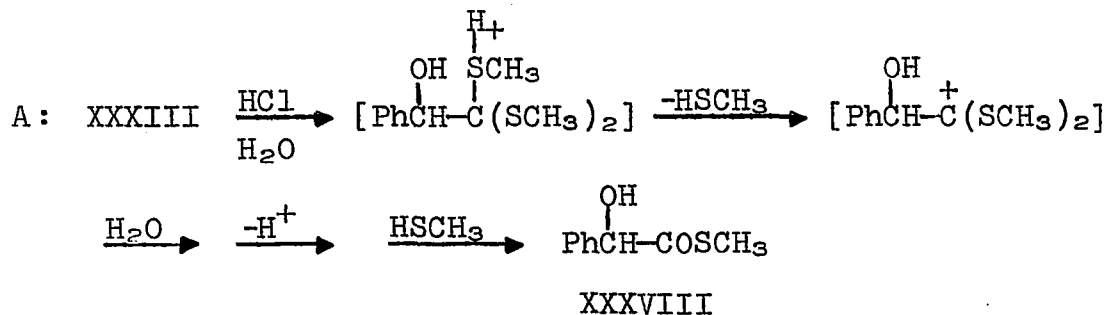$\longrightarrow$ PhCH——CHCH₃ $\xrightarrow{\text{–H}^+}$ PhCH——CHCH₃

Figure 23. Summary of the reaction schemes for the acid-catalyzed
cleavage of the methylmercapto function, respectively
for: A, α-hydroxy-orthothioester; B, α-chloromercapto;
and C, α-hydroxy sulfide.

intermediate adducts of the electrophilic halides and alkoxide

ions failed. Neighboring-group assistance offered by the α-

mercapto moiety in "E_1- type" decomposition (168) likewise

rationalizes the inherent instability of these adducts. How-

ever, the resulting episulfonium ions cannot suffer the same

fate of those derived from the 2°-alcohols (XXIVa) and (XXXIII).

Lack of hydrogen substitution at the benzylic position prevents

E_1 elimination and concomitant rearrangement upon episulfonium

tautomerism to the α-sulfonium ion (PhCR——CH═SCH$_3$, R $\neq$ H).

The subsequent loss of a mercapto function to yield the styrenes

(XLIIIb-d) as an alternative to the scheme in Figure 22, can

then be reasonably postulated to occur by chloride ion nucleo-

philic displacement on the episulfonium ion sulfur atom, Figure

24.

Evidence consistent with Route B, Figure 24, was provided by

the observation that 46% of α-methylmercapto-α-phenylbutyrl-

aldehyde (XLVIIIa) was formed on aqueous quenching at 5°C of the

acetyl chloride treated (XXIVc) alkoxide anion. This is con-

sistent with the prior formation of a rearranged β-chloro deriva-

tive (PhCR(SCH$_3$)CH(Cl)SCH$_3$). α,α-Diphenyl-α-(methylmercapto)-

acetaldehyde (XLVIIIb) was prepared in similar fashion from

benzilaldehyde thioacetal (XXIVd) in 43% yield. Evidence con-

sistent with Route A was obtained on reaction of atrolactalde-

hyde mercaptal (XXIVb) alcoholate with thionyl chloride in the

presence of cyclohexene. An appreciable fraction, 66% mole-

equivalents, of the cyclohexene was converted to <u>trans</u>-1-chloro-

XXIVb-d

$\downarrow$ NaH

$\downarrow$ YCl $OY^- = Tos^-,\ C_6H_5CO_2^-,$
                              $CH_3CO_2^-,\ ClSO_2^-$

$\overset{OY}{\underset{|}{C}}$
$PhCR$——$\underset{|}{C}HSCH_3$
              $:SCH_3$

$\downarrow$ $-OY^-$

$\overset{CH_3}{\underset{S}{|}}$
$\overset{/+\backslash}{}$
$PhCR$——$CHSCH_3$

Cl^- / A   B $\searrow\nwarrow Cl^-$
                                      $\overset{SCH_3}{\underset{|}{}}$

$PhC(R)$==$CHSCH_3$ + CH_3SCl $[PhCR$——$\underset{|}{C}HSCH_3]$
                                                              Cl
XLIIIb-d

$\overset{SCH_3}{\underset{|}{}}$
$PhCR$—CHO

XLVIII
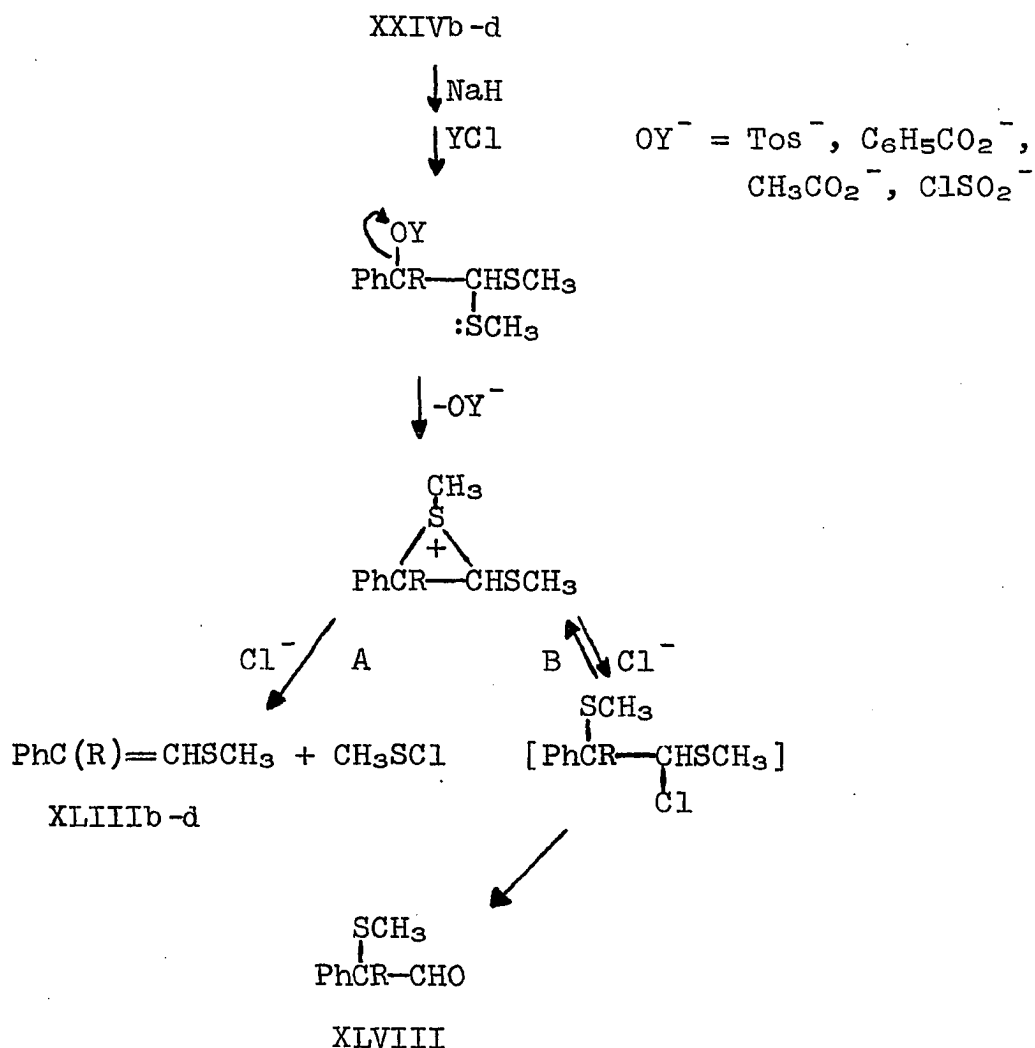
Figure 24. Proposed scheme for the generation of intermediate
episulfonium ions of the $3°$-benzylic alcohols
(XXIVb-d) and subsequent chloride ion nucleophilic
attack on: A, sulfur or B, carbon.

2-(methylmercapto)cyclohexane by trapping of the methanesulfenyl

chloride elimination product, Equation 110, 110a.

$\overset{OH}{\underset{|}{}}$
$PhC(CH_3)CH(SCH_3)_2$ $\xrightarrow{SOCl_2}$ $PhC(CH_3)$==$CH(SCH_3)$ + CH_3SCl (110)

XXIVb   XLIIIb

$$(110) \longrightarrow CH_3SCl \xrightarrow{C_6H_{10}} \underset{SCH_3}{\overset{Cl}{\diagup}} \qquad (110a)$$
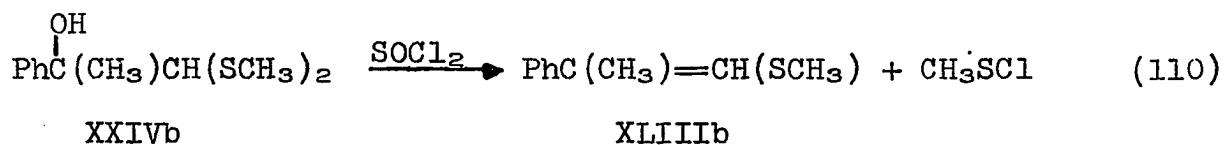
Recently, W. A. Thaler (178) has proposed that episulfonium ions do not undergo nucleophilic attack at sulfur to generate olefins. The basis of this proposal was the observed failure to form olefins on heating β-chloro sulfides under conditions wherein episulfonium ions are regenerated, Equation 111. The

$$CH_3SCH_2\overset{Cl}{\underset{|}{C}}HR \xrightarrow{\Delta} \underset{CH_2 \longrightarrow CHR}{\overset{\overset{CH_3}{|}}{\underset{+}{S}}} Cl^- \xrightarrow{//} CH_2{=}CHR + CH_3SCl \qquad (111)$$
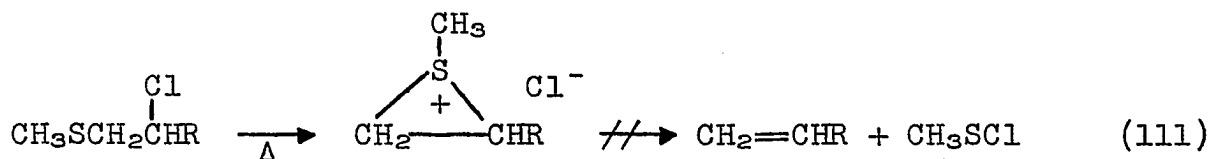
referred to "conditions" were neither described nor documented. However, the results of the present study and examples from the most recent literature do not support Thaler's proposal. Within the last ten years, a number of stable episulfonium salts, containing non-nucleophilic gegen anions, have been prepared (179-183). But an investigation between stable episulfonium ions and strong nucleophiles was not reported until June, 1969 (184). Helmkamp, et al. (184) reacted cyclooctene-S-methylepisulfonium-2,4,6-trinitrobenzenesulfonate with a wide variety of nucleophiles and observed both carbon and sulfur attack. Nucleophiles in which the nucleophilic atom was from the third or higher rows of the Periodic Table showed a marked preference for S-attack, resulting in desulfurization to yield cyclooctene. The resulting methanesulfenyl elimination products could be isolated, or in the case of methanesulfenyl halides, trapped

with cyclohexene. Furthermore, the S-attack of chloride ion was unequivocally demonstrated by the formation of a stable tetracovalent sulfur intermediate, 9-chloro-9-methyl-9-thio-bicyclo[6.1.0]nonane (183), Equation 112. The summary of this

$$\left[\begin{array}{c} \overset{+}{\underset{|}{\overset{\cdot\cdot}{S}}} \\ CH_3 \end{array}\right] TNBS^- + Ph_4AsCl \rightarrow \overset{Cl}{\underset{CH_3}{\overset{|}{S}}} + [Ph_4As]TNBS^- \qquad (112)$$
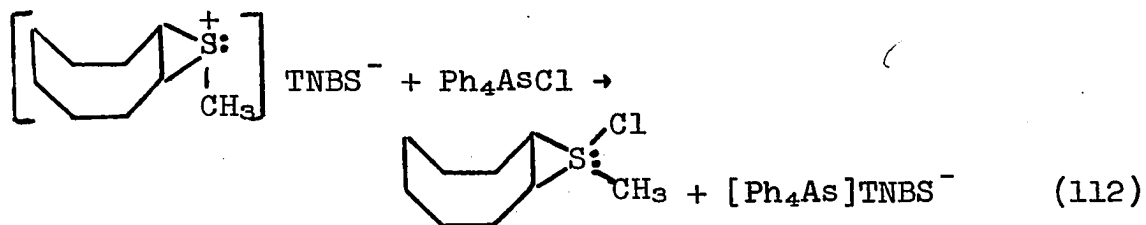
data (183, 184) suggests that two possible mechanistic pathways can be formulated for the desulfurization of episulfonium ions by nucleophiles, Figure 25. Path A would involve the
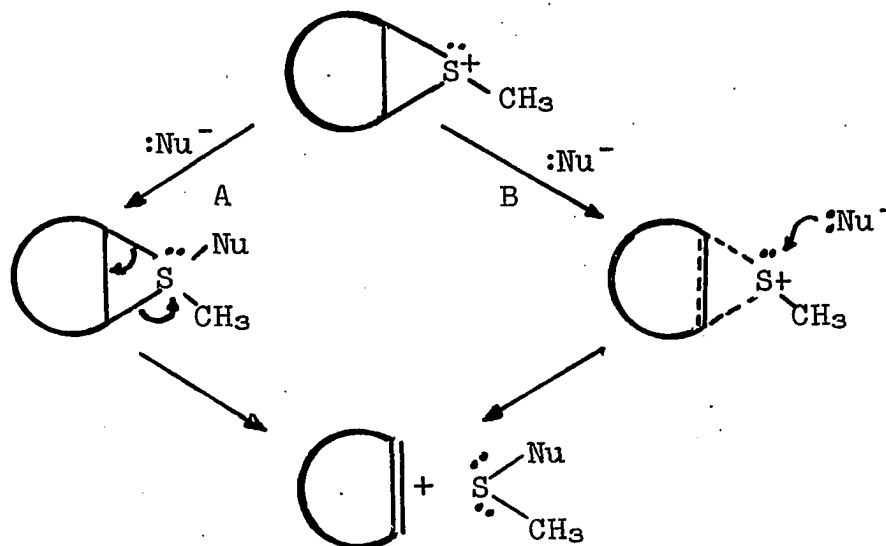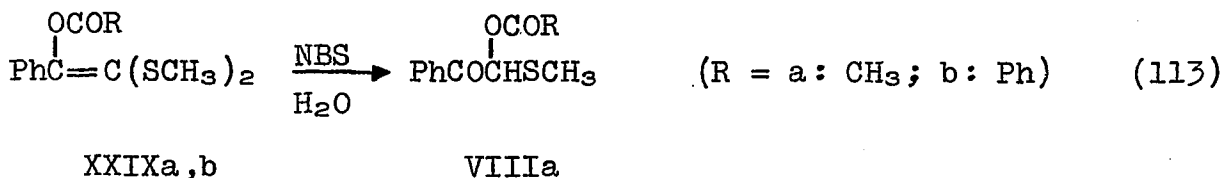

Figure 25. Proposed mechanistic pathways for the desulfurization of episulfonium ions by nucleophiles: A, tetracovalent intermediate; B, "Sn_2-like" displacement.

formation of a stable intermediate containing a tetracovalent sulfur atom, isoelectronic with the well-known SF_4 molecule, which would hybridize and decompose to products. Pathway B would involve desulfurization by a concerted "S_{n_2}-like" displacement on sulfur. Both of these proposed pathways are analogous to known nucleophilic displacements on silicon (185).

Mercapto elimination from the episulfonium ion appears to be a general scope reaction. The enol esters of the methylmercapto of glyoxal (XXIXa,b), previously described in this study, react with N-bromosuccinimide in aqueous solution to yield ω-acyloxy-ω-(methylmercapto)acetophenones in excess of 80% yields, Equation 113. The acyloxy rearrangement and

$$
\underset{\text{XXIXa,b}}{\overset{\overset{\displaystyle OCOR}{|}}{PhC}=C(SCH_3)_2} \quad \xrightarrow[\text{H}_2\text{O}]{\text{NBS}} \quad \underset{\text{VIIIa}}{\overset{\overset{\displaystyle OCOR}{|}}{PhCOCHSCH_3}} \qquad (R = a: CH_3; \ b: Ph) \qquad (113)
$$

methylmercapto elimination can be conveniently rationalized, Figure 26, in accord with nucleophilic desulfurization of an episulfonium ion similar to the scheme in Figures 24 and 25.

In the above discussion, it appears evident that ketene thio-acetal synthesis from β-hydroxymercaptals under E_1 dehydration conditions is applicable only to cyclic mercaptal derivatives such as the m-dithianes (137), wherein migration and elimination via episulfonium ion intermediates is not likely. Methods were therefore investigated to effect E_2 elimination from the acyclic
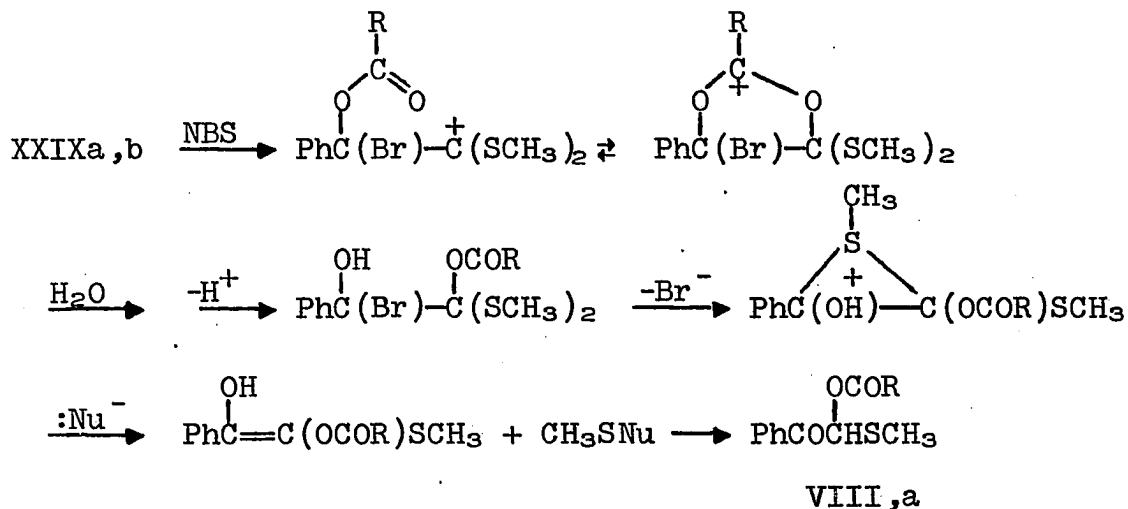
$$\text{XXIXa,b} \xrightarrow{\text{NBS}} \text{Ph}\overset{O}{\underset{O}{C}}(\text{Br})-\overset{R}{\underset{C=O}{C}}\overset{+}{(\text{SCH}_3)_2} \rightleftarrows \text{Ph}\overset{R}{\underset{O}{C}}(\text{Br})-\overset{+}{C}(\text{SCH}_3)_2$$

$$\xrightarrow{\text{H}_2\text{O}} \xrightarrow{-\text{H}^+} \text{Ph}\overset{OH}{\underset{}{C}}(\text{Br})-\overset{OCOR}{\underset{}{C}}(\text{SCH}_3)_2 \xrightarrow{-\text{Br}^-} \text{Ph}\overset{OH}{\underset{}{C}}(\text{OH})-\overset{CH_3}{\underset{S}{\overset{+}{C}}}(\text{OCOR})\text{SCH}_3$$

$$\xrightarrow{:\text{Nu}^-} \text{Ph}\overset{OH}{\underset{}{C}}=\text{C}(\text{OCOR})\text{SCH}_3 + \text{CH}_3\text{SNu} \longrightarrow \text{PhCO}\overset{OCOR}{\underset{}{C}}\text{HSCH}_3$$

VIII,a

Figure 26. Proposed scheme for the conversion of phenylglyoxal methylmercapto enolate esters (XXIXa,b) to ω-acyloxy-ω-(methylmercapto)acetophenone (VIII,a).

β-hydroxymercaptals available in the present study. The only derivatives of XXIVa-d found stable to E_1 decomposition were the benzoate ester (XLIX) of 2,2-di(methylmercapto)-1-phenethanol (XXIVa) and the O-methyl ethers (La-d) of the β-hydroxy mercaptals (XXIVa-d). Table 8 summarizes the high yields of these derivatives available by acylation with benzoyl chloride and alkylation with methyl iodide of the sodium hydride generated alcoholates in tetrahydrofuran.
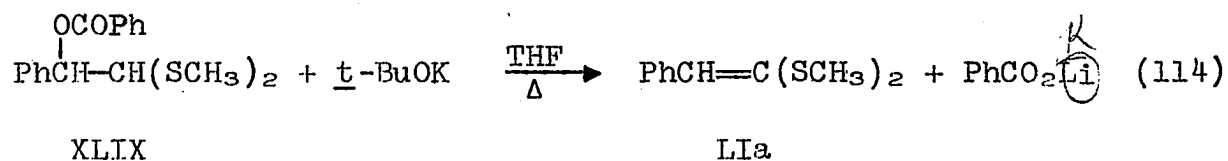
The ketene mercaptals (LIa-d) were prepared by the action of strong bases on the O-benzoate (XLIX) and O-methyl (La-d) derivatives in excellent yields, Table 9. β,β-Di(methylmercapto)styrene (LIa) was prepared in 65% yield on refluxing in tetrahydrofuran of XLIX with potassium t-butoxide, Equation 114, while the

Table 8. Yields of O-benzoyl and O-methyl β-hydroxy mercaptals

$$\text{PhCR--CH(SCH}_3)_2 \xrightarrow[\text{THF}]{\text{NaH}} \xrightarrow{\text{R'X}} \text{PhCR--CH(SCH}_3)_2 \quad (\text{R'} = \text{PhCO}_2\text{CH}_3)$$

(with OH above first structure, OR' above second)

XXIVa-d   XLIX and La-d

Product		% Yield[a]	Isolated form (°C)
XLIX	OCOPh PhCH--CH(SCH$_3$)$_2$	64.0[b]	mp 94-95.5°
La	OCH$_3$ PhCH--CH(SCH$_3$)$_2$	87.6	bp 99-100°/0.25 Torr
Lb	OH PhC(CH$_3$)CH(SCH$_3$)$_2$	96.5	bp 123-125°/0.50 Torr
LC	OCH$_3$ PhC(Et)--CH(SCH$_3$)$_2$	91.0	bp 109-112°/0.25 Torr
Ld	OCH$_3$ Ph$_2$C--CH(SCH$_3$)$_2$	93.0	bp 131-135°/0.25 Torr

[a]Isolated yields on 50 mmole preparative scale.

[b]Single crop batch crystallization from hexane.

$$\text{PhCH--CH(SCH}_3)_2 + \underline{t}\text{-BuOK} \xrightarrow[\Delta]{\text{THF}} \text{PhCH=C(SCH}_3)_2 + \text{PhCO}_2\text{Li} \quad (114)$$

(with OCOPh above first structure)

XLIX   LIa

methoxy derivatives La-d were inert to potassium $\underline{t}$-butoxide.
However, La-d reacted cleanly at room temperature with an equivalent of the stronger base $\underline{n}$-butyllithium, Equation 115.
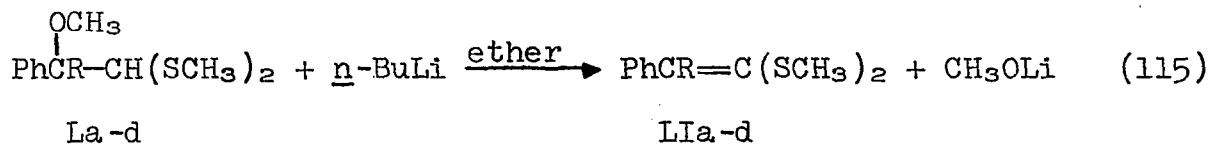
$$\text{PhCR-CH(SCH}_3)_2 + \underline{n}\text{-BuLi} \xrightarrow{\text{ether}} \text{PhCR=C(SCH}_3)_2 + \text{CH}_3\text{OLi} \qquad (115)$$
$$\overset{\overset{\displaystyle OCH_3}{|}}{}$$

$$\text{La-d} \qquad\qquad\qquad\qquad \text{LIa-d}$$

Table 9. Yields of ketene mercaptals (LIa-d)

$$\overset{\overset{\displaystyle OR'}{|}}{\text{PhCR-CH(SCH}_3)_2} \xrightarrow{\text{B}^-} \text{PhC(R)=C(SCH}_3)_2 \qquad (R'\text{=PhCO,CH}_3)$$

XLIX and La-d   LIa-d

Products	% Yield	Isolated form (°C)
LIa PhCH=C(SCH$_3$)$_2$	91.3[a], 64.5[b]	bp 94-96°/0.25 Torr
LIb PhC(CH$_3$)=C(SCH$_3$)$_2$	78.5[a]	bp 97-99°/0.25 Torr
LIc PhC(Et)=C(SCH$_3$)$_2$	84.5[a]	bp 94-95°/0.25 Torr
LId Ph$_2$C=C(SCH$_3$)$_2$	84.0[a]	mp 83-84°

[a]Yields from the reaction of β-methoxy mercaptals (La-d) with $\underline{n}$-butyllithium base.

[b]Yields from the reaction of XLIX and potassium $\underline{t}$-butoxide base.

Hydrations and Hydroborations of
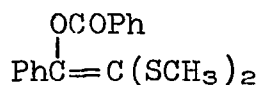## β-Styrenyl Sulfides

Previous work by Professor Russell and co-workers (60, 91) and the present study have provided for the synthesis of a wide variety of styrenyl sulfides, including ketene mercaptals, by the utilization of β-keto sulfoxides as the initial precursors. Arens, et al. (186, 187) have previously studied the acid-catalyzed hydration of vinyl and acetylenic sulfides in order to elaborate the electron-donor properties of sulfur toward conjugated electrophilic attack by acids. They observed that hydration usually occurred at the carbon alpha to the sulfur moiety, consistent with an α-sulfonium ion intermediate, and led to carbonyl formation after desulfurization of the initially formed hemimercaptals. Thus, the vinyl sulfides available in this study, tabulated in Chart 4, were systematically investigated to further extend the synthetic utility of β-keto sulfoxides through the preferred mode of vinyl sulfide hydration.

The hydration of the ketene mercaptals was anticipated to yield α-substituted S-methyl-α-(phenyl)thioacetates by preferred protonation in acidic media at the alpha styrenyl carbon to form the sulfur stabilized α-disulfonium ions, Equation 116.

$$PhC(R)\!=\!C(SCH_3)_2 \xrightarrow{H^+} [PhCR\!-\!\overset{H}{\underset{SCH_3}{C}}\!\!\overset{SCH_3}{\diagup}+] \xrightarrow{H_2O} \xrightarrow{-HSCH_3} PhC(R)HCOSCH_3$$

$$(116)$$

OCH₃
|
PhC=C(SCH₃)₂

XXVIII

OCOPh
|
PhC=C(SCH₃)₂

XXIXb

SCH₃
|
PhC=C(SCH₃)₂

XLV

PhCH=C(SCH₃)₂

LIa

PhC(CH₃)=C(SCH₃)₂

LIb

PhC(Et)=C(SCH₃)₂

LIc

Ph₂C=C(SCH₃)₂

LId

SCH₃
|
PhC=CHSCH₃

XLIIIa

Cl
|
PhC=CHSCH₃

XLIV

PhCH=CHSCH₃

XLII

PhC(CH₃)=CHSCH₃

XLIIIb

PhC(Et)=CHSCH₃

XLIIIc

Ph₂C=CHSCH₃
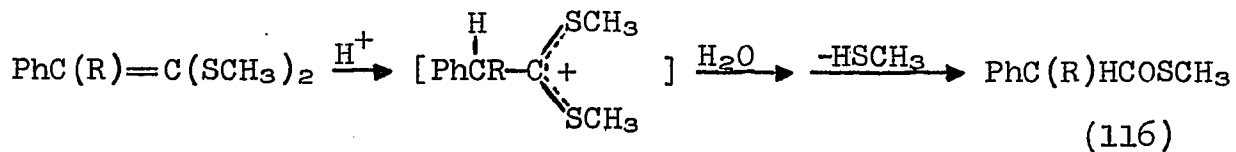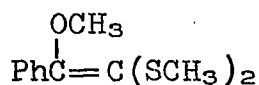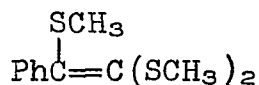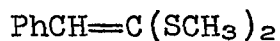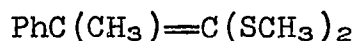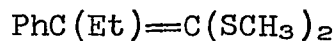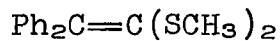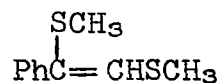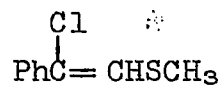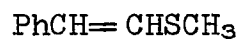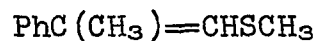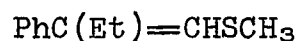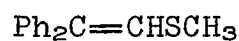
XLIIId

Chart 4. Styrenyl sulfides utilized for hydration studies.

Treatment of the ketene mercaptals (LIa-c) with 30% ethanolic 3N sulfuric acid did yield the corresponding α-substituted-S-methyl-α-(phenyl)thioacetates (LIIa-c), Table 10, in accord with the scheme in Equation 116. Likewise, α,β,β-tri(methyl-mercapto)styrene (XLV) hydrated at the <u>beta</u> carbon to yield

S-methyl-α-methylmercapto-α-(phenyl)thioacetate (LIII). How-
ever, the α-oxy-substituted derivatives (XXVIII) and (XXIXb)
hydrated at the <u>alpha</u> carbon to yield the methylmercaptal of
phenylglyoxal, Equation 117. The formation of XII could also

$$\underset{\substack{\text{XXVIII or} \\ \text{XXIXb}}}{\overset{\overset{\displaystyle OR}{\displaystyle |}}{Ph\overset{}{C}}=C(SCH_3)_2} \xrightarrow{H^+} [Ph\overset{+}{C}(OR)CH(SCH_3)_2] \xrightarrow{H_2O} \underset{XII}{PhCOCH(SCH_3)_2} + ROH \qquad (117)$$
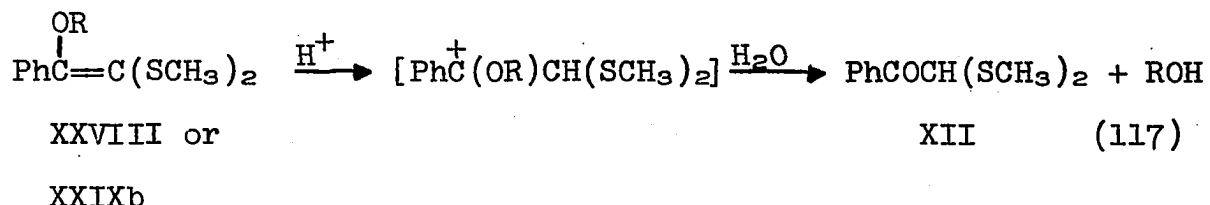
be formulated as due to hydrolysis of the enol ether (XXVIII)
and enol ester (XXIXb), rather than hydration of the double
bond. 1,1-Di(methylmercapto)-2,2-diphenylethylene (LId) also
hydrated in reverse fashion to the mono-phenyl derivatives (LIa-
c). The major hydration product, 68% of 1-(methylmercapto)-
2,2-diphenylethylene (XLIIId), was accompanied by a trace, 5%,
of α-(methylmercapto)-α,α-diphenylacetaldehyde (XLVIIIb),
Equation 118. These products are identical to those resulting

$$Ph_2C=C(SCH_3)_2 \xrightarrow{H^+} [Ph_2\overset{}{C}\underset{\overset{+S}{\underset{|}{CH_3}}}{----}CHSCH_3] \xrightarrow{:Nu^-} Ph_2C=CHSCH_3 + \\ CH_3SNu \qquad (118)$$
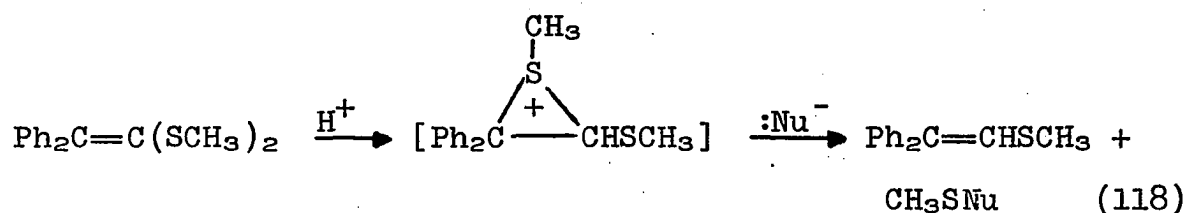
from acid-catalyzed dehydration of 1,1-di(methylmercapto)-2,2-
diphenylethanol (XXIVd) according to the scheme proposed in
Figure 24.

Table 10. Products of ketene mercaptal hydration[a]

Substrate	Product	% Yield[b]
XXVIII	PhCOCH(SCH₃)₂ XII	92.0
XXIXb	PhCOCH(SCH₃)₂ XII	71.0[c]
XLV	PhCH(SCH₃)COSCH₃ LIII	71.6
LIa	PhCH₂COSCH₃ LIIa	83.0
LIb	PhCHSCH₃COSCH₃ LIIb	88.5
LIc	PhCH(Et)COSCH₃ LIIc	80.0
LId	Ph₂C=CHSCH₃ XXIVd	68.0[d]

[a]Hydration was performed in 30% aqueous ethanolic 3N sulfuric acid catalyst at –90°C.

[b]Isolated yields by column chromatography on silica gel.

[c]22% of phenylglyoxal as co-product.

[d]5% of XLVIIIb isolated as co-product.

Hydration under acid-catalysis of the β-(methylmercapto)-styrenes (XLIIa) and (XLIIIb-d) occurred with difficulty and yielded the phenylacetaldehydes (LIVa-d) in low yields, Table 11, even after prolonged reflux in 50% aqueous ethanol-3N sulfuric acid catalyst, Equation 119. However, protonation of

$$PhC(R) = CHSCH_3 \xrightarrow{H^+} [Ph\overset{H}{\underset{|}{C}}R - \overset{+}{CH} = SCH_3] \xrightarrow{H_2O} \xrightarrow{-HSCH_3} PhCH(R)CHO$$

XLII and XLIIIb-d   LIVa-d (119)
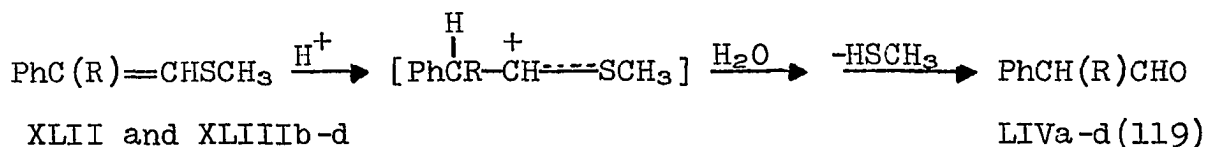
α,β-di(methylmercapto)styrene XLIIIa and α-chloro-β-(methyl-mercapto)styrene (XLIV) occurred readily under the conditions of ketene mercaptal hydrolysis to yield in both cases ω-(methyl-mercapto)acetophenone (LV) in ~80% yields, Equation 120.

$$PhC(SCH_3) = CHSCH_3 \xrightarrow{H^+} [Ph\overset{+}{C}(SCH_3)CHSCH_3] \xrightarrow{H_2O} \xrightarrow{-HSCH_3} PhCOCH_2 -$$

                                                                                                SCH_3
XLIIIa   LV   (120)
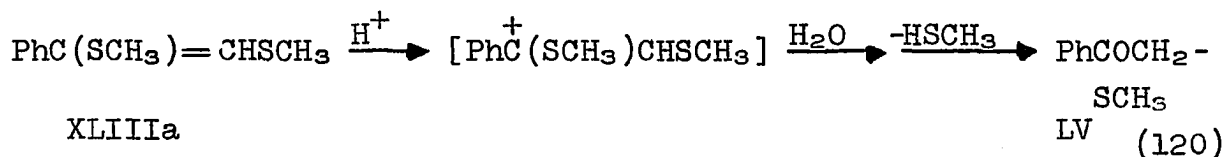
The products of the ketene mercaptals and β-(methylmercapto)-styrenes hydration can be interpreted as due to olefin protona-tion which yields a sequence of carbonium ion stabilities:

$Ph_2\overset{+}{C}R$, $Ph\overset{+}{C}(OR')R > R\overset{+}{C}(SCH_3)_2 > Ph\overset{+}{C}(SCH_3)R$, $Ph\overset{+}{C}(Cl)R > R\overset{+}{C}HSCH_3$.
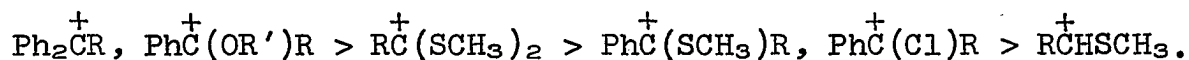
However, the opposite modes of hydration of α-methoxy-β,β-di-(methylmercapto)styrene (XXVIII) at the <u>alpha</u> carbon and α,β,β-tri(methylmercapto)styrene (XLV) at the <u>beta</u> carbon was unexpect-ed. These results perhaps reflect a reversible hydration proc-ess for XLV and a more facile elimination of methylmercaptan

from the dimercapto-substituted <u>beta</u> carbon. Alternatively,
hydrolysis rather than hydration occurs in the case of the oxy-
derivatives.

The high resistance of the β-(methylmercapto)styrenes
(XLII) and (XLIIIb-d) to acid-catalyzed hydration in aqueous
media prompted investigation into alternative methods for their
conversion to phenylacetaldehydes (LIVa-d). Previously reported
hydrations of vinyl sulfides had employed mercuric chloride in
water-saturated solvents (187), in addition to aqueous mineral
acid conditions similar to those of the present study. However,
the β-(methylmercapto)styrenes proved inert to mercuric chloride-
catalysis. Forcing conditions with a wide variety of other Lewis
acid catalysts, including silver sulfate, aluminum trichloride
and boron trifluoride etherate, proved comparable to the aqueous
acid conditions and afforded low conversion to aldehydes (LIVa-d).

Under aqueous basic conditions, including vigorous ethanolic
potassium hydroxide reflux, the β-(methylmercapto)styrenes
(XLII) and (XLIIIb-d) proved nearly inert. Only traces of
ketones from olefin cleavage were formed. This cleavage reaction
has been previously employed by Marshall (188) to regenerate
ketones from the vinyl sulfide protecting group. Compounds
XLIIIa and XLIV reacted with hydroxide ion in aqueous solution
by an olefin addition-reelimination mode to yield ω-(methyl-
mercapto)acetophenone, a reaction previously demonstrated by
Truce (189), Equation 121.

$$\underset{\substack{\text{XLIV or}\\\text{XLIIIa}}}{\overset{\overset{\displaystyle Cl}{|}}{PhC}=CHSCH_3} \xrightarrow{OH^-} [\overset{\overset{\displaystyle Cl}{|}}{\underset{\substack{|\\OH}}{PhC}}\text{--}CHSCH_3]^- \xrightarrow{-Cl^-} \underset{LV}{PhCOCH_2SCH_3} \qquad (121)$$
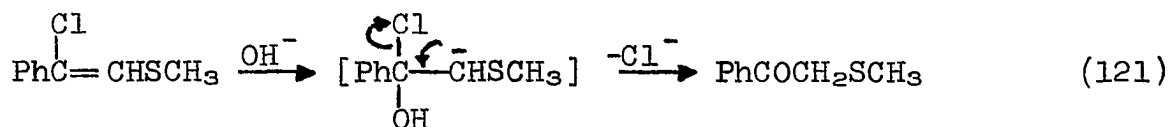
All of the above unsatisfactory attempts led to the investigation of hydroboration as a synthetic route to β-(methylmercapto)styrene conversion to phenylacetaldehyde (LIVa-d). It was anticipated that the borane-styrene adducts could be oxidized to the aldehyde hemimercaptals, which readily desulfurize to the aldehydes, Equation 122, 123. However, the direct

$$\underset{\substack{\text{XLII and}\\\text{XLIIIb-d}}}{PhC(R)}=CHSCH_3 \xrightarrow{BH_3} [PhCH(R)CH(SCH_3)]_3B \qquad (122)$$

$$\xrightarrow[OH^-]{H_2O_2} PhCH(R)CH(OH)SCH_3 \xrightarrow{-HSCH_3} \underset{\text{LIVa-d}}{PhCH(R)CHO} \qquad (123)$$
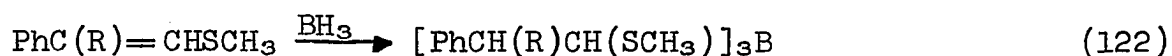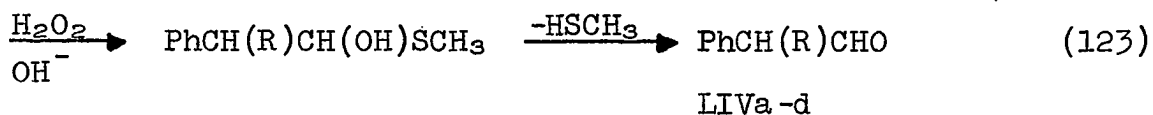
transformation to aldehydes could not be affected. Peroxide oxidation of the in situ generated organoboranes yielded β-phenethanols (LVIa-d) instead of the phenylacetaldehydes (LIVa-d). Apparently, reaction of the β-(methylmercapto)styrenes with borane leads to desulfurization and mixed alkyl-S-methyl organoborane adducts, Equation 124. All attempts to isolate the organoborane intermediates failed. Removal of the tetrahydrofuran solvent yielded a yellow amorphous residue which rapidly

$$PhC(R)=CHSCH_3 \xrightarrow{BH_3} [PhCHRCH_2-B(SCH_3)] \xrightarrow[OH^-]{H_2O_2} PhCH(R)CH_2OH \quad (124)$$

XLII and   LVIa-d
XLIIIb-d
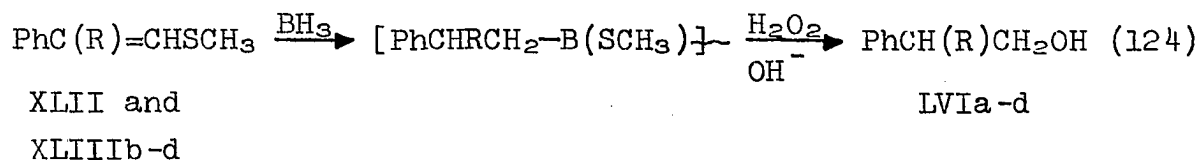
decomposed to dark multi-product oils, even at 0°C under a
nitrogen atmosphere. However, the phenylacetaldehydes were
prepared in satisfactory yields by _in situ_ chromium trioxide
oxidation of the organoborane adducts. The procedure employed
was a modification of H. C. Brown's (190, 191) aldehyde
synthesis procedure. Yields of the alcohols (LIVa-d) and
aldehydes (LVIa-d) derived from the hydroboration of styrenyl
sulfides are summarized in Table 11.

Table 11.   Yields of phenylacetaldehydes (LIVa-d) and β-
phenethanols (LVIa-d) from hydroboration of
β-styrenyl sulfides (XLII) and (XLIIIb-d)

		% Yield			
Substrate	Aldehydes	Method A[a]	Method B[b]	Alcohols	% Yield[c]
XLII	PhCH$_2$CHO LIVa	50	20	PhCH$_2$CH$_2$OH LVIa	88[d]
XLIIIb	PhCH(CH$_3$)CHO LIV	68	25	PhCH(CH$_3$)CH$_2$OH LVIb	71
XLIIIc	PhCH(Et)CHO LIVc	52	35	PhCH(Et)CH$_2$OH LVIc	74
XLIIId	Ph$_2$CHCHO LIVd	61	40	Ph$_2$CHCH$_2$OH LVId	80

[a]Isolated from hydroboration in diglyme followed by 10%
excess of chromium trioxide.

[b]Isolated from hydration of β-styrenyl sulfides in 50%
ethanolic-3$\underline{N}$ sulfuric acid at ~90°C.

[c]Isolated from hydroboration in diglyme followed by oxi-
dation with basic 30% hydrogen peroxide.

[d]23/77 Ratio of α- and β-phenethanol.

Preparation of Acetylenic and Vinylic Sulfoxides

The utility of β-keto sulfoxides as precursors to styrenyl
sulfides, tabulated in Chart 4, has been described in this
study. Synthesis of compounds XLII and XLIV had been pre-
viously described, and α-chloro-β-(methylmercapto)styrene
(XLIV) was demonstrated to conveniently yield methyl phene-
thynyl sulfide (LVII) on dehydrochlorination (16, 60). More-
over, a route to α,β-unsubstituted vinyl sulfoxides was
demonstrated (60), Equation 125. Subsequently, β-(methyl-
sulfinyl)styrene (LXIIIa) was examined with respect to its

$$\text{I} \xrightarrow{\text{BH}_4^-} \underset{\overset{|}{\text{OH}}}{\text{Ph}\overset{}{\text{C}}\text{HCH}_2\text{SOCH}_3} \xrightarrow{\text{B}^-} \xrightarrow{\text{CH}_3\text{I}} \underset{\overset{|}{\text{OCH}_3}}{\text{Ph}\overset{}{\text{C}}\text{HCH}_2\text{SOCH}_3} \xrightarrow{\text{B}^-} \text{PhCH=CHSOCH}_3$$

(125)

LXIIIa
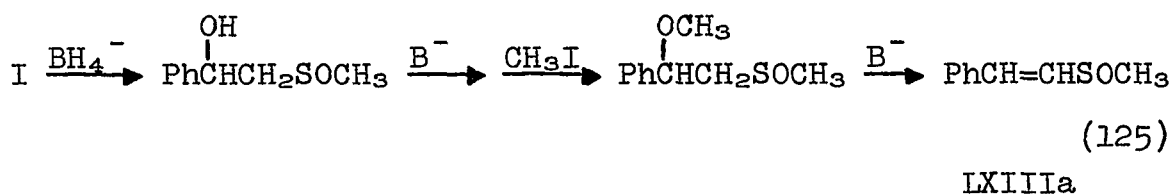
electron impact induced chemistry, and revealed a novel vinyl
sulfoxide to vinyl sulfenylester rearrangement mode, of
interest for further study (192). Therefore, oxidative routes
to the sulfoxide derivatives of the styrenyl and acetylenic
sulfides at hand were investigated. When the sulfoxide deriva-
tives were made available, a systematic investigation of their
thermal and electron impact chemistry was undertaken in collab-
oration with Professor T. H. Kinstle and co-workers. The
results and discussion of these studies are reported elsewhere
(192, 193).

Preparation of an acetylenic sulfoxide was in itself of interest. As of the present study, acetylenic sulfoxides were unknown. However, Truce had described the preparation of phenyl phenethynyl sulfone (189). Moreover, he has recently reported a study of nucleophile additions to unsaturated carbon bonds of a number of acetylenic sulfones and sulfoxides, but to date the preparation of the sulfur substrates has not been described (194).

Mono-alkyl thioacetylenes were first prepared by dehydro-bromination of α,β-di(bromo)-α-(mercapto)alkanes in 1956 (195). Analogous attempts in the present study to convert β-(methyl-mercapto)styrene (XLII) to the acetylenic sulfide, by the standard bromination-dehydrobromination techniques (189, 195, 196), resulted in only a 13% yield of methyl phenethynyl sulfide (LVIII). However, more practical methods are recently available for acetylenic sulfide synthesis. Perhaps the most general method is that of Raap and Micetich(197), employing 1,2-(3)-thiodiazoles as starting materials, Equation 126. An alternative

$$(126)$$
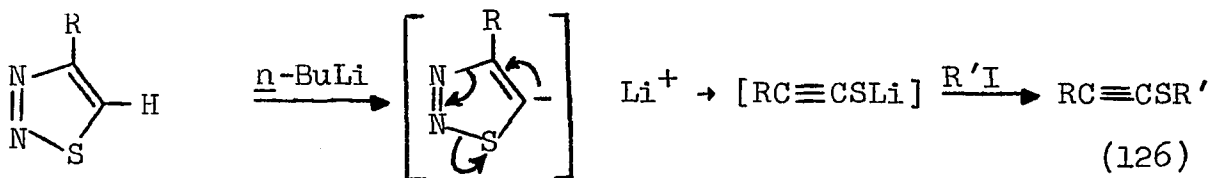
method, utilized in the present study, involves the overall conversion of a β-keto sulfoxide (I) to an acetylenic sulfide (XLII) in excess of 65% yield (60), Figure 27.

$$RCOCH_2SOCH_3 \xrightarrow{\text{LAH}} \overset{\overset{\displaystyle OH}{|}}{RCHCH_2SCH_3} \xrightarrow[\Delta]{H^+} RCH\!=\!CHSCH_3$$

$$RCOCH_2SOCH_3 \downarrow BH_4^-$$

$$\overset{\overset{\displaystyle OH}{|}}{RCHCH_2SOCH_3}$$

$$RCH\!=\!CHSCH_3 \downarrow NaIO_4$$

$$RCH\!=\!CHSOCH_3$$

$$2\ SOCl_2 \qquad SOCl_2$$

$$\overset{\overset{\displaystyle Cl}{|}}{RC\!=\!CHSCH_3}$$

$$\downarrow KOH/EtOH$$

$$RC\!\equiv\!CSCH_3$$
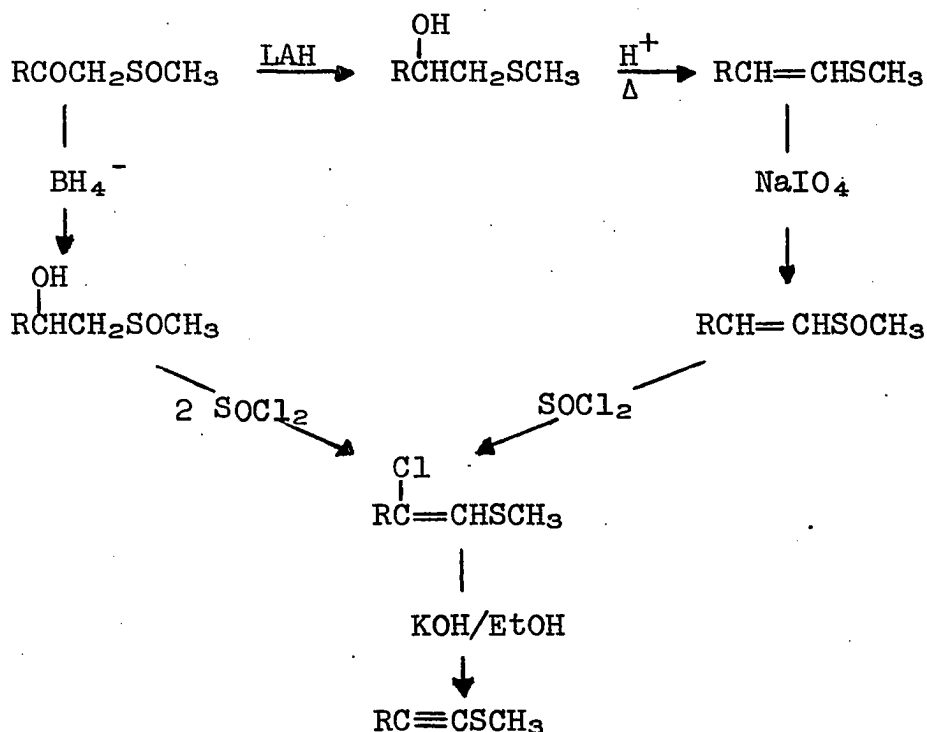
Figure 27.   Reaction scheme for the conversion of β-keto-
sulfoxides to acetylenic sulfides (60).

The oxidation of vinyl sulfides to vinyl sulfoxides with
peroxy oxidants can be complicated by epoxidation of the double
bond and the possibility of over-oxidation to yield sulfones.
Recently, a number of active halogen oxidants have been
described, which alleviate the problem of over-oxidation, but
react competitively with the olefinic double bond (55-57).
However, preliminary examination of sodium-meta-periodate as
oxidant for vinyl sulfides was encouraging on all accounts (2,
60). Therefore, sodium meta-periodate was employed in a modifi-
cation of the procedure by Leonard and Johnson (198, 199).

Nearly quantitative yields of vinyl sulfoxides, Table 12, were
obtained by use of an equivalent of 0.5 M sodium meta-periodate
in 50% aqueous acetonitrile solution at -10°C. A recent kinetic
and mechanistic investigation of meta-periodate-sulfide oxida-
tions has confirmed the advantages offered by this oxidant (200).

An alternate procedure for vinyl sulfoxide synthesis, which
is greatly preferred for conversion of methyl phenethynyl
sulfide (LVII) to the sulfoxide (LVIII), involves the use of
one equivalent of m-chloroperbenzoic acid at -20°C in chloro-
form solution (201), Table 12. The oxidant is highly selective,
yielding single stereoisomers of the ketene mercaptal (LIb,c)
monosulfoxides, and m-chlorobenzoic acid by-product, which is
insoluble in chloroform, and can be conveniently separated by
filtration. However, in the case of the ketene mercaptals,
(LIb-d), control of the oxidation temperature is critical.
Above -20°C, mixtures of monosulfoxide stereoisomers, disulfoxides
and sulfones result, which cannot be separated. Moreover, β,β-
di(methylmercapto)styrene (LIa) could not be selectively oxi-
dized to its corresponding sulfoxide by either sodium meta-
periodate or m-chloroperbenzoic acid. In both cases, the only
insoluble oxidation product was S-methyl-α-(methylmercapto)α-
(phenyl)thioacetate (LIII). The product (LIII) quite likely
results from epoxidation of the double bond and subsequent
epoxide rearrangement, Equation 127. The similar rearrangement
of α-chloroepoxides is known (202).

$$\text{PhCH}=\text{C(SCH}_3)_2 \xrightarrow{[O]} [\text{PhCH}\overset{O}{\overbrace{\quad}}\text{C(SCH}_3)]_2 \rightarrow [\text{Ph}\overset{+}{\text{C}}\text{HC}\overset{O^-}{\underset{\text{SCH}_3}{\overset{\|}{\text{SCH}_3}}}] \rightarrow \text{LIII} \quad (127)$$
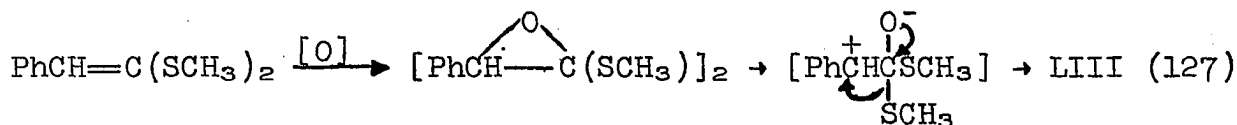
Table 12.   Yields of sulfoxides from oxidation of styrenyl and phenethynyl sulfides

Sulfide	Sulfoxide	% Yield Method	
		A[a]	B[b]
XLII	PhCH=CHSOCH$_3$ (LXIIIa)	77[c]	
XLVII	PhCH=C(CH$_3$)SOCH$_3$ (LXV)	74	
XLIIIb	PhC(CH$_3$)=CHSOCH$_3$ (LXIIIb)	>99	
XLIIIc	PhC(Et)=CHSOCH$_3$ (LXIIIc)	>99	
XLIIId	Ph$_2$C=CHSOCH$_3$ (LXIIId)	96	79
XLIV	PhC(Cl)=CHSOCH$_3$ (LX)	73	
LIb	PhC(CH$_3$)=C(SCH$_3$)SOCH$_3$ (LXIVa)	90[d]	90[d]
LIc	PhC(Et)=C(SCH$_3$)SOCH$_3$ (LXIVb)	68[d]	86[d]
LId	Ph$_2$C=C(SCH$_3$)SOCH$_3$ (LXIVc)	96	97
LVII	PhC≡CSOCH$_3$ (LVIII)	46	92[e]

[a]Isolated yields from sodium meta-periodate oxidation in 50% aqueous acetonitrile solution at -10°C.

[b]Isolated yields from m-chloroperbenzoic acid oxidation in chloroform at -23°C.

[c]Yield reported in reference 60, and reproduced in the present study.

[d]Single stereoisomer isolated, but absolute configuration could not be assigned on the basis of analytical data.

[e]Oxidation of sulfide (LVII) with two equivalents of m-chloroperbenzoic acid yielded 81% of methyl phenethynyl sulfone (LIX) by method B.

An alternative reaction sequence for the preparation of methyl phenethynyl sulfoxide (LVIII) can utilize the dehydrochlorination of α-chloro-β-(methylsulfinyl)styrene (LX), Equation 128. Use of potassium $\underline{t}$-butoxide in tetrahydrofuran, a base of low nucleophilicity, produced LVIII in an overall yield .
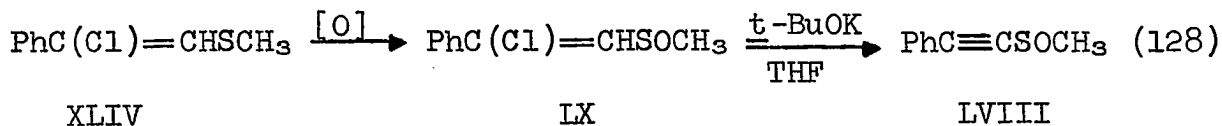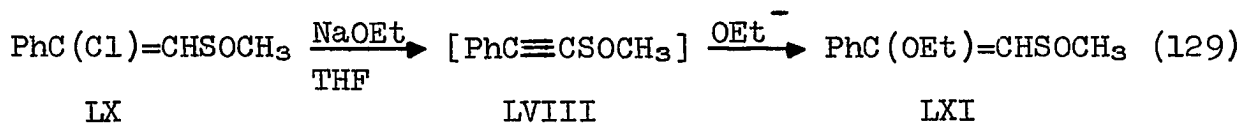
$$PhC(Cl){=}CHSCH_3 \xrightarrow{[O]} PhC(Cl){=}CHSOCH_3 \xrightarrow[THF]{\underline{t}\text{-BuOK}} PhC{\equiv}CSOCH_3 \quad (128)$$

XLIV   IX   LVIII

of 89% from the chlorovinyl sulfide (XLIV). However, a nucleophilic base, such as sodium ethoxide, resulted in the formation of α-ethoxy-β-(methylsulfinyl)styrene (LXI), Equation 129.

$$PhC(Cl){=}CHSOCH_3 \xrightarrow[THF]{NaOEt} [PhC{\equiv}CSOCH_3] \xrightarrow{OEt^-} PhC(OEt){=}CHSOCH_3 \quad (129)$$

IX   LVIII   LXI

Ethoxide ion is known to add readily to acetylenic sulfides (196, 203), and would presumably add even more readily to acetylenic sulfoxides.

The oxidation of methyl phenethynyl sulfide (LVII) or sulfoxide (LVIII) to the corresponding sulfone (LIX) proved difficult. Use of hydrogen peroxide in acetic acid led only to polymer under conditions reported to be satisfactory for the oxidation of phenyl phenethynyl sulfide to its sulfone (189). However, difficulties were overcome and LIX was prepared in 81% yield by oxidation of LVII with two equivalents of $\underline{m}$-chloroperbenzoic acid in chloroform on four days reaction below -20°C.

Extended investigation of the chemistry of methyl phenethynyl sulfoxide was discouraged by inability to stabilize and store a convenient quantity of LVIII. The crude preparation of LVIII decomposed almost immediately, but storage-life was improved with immediate purification by column chromatography on silica gel. Samples purified in this fashion completely polymerized after two weeks storage at 0°C. The only results of synthetic interest derived from LVIII were due to reaction with thionyl chloride. Treatment of methyl phenethynyl sulfoxide (LVIII) with one equivalent of thionyl chloride in methylene chloride solution resulted in sulfoxide reduction and addition of chlorine across the acetylenic bond, Equations 130, 131. The mixture

$$PhC \equiv CSOCH_3 \xrightarrow[CH_2Cl_2]{SOCl_2} [Ph\overset{+}{C}=C=\overset{Cl-\overset{O}{\underset{\|}{S}}-O}{\underset{|}{S}}CH_3]C\bar{l} \qquad (130)$$

LVIII

$$\xrightarrow{-SO_2} [Ph\overset{Cl}{\underset{|}{C}}=C^{\cdots\cdots}\overset{+}{S}CH_3]Cl^- \longrightarrow PhC(Cl)=C(Cl)SCH_3 \qquad (131)$$
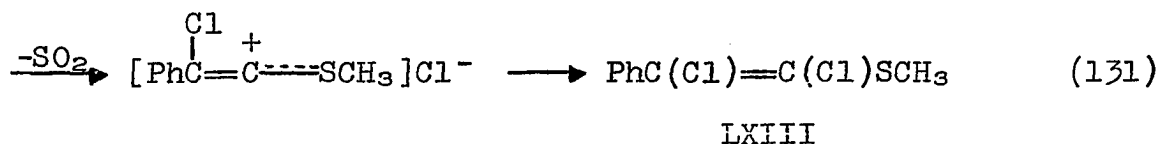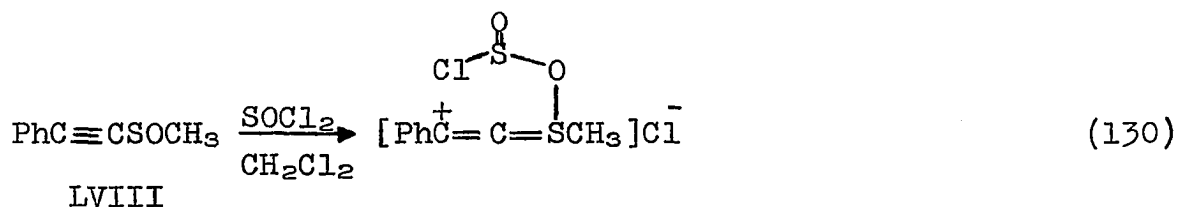
LXIII

of cis- and trans-α,β-di(chloro)-β-(methylmercapto)styrene (LXIII) proved remarkably stable. Hydrolysis of 1-chloro-1-(mercapto)ethylenes in acidic or basic aqueous solution to yield acetic acid derivatives has been observed to occur readily (189, 204). However, LXIII proved resistant to hydrolysis even in refluxing 50% sulfuric acid or in 2N potassium hydroxide. Likewise, no reaction was observed in ethanolic potassium hydroxide.

During the course of the electron impact studies of the styrenyl sulfoxides, deutero-(methylsulfinyl) derivatives were desired as substrates to elucidate molecular ion fragmentation (192). Deuterium exchange in basic deuterium oxide proved a successful approach, Equation 132. However, β-styrenyl proton

$$PhCH{=}CHSOCH_3 \xrightarrow[D_2O]{Na_2CO_3} PhCH{=}CDSOCD_3 \qquad (132)$$

LXIIIa   XLIIIe
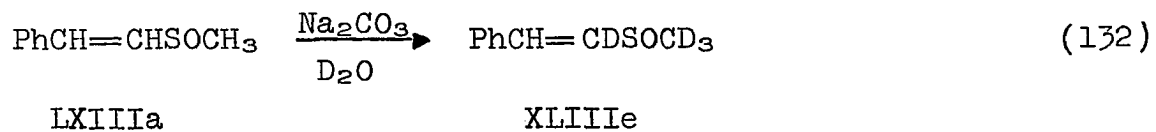
exchange was concurrent with methylsulfinyl proton exchange (XLIIIe).

EXPERIMENTAL

All melting points were determined on a Uni-melt, Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Schwartzkopf Microanalytical Laboratories, Woodside, New York, or by Ilse Beetz Microanalytical Laboratories, Krönach, West Germany. Molecular weight determinations, by thermoelectric osmometric technique, were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan. Infrared spectra were taken on a Perkin-Elmer Model-21 double beam infrared spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 spectrophotometer, and chemical shifts are reported as parts per million (δ scale) from tetramethylsilane. Mass spectra were measured using an Atlas CH_4 mass spectrometer, with a direct solid inlet system. Only diagnostic and higher than 10% relative intensity peaks are reported.

Baker Analyzed reagent grade dimethyl sulfoxide was used as commercially available for condensation reactions of one molar or larger scale. For smaller scale condensation reactions, dimethyl sulfoxide was distilled from calcium hydride under reduced pressure and stored over Fisher Type-4A Molecular Sieves in sealed glass containers. Tetrahydrofuran was distilled as needed from lithium aluminum hydride. Baker Analyzed anhydrous ethyl ether was dried over sodium ribbons prior to use as reaction solvent. Sodium hydride was obtained as a 50-60%

suspension in mineral oil from Metal Hydrides, Incorporated.
The mineral oil was removed just prior to use by washing with
pentane under a nitrogen sweep, and suction filtration of
liquid away from the reaction flask through an ultra-fine grade,
fritted glass gas dispersion tube. All reactions, performed
under anhydrous conditions, were carried out under a nitrogen
atmosphere. Sodium borohydride was obtained from Ventron,
Metal Hydrides Division. Organolithium reagents were obtained
from Foote Mineral Co. All other chemicals were commercially
readily available, and unless otherwise stated, were used as
received.

Whenever possible, chromatographic procedures were employed
for separation and purification of products. Microanalytical,
air dried tlc plates were prepared by immersion coating of
microscope slides in a chloroform suspension of Merck silica
gel H, obtained from Merck Distributors, Brinkmann Instruments,
Inc., Westbury, New York. Preparative tlc plates were prepared
by manual spreading of a 2/1 aqueous-silica gel (20% Merck sili-
ca gel H, 80% Merck silica gel Pf_{254} with $CaSO_4$ binder) slurry
on 20 x 60 cm glass plates, followed by 8 hrs of activation at
110°C. Column chromatography was performed on Baker Analyzed
silica gel (60-200 mesh). Elution solvents were established by
microanalytical tlc, and column elution was followed by tlc
analysis of consecutive effluent aliquots.

Preparation of β-keto sulfoxides, ω-(methylsulfinyl)aceto-
phenone (I) and ω-(methyl)-ω-(methylsulfinyl)acetophenone (Ia)

Compounds I and Ia were prepared as previously reported
(16, 22, 60). The preparation of I, from dimsyl sodium and
ethyl benzoate condensation, was modified by the addition of
Dow Corning antifoam-A, in order to suppress foaming during
dimsyl sodium preparation and subsequent ester condensation.

Preparation of γ-hydroxy-γ-(phenyl)propyl methyl sulfoxide (II)

This compound was prepared by addition of 24.3 ml (~200 mmol)
of styrene oxide at -5° to a solution (150 ml) of 200 mmol of
sodium hydride dissolved in DMSO under nitrogen. After 4 hrs
at 25° the reaction mixture was poured into 1 liter of aqueous
saturated sodium chloride solution, and acidified with hydro-
chloric acid to pH of 4.5. The aqueous solution was extracted
with four 125 ml portions of chloroform, dried (MgSO$_4$) and
concentrated under water aspirator pressure. The crude oil was
chromatographed from silica gel by 30% methylene chloride-70%
hexane to yield 15.4 g of product; nmr (CDCl$_3$) 2.32δ and 2.38δ
(d, 3 total, SOC$\underline{H}_3$, diastereomeric mixture); 4.25δ (s, 1, O$\underline{H}$,
deuterium oxide exchanged); 4.70δ (t, 1, $\underline{J}$ = 7 Hz, C(OH)$\underline{H}$).

Anal. Calcd. for C$_{10}$H$_{14}$SO: C, 60.59; H, 7.12; S, 16.15.
Found: C, 60.64; H, 7.13; S, 16.08.

Treatment of γ-hydroxy-γ-phenylpropyl methyl sulfoxide with
acetic anhydride, brought about the Pummerer reaction and the
substitution of the acetoxy group in the methyl position to yield

1,5-diacetoxy-5-phenyl-2-thiobutane, PhCH(O$_2$CCH$_3$)CH$_2$CH$_2$SCH$_2$O$_2$-CCH$_3$ (IIa), as an oil in 62% yield; mass spectrum (70 eV) m/e = 282. The nmr spectrum was consistent with the assigned structure.

Oxidation of γ-hydroxy-γ-phenylpropyl methyl sulfoxide (60) yielded 60% of the γ-hydroxy-γ-phenylpropyl methyl sulfone (IIb) as an oil; nmr (CDCl$_3$) 2.82δ (s, 3, SO$_2$CH$_3$); 4.84δ (t, 1, $\underline{J}$ = 6.8 Hz, C(OH)$\underline{H}$); 2.96δ (s, 1, O$\underline{H}$, deuterium oxide exchanged).

Anal. Calcd. for C$_{10}$H$_{14}$SO$_3$: C, 56.07; H, 6.59; S, 14.94. Found: C, 56.29; H, 6.56; S, 14.93.

Condensation of benzonitrile and methylsulfinylcarbanion, preparation of I

The condensation product, ω-(methylsulfinyl)acetophenone imine (C$_6$H$_5$C(=NH)CH$_2$SOCH$_3$), was hydrolyzed to the ketone prior to isolation. Treatment of benzonitrile with the sodium salt of methylsulfinylcarbanion yielded only tar. However, when lithium iodide was present the condensation proceeded normally (114). To 250 ml of DMSO solution in which 250 mmol of sodium hydride had been dissolved was added 65 g of anhydrous lithium iodide. After 1 hr of equilibration, 200 mmol (20.6 g) of benzonitrile was added (dropwise) at 0°. The blue reaction mixture was poured into 500 ml of ice-water, acidified to pH = 3 with hydrochloric acid and extracted with 3 portions of 200 ml of chloroform. After drying (MgSO$_4$) and concentration, the residue crystallized from ether to yield 19.0 g of ω-(methylsulfinyl)-acetophenone (52%), mp 86°, (lit (16) mp 86-87°).

Attempted preparation of ω-(methylsulfinyl)propiophenone (III)

To a preformed solution of dimsyl sodium (250 mmol of 1 molar solution) was added 200 mmol (30.8 g) of phenacyl chloride dissolved in 50 ml of dimethyl sulfoxide. The reaction mixture was cooled prior to halide addition in an ice bath to semi-frozen slurry. Two minutes after complete addition of reactants, the reaction had turned dark and started to reflux, even though immersed in an ice bath. In five minutes the reaction was completely solidified. The crude residue was leached with cold hydrochloric acid (pH=2) and 300 ml of chloroform. The chloroform extracts were dried (MgSO$_4$) and evaporated under vacuum. The resulting black tar was chromatographed on a column of silica gel with methanol to yield 0.73 g of recovered phenacylchloride and 12.7 g (29.8%) of ω-(methylsulfonyl)propiophenone (IIIa). No other monomeric products could be eluted from the column. IIIa was recrystallized from ether to yield a white powder, mp 91-92° (lit (2) mp 90-92°).

Preparation of ethyl β-(methylsulfinyl)-β-benzoylpropionate (IV)

The sodium salt of ω-(methylsulfinyl)acetophenone (25 mmol) was prepared as described previously (60) in 150 ml of THF. At 5° a solution of 4.2 ml of ethyl bromoacetate in 10 ml of THF was added dropwise. The solution was stirred for 2 hrs at 25°, filtered, concentrated under vacuum, diluted with 200 ml of water, and the pH adjusted to 5 with hydrochloric acid. Extraction with three 100 ml portions of chloroform yielded a yellow oil after drying (MgSO$_4$) and solvent removal. The oil was

chromatographed on a silica gel column. Non-polar impurities were eluted with hexane (95%)—ethyl acetate (5%). The propionate ester was eluted away from unreacted β-keto sulfoxide by chloroform to yield 4.08 g (61%) of a viscous oil whose nmr spectrum (CDCl$_3$) was consistent with a mixture of diastereomers: 2.32, 2.49δ (set of singlets, 3, SOC$\underline{H}_3$), 3.03-3.35δ (complex set of overlapping methylene doublets, 3, $\underline{J}_{AB_2}$ = 13.8 Hz, ~C$\underline{H}_2$-C$\underline{H}_2$~); 5.12-5.59δ (complex set of overlapping methine triplets, 1; J as above, C$\underline{H}$SOCH$_3$); 1.13δ and 4.09δ (t, 3; q, 2; $\underline{J}$ = 7.8 Hz, C$\underline{H}_2$C$\underline{H}_3$) actually two ethyl resonance sets with $\Delta\delta$ ~ 0.02 Hz; (m, 3, 7.30-7.65δ), (m, 2, 7.88-8.18δ); mass spectrum (70 eV), $\underline{m}/\underline{e}$ (relative intensity) = 268 (8), 275 (10), 223 (10), 204 (40), 131 (35), 105 (100). Attempts to prepare an analytical sample for elemental analysis by chromatography or distillation resulted in elimination of methylsulfinic acid and conversion to IVb.

Preparation of ethyl γ-(methylsulfinyl)-γ-benzoylbutyrate (V)

The sodium salt of ω-(methylsulfinyl)acetophenone (25 mmol) was prepared as described previously (60) in 200 ml of THF. To this solution was added 2.6 g of ethyl acrylate. The solution was stirred for 6 hrs at 25° and quenched with 10 ml of water. The solution was concentrated under vacuum and diluted with 300 ml of saturated aqueous ammonium chloride. Extraction with three 100 ml portions of chloroform, followed by drying (MgSO$_4$) and vacuum evaporation yielded a yellow oil that was chromatographed on a silica gel column. Non-polar impurities were

removed with hexane (80%)—ethylacetate (20%). Hexane (50%)—
ethyl acetate (50%) yielded 0.4 g of VI. The major product (V)
was eluted with ethyl acetate to yield 5.3 g (75%) of a color-
less oil whose nmr (CDCl$_3$) was consistent with a mixture of
diastereomers: 2.47δ and 2.49δ (set of singlets, total area is
estimated at 3, SOC$\underline{H_3}$); (complex set of methylene doublets with
estimated center ~2.9δ , underlying methylsulfinyl resonance,
total area of this resonance band is 7); (complex set of methine
triplets with estimated center ~4.97δ , area 1), 1.18δ and
4.09δ (q, 2; t, 3; $\underline{J}$ = 9.0 Hz, C$\underline{H_2}$C$\underline{H_3}$) actually two ethyl
resonance sets are observed with $\Delta\delta$ ~0.05 Hz; (m, 3, 7.30-7.70);
(m, 2, 7.93-8.18δ); mass spectrum (70 eV), $\underline{m}$/$\underline{e}$ (relative
intensity) = 282 (5), 264 (15), 237 (10), 204 (40), 131 (35),
and 105 (100). An analytical sample of V could not be prepared,
due to its thermal instability.

Preparation of 2-carboethoxy-4-(methylsulfinyl)-4-benzoylcyclo-hexanone (VI)

To 25 mmol of the anion of ω-(methylsulfinyl)acetophenone in
200 ml of THF was added 20 ml of ethyl acylate. The reaction
mixture was stirred for 6 hrs at 25°, quenched by the addition
of 15 g of ammonium chloride, stirred for an additional hr, and
poured into 300 ml of water. Extraction with three 100 ml por-
tions of chloroform gave a product that was washed and dried
(MgSO$_4$) and chromatographed on silica gel as described previous-
ly for V, to yield 5.03 g (60%) of the substituted cyclohexanone

(VI) and 1.74 g of V. The nmr spectrum of VI was very complex because of the presence of three asymmetric centers and the possibility of keto-enol equilibria. The following resonances are diagnostic: 2.49δ and 2.53δ (set of singlets, total area estimated at 3, SOC$\underline{H}_3$); 3.13δ (broad 2-position methine multiplet, area ~0.7, deuterium oxide exchangeable); (complex set of at least four quartets and three triplets with estimated centers respectively, 4.13δ and 1.24δ, C$\underline{H}_2$C$\underline{H}_3$; $\underline{J}$ ~ 7.5 Hz); (m, 3, 7.36-7.60δ); (m, 2, 7.85-8.13δ); mass spectrum (70 eV), $\underline{m}/\underline{e}$ (relative intensity) = 336 (3), 320 (8), 318 (5), 272 (55), 226 (50), 110 (100), 105 (70). Due to the thermal instability of VI, a satisfactory analytical sample could not be prepared.

Conversion of IV into ethyl β-benzoyl-propionate (IVa)

Reduction with zinc and acetic acid (58) of IV for 10 hrs yielded 4.65 g (86%) of ethyl β-benzoylpropionate (IVa) from 7 g of the sulfoxide (IV). The β-benzoylpropionate was isolated by extraction with ethyl acetate followed by chromatography on a silica gel column with hexane (90%)—ethyl acetate (10%) as the eluent. The product had bp 118-120° (2 Torr), (lit (205) bp 123° (2 Torr)).

Conversion of V into ethyl γ-benzoylbutyrate (Va)

The identical technique employed for the reduction of IV and isolation of IVa yielded 3.44 g (80%) of ethyl γ-benzoylbutyrate from 5.50 g of the sulfoxide V, bp 157-158° (10 Torr), (lit (206) bp 315° (750 Torr)).

Conversion of VI into 2-carboethoxy-4-benzoylcyclohexanone (VIa)

Reduction of zinc and acetic acid as described for IVa and Va yielded 2.96 g (91%) of 2-carboethoxy-4-benzoylcyclohexanone (VIa) from 4 g of the sulfoxide (VI). VIa was isolated by column chromatography in identical fashion to IVa, and the purified material was crystallized from pentane (90%)—ethyl acetate (10%) to give a product with mp 49-51°. The nmr (CDCl₃) spectrum was consistent with a mixture of keto and enol forms: 1.8-2.7δ (two sets of complex multiplets, 6); 3.2-3.7δ (broad multiplet, area 1.2, which decreased to area 1 on deuterium oxide exchange); 12.3δ (enol, 0.8, deuterium oxide exchangeable); 1.26δ and 4.22δ (t, 3; q, 2; J = 6.8 Hz, C$\underline{H}_2$C$\underline{H}_3$); (m, 3, 7.28-7.65δ); (m, 2, 7.83-8.14δ).

<u>Anal</u>. Calcd. for $C_{16}H_{28}O_4$: C, 70.05; H, 6.61. Found: C, 70.26; H, 6.44.

Pyrolysis of IV and conversion into ethyl β-benzoylacrylate (IVb)

1.40 g of the sulfoxide (IV) was heated in a 25 ml round-bottom flask fitted with a reflux condenser at 120° (2 Torr). After refluxing for two hours, the products were chromatographed on a column of silica gel with hexane (95%)—ethyl acetate (5%) as eluent to yield 0.93 g (98%) of ethyl β-benzoylacrylate, bp 119-120° (2 Torr), (lit (207) bp 192° (32 Torr)). The nmr (CDCl₃) spectrum was consistent with the <u>trans</u> isomer; 1.30δ and 4.27δ (t, 3; q, 2; J = 7.5 Hz, C$\underline{H}_2$C$\underline{H}_3$); 7.35δ (q, 2, J_{AB} =

19.2 Hz, <u>trans</u> C$\underline{H}$=C$\underline{H}$); (m, 2, 7.25-7.65δ); (m, 3, 7.80-8.10δ).

<u>Pyrolysis of V and conversion into ethyl-4-benzoyl-3-butenate</u>
<u>(Vc)</u>

In a similar fashion to the pyrolysis of IV, 1.1 g of the
sulfoxide (V) was heated at 140° (2 Torr). The crude product
was chromatographed, in identical fashion to IVb, to yield
0.44 g (51.5%) of the unsaturated ester (Vc), bp 152-156° (4
Torr). The nmr (CDCl$_3$) was consistent with the <u>cis</u> isomer:
1.32δ and 4.30δ (t, 3; q, 2; $\underline{J}$ = 7.5 Hz, C$\underline{H_2}$C$\underline{H_3}$); 3.4δ (broad
singlet at sweep with 500 Hz, 2, $\underline{J}$ <0.01 Hz, C$\underline{H_2}$CO$_2$Et); calcd.
~ 7.2δ (half visible q, 1, $\underline{J}_{AB}$ = 9.0 Hz, <u>cis</u> C$\underline{H}$=C$\underline{H}$); (m, 4,
7.30-7.68δ); (m, 2, 7.80-8.15δ).

<u>Anal</u>. Calcd.for C$_{13}$H$_{14}$O$_3$: C, 71.54; H, 6.47. Found: C,
71.80; H, 6.53.

<u>Conversion of V into ethyl δ-phenylvalerate (Vb)</u>

V Could be reduced to Vb under vigorous conditions with
zinc in acetic acid. 2.85 g of the sulfoxide (V) was dissolved
in 30 ml of ethanol to which 6.5 g of zinc and 35 ml of acetic
acid was added slowly so that the temperature did not exceed
30°. The reaction was stirred 6 hrs at 25° and then refluxed
for 4 hrs. The cooled reaction mixture was filtered and the
filtrate concentrated under vacuum. The residue was dissolved
in 100 ml of chloroform, washed with two 100 ml portions of
diluted aqueous sodium bicarbonate, dried (MgSO$_4$), and con-
centrated under vacuum. Chromatography on silica gel yielded

1.1 g (54%) of an oil eluted by hexane (95%)-ethyl acetate (5%), bp 143-147° (10 Torr), (lit (208) bp 159° (11 Torr)). The nmr (CDCl$_3$) was consistent with ethyl δ-phenylvalerate: 1.25δ and 4.17δ (t, 3; q, 2; $\underline{J}$ = 6.8 Hz, CH$_2$CH$_3$); (m, 8, 1.55-2.66δ); (s, 5, 7.30δ).

Conversion of VI into 2-carboxy-4-benzylcyclohexanone (VIb)

Using the modified reduction procedure that converted V into the valeric acid derivative (Vb), 1.70 g of VI was reduced to 0.53 g (41%) of VIb. The product was isolated as an oil by column chromatography on silica gel with hexane eluent. The nmr (CDCl$_3$) was consistent with a mixture of the keto and enol forms: 1.21δ and 4.13δ (t, 3; q, 2; $\underline{J}$ = 6.9 Hz, CH$_2$CH$_3$); 1.45-2.65δ (m, 9, ring protons of cyclohexane and PhCH$_2$);3.5-3.8δ (m, 0.4, 2-position proton deuterium exchangeable); 11.7δ (m, 0.6, enol proton, deuterium exchangeable); 7.25δ (s, 5, Ph).

<u>Anal</u>. Calcd. for C$_{16}$H$_{20}$O$_3$: C, 73.82; H, 7.74. Found: C, 73.60; H, 7.51.

Reaction of the ω-(methylsulfinyl)acetophenone with ethyl chloroformate; preparation of β-(methylsulfinyl)-α-(oxycarboethoxy)-styrene (VII)

4.55 g (25 mmol) of I was converted to its sodium salt by the reaction of 1 equivalent of sodium hydride in 60 ml of THF. The heterogeneous mixture was diluted to 250 ml with hexane at 0° and 2.7 ml of ethyl chloroformate in 50 ml of hexane was added dropwise. After 3 hrs at 25°, the reaction mixture was filtered,

concentrated under vacuum and chromatographed on a 2.5 x 28 cm silica gel column with ethyl acetate (50%)—hexane (50%) as the solvent. After elution of 1.1 g of phenylglyoxal, there was recovered 4.2 g of the styrene (VII) (66%) that showed only one component by tlc. The viscous oil was evacuated at 0.1 Torr for 8 hrs to give the following analysis: nmr (CDCl$_3$) 1.30δ and 4.25δ (t, 3; q, 2; $\underline{J}$ = 7.6 Hz, C$\underline{H_2}$CH_3); 2.84δ (s, 3, SOC$\underline{H_3}$); 6.85δ (s, 1, C$\underline{H}$(SOCH$_3$)); (m, 5, 7.20-7.68δ).

Anal. Calcd. for C$_{12}$H$_{14}$O$_4$S: C, 56.69; H, 5.55; S, 12.55. Found: C, 56.75; H, 5.40; S, 12.68.

Reaction of the ω-(methylsulfinyl)acetophenone anion with ethylacetate; preparation of ω-acetoxy-ω-(methylmercapto)-acetophenone (VIII)

To 25 mmol of ω-(methylsulfinyl)acetophenone anion, generated in identical fashion to the reaction yielding VII, was added 2 equivalents of ethyl acetate. After 3 hrs reaction time, the reaction was washed with 200 ml of saturated ammonium chloride solution, dried (MgSO$_4$) and concentrated. The yellow oil residue was distilled under vacuum to yield 3.90 g (70%) of VIII, bp = 109-111°C (0.2 Torr), (lit (60) bp 98-100° (0.1 Torr)). The sample was identical to an authentic sample prepared by Pummerer rearrangement of I in acetic anhydride (2, 60).

Reaction of ω-(methylsulfinyl)acetophenone anion with acetyl halides; preparation of α-acetoxy-β-(methylsulfinyl)styrene (IX)

In identical fashion to the preparation of VII, 25 mmol of the anion of I was treated with 1 equivalent of acetyl chloride. After 5 minutes, the reaction was filtered, concentrated under vacuum at 25° and chromatographed on a silica gel column with (50-50) hexane-ethyl acetate. The initial component eluted was 1.62 g (29%) of VII, followed by 3.10 g (55.6%) of IX, as a colorless, unstable oil. An analytical sample of IX could not be prepared due to slow rearrangement into VII. The sample was 1/2 decomposed after three days at room temperature. The nmr (CDCl$_3$) of IX was consistent with a single stereoisomer: 2.28δ (s, 3, CH$_3$CO$_2$); 2.75δ (s, 3, SOCH$_3$); 6.79δ (s, 1, CH(SOCH$_3$)); (m, 5, 7.20-7.65δ). Comparable results were obtained with acetyl fluoride in hexane or ether solvents.

Base-catalyzed rearrangement of IX into VII

To a tetrahydrofuran solution containing 2.0 g of IX and 5 ml of solvent was added 15 mg of sodium methoxide. The mixture was stirred under a nitrogen atmosphere at 25° for 1 hr and the solvent removed under vacuum to yield 2.0 g of yellow oil residue. The crude nmr indicated complete conversion to VII. The identical rearrangement under the catalysis of mineral acid or boron trifluoride etherate was only 1/3 to 1/2 complete after 1 hr.

Addition of dibenzoylmethane anion to methylsulfinyl chloride (209); Pummerer rearrangement and hydrolysis of adduct to yield diphenyltriketone hydrate (X)

In a flask fitted with a nitrogen inlet and a pressure-equalizing side-arm, 2.25 g (10 mmol) of dibenzoyl methane was converted to the diketone sodium salt with 1 equivalent of sodium hydride in 90 ml of tetrahydrofuran. The diketone salt solution was added directly to 1.48 g (15 ml) of methylsulfinyl chloride in 200 ml of anhydrous ether maintained at 0°C under a nitrogen atmosphere. The reaction was allowed to come to room temperature. After stirring for 1 hr, the reaction was poured into 300 ml of ice water; phases separated and the aqueous phase extracted with a second 100 ml portion of ether. The ether was evaporated and yellow oil residue heated in 300 ml of 2$\underline{\text{N}}$ hydrochloric acid at 90° for 1 1/2 hrs. The cooled solution was extracted with three 100 ml portions of ethyl acetate. The organic phase was dried (MgSO$_4$) and concentrated to yield a brown tar. Column chromatography on silica gel with 30% ethyl acetate-70% hexane yielded 1.42 g of diphenyltriketone as a mixture of hydrate and anhydrous form. The hydrate (X) was crystallized from 0.2$\underline{\text{N}}$ acetic acid solution as a white powder, mp 86-89° (lit (210) mp 90°). The spectral features of X were identical to an authentic sample prepared by the method of J. D. Roberts (210).

Preparation of the methyl hemimercaptal of phenylglyoxal (XI)

ω-(Methylsulfinyl)acetophenone was converted to XI by
Pummerer rearrangement in aqueous-dimethyl sulfoxide solution
under hydrochloride acid-catalysis as previously described (16).

Reaction of anhydrous phenylglyoxal with methyl mercaptan;
preparation of XI

Anhydrous phenylglyoxal was prepared by the method of Russell
and Mikol (58). In a flask, fitted with a nitrogen inlet and a
1500 ml Dry Ice condenser and Dean Stark trap, 150 ml of benzene
was saturated with hydrogen chloride. To the benzene was added
4.56 g (34 mmol) of the anhydrous phenylglyoxal, followed by the
addition of 30 ml of methyl mercaptan. The yellow glyoxal color
was immediately discharged on addition of the thiol. The re-
action was stirred for 2 hrs with reflux under the Dry Ice con-
denser. No azeotroping of water occurred. The benzene was re-
moved under vacuum to yield 5.80 g (95%) of crystals from hexane
of the methyl hemimercaptal of phenylglyoxal, mp 105°, (lit (16)
mp 101°). The product was identical to an authentic sample of XI.

Under identical reaction conditions, the hemihydrate of
phenylglyoxal yielded 59% of XI, which was separated from unre-
acted glyoxal by hexane elution on a silica gel column.

Treatment of phenylglyoxal hydrate (XIII) with methyl mercaptan
under acid-catalysis

The hydrate of phenylglyoxal, mp 80-82°, was prepared accord-
ing to the directions of Sisido and Nozaki (211). Under

identical conditions to the reaction with anhydrous phenyl-
glyoxal, 1.22 g (8 mmol) of XIII was refluxed for a period of 8
hrs in the presence of 10 ml of methylmercaptan in 40 ml of
benzene. The crude product was recovered by chromatography
with ethyl acetate (10%)-hexane (90%) on a silica gel column to
yield 769 mg (71.5%) of phenylglyoxal (weighed as the anhydrous
material), 27 mg (1.6%) of phenylglyoxal methyl mercaptal (XII)
and 14 mg (1%) of phenylglyoxal hemimercaptal (XI).

Acid-catalyzed disproportionation of the methyl hemimercaptal
of phenylglyoxal (XI); preparation of phenylglyoxal methyl
mercaptal (XII)

To 50 ml of water was added 20 ml of 85% phosphoric acid,
and 5.55 g (30.5 mmol) of XI. The mixture was heated at 80-90°
for 3 hrs. On cooling, the mixture was diluted with 100 ml of
water, extracted with 300 ml of hexane and the hexane evaporated
to yield a semi-solid yellow residue. The residue was dissolved
in 200 ml of chloroform, extracted by 200 ml of aqueous bi-
carbonate (pH = 8) and the aqueous phase discarded. After
drying (MgSO$_4$), the chloroform was evaporated and the residue
crystallized from hexane to yield 2.85 g (44%) of the methyl
mercaptal of phenylglyoxal (XII), mp 67°, (lit (16) mp 66-67°).

When 7.5 g of the methyl hemimercaptal of phenylglyoxal (XI)
was refluxed for 8 hrs, under a Dry Ice condenser fitted with a
Dean Stark trap, in 200 ml of benzene containing 30 ml of methyl
mercaptan and under the continuous passage of a stream of

hydrogen chloride, there was no observed azeotroping of water. Removal of solvent and chromatography on silica gel yielded 2.94 g (34%) of XII, 0.93 g (12%) of recovered XI and 2.50 g (39%) of phenylglyoxal hydrate (weighed as anhydrous material). Mercaptan exchange reaction of the methyl hemimercaptal of phenylglyoxal (XI) in 85% phosphoric acid media; preparation of XIa, b

To 5.55 g (30.4 mmol) of XI suspended in 10 ml of 85% phosphoric acid and 2.5 ml of water was added 4.65 of thiophenol. The mixture was stirred at 40° for 24 hrs, diluted with 200 ml of water and neutrallized with sodium bicarbonate. The neutralized mixture was extracted with two 100 ml portions of chloroform, dried (MgSO₄) and chloroform evaporated to yield a light yellow oil residue which solidified on standing. Crystallization of the residue from ethanol (10%)-hexane (90%) yielded 5.85 g (89%) of phenyl hemimercaptal of phenylglyoxal (XIa), mp 92-93°. The nmr (CDCl₃) was consistent with XIa: (AX quartet with δA = 4.27, deuterium oxide exchangeable, δX = 6.20, J_{AX} = 9.5 Hz, C$\underline{H}$(O$\underline{H}$)); (m, 8, 7.15-7.65δ); (m, 2, 7.82-8.05δ).

Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 68.84; H, 4.95; S, 13.10. Found: C, 68.59; H, 5.05; S, 13.02.

In identical fashion XI was converted to ethyl hemimercaptal of phenylglyoxal (XIb) in 65% yield, mp 78°. The nmr (CDCl₃) is consistent with the structure of XIb: (AX quartet with δA = 4.14, deuterium oxide exchangeable, δX = 6.03, J_{AX} = 9.1 Hz, C$\underline{H}$(O$\underline{H}$)).

Anal. Calcd. for $C_{10}H_{12}O_2S$: C, 61.21; H, 6.17; S, 16.31. Found: C, 60.97; H, 6.25; S, 16.24.

Preparation of the ethanedithiol dimercaptal of phenylglyoxal (XIV)

The methyl hemimercaptal of phenylglyoxal (XI), 6.0 g (33 mmol), was dispersed in 60 ml of 85% phosphoric acid. Ethane-1, 2-dithiol, 6.1 ml, was added and the solution stirred at 50° for 18 hrs. The solution was poured into 300 ml of 0.5N sodium hydroxide and extracted with two 100 ml portions of chloroform. The chloroform extracts were washed with 100 ml of water, dried (MgSO₄), concentrated and crystallized from chloroform (30%)-ethanol (70%) to give 8.8 g (77%) of colorless cubic crystals, mp 178°. The nmr (CDCl₃) of the product failed to distinguish between the possibility of a bis-1,3-dithiolane, structure a, and the bis-1,4-dithiane, structure b. The product can be identified by a singlet methine resonance at δ4.95 (s, 1, CH⟨S/S⟩). The mass spectrum (70 eV) m/e (relative intensity); 286 (66), 194 (100), 181 (29), 166 (15), 121 (59), 105 (9); metastable peaks at 142.0 (194→166) and 131.6 (286→194) does not uniquely distinguish between structures a and b.

Structure a is most consistent with the ions m/e = 105 and 181. However, the predominant ion m/e = 194 supports structure b. Recently, D. L. Coffen, et al. (134) has carried out a mass spectra ring-cleavage study of bis-1,3-dithiolanes and bis-1,3-dithianes. The exclusive mode of fragmentation for the
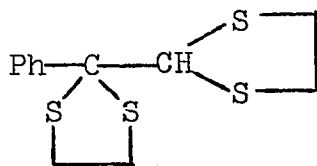
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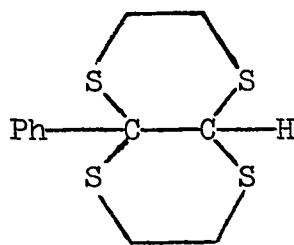
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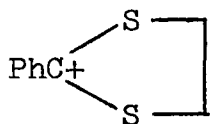
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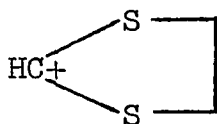
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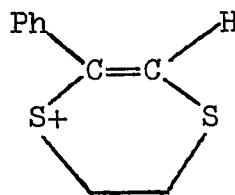
194

bis-1,3-dithiolanes of biacetyl and glyoxal was symmetrical C-C

bond cleavage to exhibit, in addition to the molecular ion peak,

only one intense peak with $\underline{m}/\underline{e}$ = 1/2 M^+. By comparison in this

case, the fused bicyclic structure $\underline{b}$ appears more likely for

XIV.

<u>Anal</u>. Calcd. for $C_{12}H_{14}S_4$: C, 50.35; H, 4.93; S, 44.72.

Found: C, 50.38; H, 5.07; S, 44.59.

<u>Preparation of the ethylene glycol diacetal of phenylglyoxal</u>

(XV)

In a flask equipped with a Dean Stark trap was placed 200

ml of benzene, 75 mmol of the methyl hemimercaptal of phenyl-

glyoxal, 1 equivalent of ethylene glycol and 20 g of powdered

mercuric chloride. The reaction mixture was dehydrated under

reflux for 18 hrs. The solution was filtered of inorganic salt

and concentrated to a yellow oily residue. The oily residue
was dissolved in 200 ml ether, extracted with 200 ml of saturated
aqueous sodium bicarbonate, dried (MgSO$_4$) and concentrated to a
semi-solid residue that was recrystallized from tetrahydrofuran-
water (1:1) solvent to yield 19.8 g (58.5%) of white crystals,
mp 113°, of the bis-acetal. As in the case of XIV, the nmr
(CDCl$_3$) spectrum could not be unequivocally interpreted in
terms of the bis-1,3-dioxylane, structure a, as opposed to the
bis-1,4-dioxane, structure b. The product can be identified by
a singlet methine resonance at δ5.13 (s, 1, C$\underline{H}$). The mass
spectrum (70 eV) m/e (relative intensity) 222 (12), 194 (3),
162 (1), 149 (11), 123 (45), 122 (9), 105 (100), 77 (48), 73
(8); metastable peaks at 169.0, 112.9, 100.0, 90.4, 68.1, 56.4,
50.9, seems to clearly indicate a preference for structure a
over b. Unfortunately the predominant ion (m/e = 105) is
derived from both the fragments of m/e = 149 and 162.
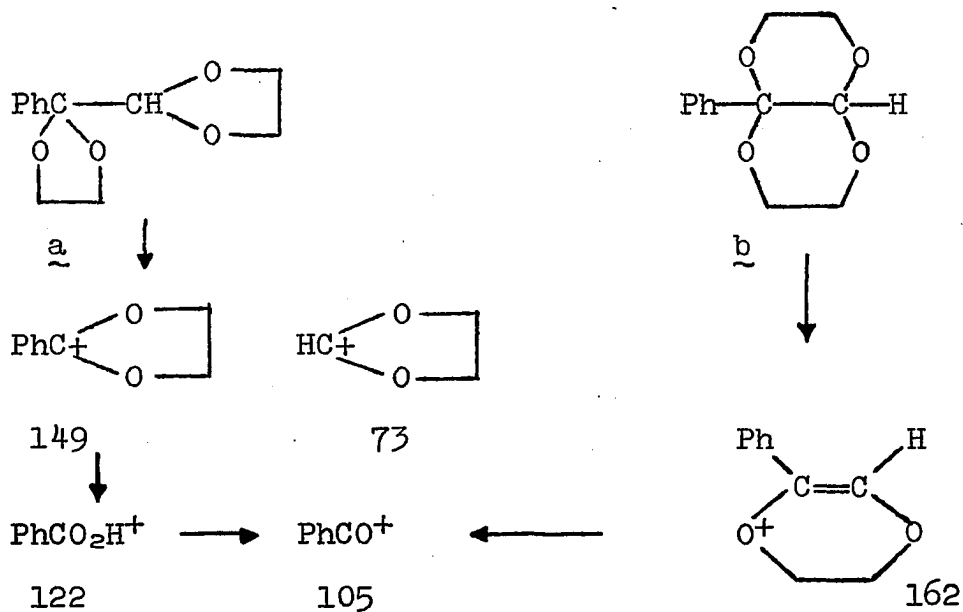
<u>Anal</u>. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.03; H, 6.42.

<u>Preparation of ω-chloro-ω-(methylmercapto)acetophenone XVI</u>

To 48.6 g (266 mmol) of ω-(methylsulfinyl)acetophenone in 250 ml of methylene chloride at 0° was added 19.5 ml of thionyl chloride (275 mmol) over a 5 min period. The reaction flask was swept with a stream of dry nitrogen and stirred for 4 hrs to complete the elimination of sulfur dioxide and hydrogen chloride. A 10 ml aliquot was withdrawn and diluted to 25 ml with methylene chloride. This solution was filtered through a bed (1:1) of magnesium sulfate and sodium bicarbonate, concentrated and distilled in a short-path still to yield 0.73 g of material, bp 105-108° (2 Torr), nmr (CCl$_4$) 6.40δ (s, 1, C$\underline{H}$(Cl)SCH$_3$); 2.18δ (s, 3, SC$\underline{H}_3$). The remaining bulk-product could be distilled, but slowly decomposed at room temperature. However, it could be stored for three months at -10° with little decomposition if exposure to light and air was avoided.

<u>Conversion of ω-chloro-ω-(methylmercapto)acetophenone (XVI) into</u>
<u>the methyl mercaptal of phenylglyoxal (XII); method of choice</u>
<u>for the preparation of XII and XVII</u>

A solution of 260 mmol of ω-chloro-ω-(methylmercapto)aceto-phenone in 250 ml of methylene chloride was prepared as previously described. The flask was equipped with a Dry Ice-carbon tetrachloride condenser. To the solution at 0° was added 50 g of methyl mercaptan over a period of 20 minutes. The solution

was stirred and swept with a stream of nitrogen to remove the hydrogen chloride formed. After 1 hr the solution was allowed to reflux at approximately room temperature for 2.5 hrs. The solvent was removed by water aspirator vacuum to give a solid that crystallized from pentane (50%)-hexane (50%) to yield 52.0 g of the mercaptal, mp 67° (94%). Recrystallization from ethanol raised the mp to 69° (lit (16) mp 68°).

In identical fashion, XVI was converted to ethyl-methyl mixed mercaptal of phenylglyoxal (XVII) in 84% yield, mp 33°, nmr (CDCl$_3$): 5.43δ (s, 1, C$\underline{H}$$\overset{S}{\underset{S}{<}}$); 2.05δ (s, 3, SC$\underline{H}_3$); 2.68δ and 1.27δ (q, 2; t, 3, $\underline{J}$ = 7.6 Hz, C$\underline{H}_2$C$\underline{H}_3$); (m, 3, 7.25-7.50δ); (m, 2, 7.83-8.15δ).

$\underline{Anal}$. Calcd. for C$_{11}$H$_{14}$OS$_2$: C, 58.40; H, 6.24; S, 28.29. Found: C, 58.20; H, 6.20; S, 28.24.

Alternative method for the in situ preparation of XVI and conversion into the methyl mercaptal of phenylglyoxal in methyl mercaptan solvent

In 100 ml of methyl mercaptan in a separatory funnel was suspended 11 g (60 mmol) of the hemimercaptal of phenylglyoxal (XI). The separatory funnel was immersed in a bath at -23° and was equipped with a condenser filled with a slush of carbon tetrachloride. Hydrogen chloride was slowly passed through the solution. After 35 min, the hemimercaptal had dissolved and 3 ml of water was drained from the separatory funnel. The addition of hydrogen chloride was terminated, the -23° bath removed, and the solution refluxed under vacuum at 0° for 10 hrs.

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The excess methyl mercaptan was allowed to evaporate to give an oily residue that was dissolved in hexane and crystallized to yield 0.5 g of the mercaptal (XII) (74%), mp 65-67°.

Preparation of 2-benzoyl-m-dithiane (XVIII)

ω-(Methylsulfinyl)acetophenone (3.64 g, 20 mmol) was converted to ω-chloro-ω-(methylmercapto)acetophenone (XVI) by 1.45 ml of thionyl chloride in 200 ml of methylene chloride. To this reaction product was added 1.40 g (14 mmol) of 1,3-propanedithiol. The reaction mixture was swept with nitrogen for 3 hrs, the solvent evaporated, and the residue chromatographed on a silica gel column. The material was eluted by hexane (95%)-ethyl acetate (5%). The separation was followed by tlc. The fractions containing the major component were concentrated and the product crystallized from hexane-ethyl acetate to give 1.5 g (51% based on dithiol) of the m-dithiane, mp 80-83°, (lit (137) mp 80-82°). The nmr (CDCl$_3$) spectrum was consistent with the assigned structure: 1.90-2.30δ (m, 2); 2.35-2.85δ (m, 2); 3.20-3.60δ (m, 2); 5.19δ (s, 1); (m, 3, 7.25-7.60δ); (m, 2, 7.80-8.05δ); mass spectrum (70 eV) m/e (relative intensity) 224 (22), 119 (100), 105 (85).

Anal. Calcd. for C$_{11}$H$_{12}$OS$_2$: C, 58.92; H, 5.40; S, 28.54. Found: C, 58.66; H, 5.25; S, 28.77.

Preparation of 2-benzoyl-1,3-dithiolane (XIX)

The same procedure as reported for XVIII was employed.

Elution from a silica gel column and crystallization of the product with hexane (70%)-ethyl acetate (30%) yielded 76% of XIX (based on ethylenedithiol), mp 136-139°. Recrystalliza-tion from chloroform gave mp 138.5-139.5°. The nmr (CDCl$_3$) was consistent with XIX: 2.95δ (broad s, 1.6); 2.12δ (broad s, 2.4); 5.43δ (s, 1); (m, 3, 7.25-7.60δ); (m, 2, 7.85-8.15δ). Mass spectrum (70 eV , $\underline{m}/\underline{e}$ (relative intensity) = 210 (trace), 209 (29), 166 (35), 165 (30), 137 (20), 105 (100), 93 (5), $\underline{m}$* = 130 (209 → 165), 113.1 (166 → 137), 66.5 (166 → 105), 56.5 (105 → 77).

$\underline{Anal}$. Calcd for C$_{10}$H$_{10}$OS$_2$: C, 57.14; H, 4.80; S, 30.45. Found: C, 56.99; H, 5.01; S, 30.26.

Conversion of XVI to the methyl acetal of phenylglyoxal (XX)

ω-(Methylsulfinyl)acetophenone (2.25 g, 13 mmol) was con-verted to ω-chloro-ω(methylmercapto)acetophenone in 50 ml of methylene chloride with 0.95 ml (1 equivalent) of thionyl chloride. The reaction mixture was swept with nitrogen for 30 min to eliminate acidic fumes. Anhydrous methanol (80 ml) was added and the reaction mixture was allowed to stir for 30 min under a stream of nitrogen. The solvents were removed by vacuum evaporation at 70° to yield 2.15 g of a yellow oil. Distilla-tion yielded 1.98 g of material, bp 60-62° (0.3 Torr), identi-cal to a sample prepared by the method of Moore (76). The nmr (CDCl$_3$) of the crude preparation indicated pure acetal: 3.42δ (s, 6, OC$\underline{H_3}$); 5.18δ (s, 1, C$\underline{H}{<}^O_O$); (m, 3, 7.28-7.55δ); (m, 2,

7.95-8.20δ).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.81; H, 6.63.

Reaction of diazomethane with ω-(methylsulfinyl)acetophenone (I); Pummerer rearrangement formation of ω-(methoxy)-ω-(methylmercapto)acetophenone and disproportionation into XII and XX

ω-(Methylsulfinyl)acetophenone (4.55 g, 25 mmol) was dissolved in 150 ml of tetrahydrofuran. To the cooled solution, 0°, was added a 10% excess of freshly distilled diazomethane in 150 ml of ether. In a dropwise fashion, 2.5 ml of boron trifluoride etherate was added and rapid evolution of nitrogen occurred and was complete in 5 min. In the absence of Lewis acid catalyst, no reaction occurred. The reaction was immediately washed with three 100 ml portions of saturated aqueous bicarbonate solution, after the addition of 10 ml of acetic acid, to destroy excess diazomethane. The ether extracts were dried (MgSO₄) and chromatographed by preparative tlc. The crude nmr, prior to purification by tlc, indicated a 40/60 mixture of XII to XX. No evidence for ω-(methoxy)-ω-(methylmercapto)acetophenone was observed. Purification yielded 1.28 g (26%) of XII and 1.92 g (42.6%) of XX. Considerable immobile polymer was not recovered.

Reaction of ω-methyl-ω-(methylsulfinyl)acetophenone (Ia) with thionyl chloride; preparation of 1-phenyl-2-(methylmercapto)-3-(chloropropanone (XXII)

In identical fashion to the preparation of XVI, 9.75 g

(50 mmol) of Ia was dissolved in 200 ml of methylene chloride

and treated with one equivalent (6 g) of thionyl chloride.

After 2 hrs, acidic fumes had ceased and the solvent was re-

moved to yield 10.9 g of crude yellow residue. The crude nmr

($CDCl_3$), Figure 9, showed a major component (~85% by inter-

gration) containing a complex ABC pattern ($C\underline{H}$-$C\underline{H_2}$-Cl) which is

overall consistent with XXII. In addition, the spectrum re-

vealed (~10%) the presence of 1-phenyl-2-(methylmercapto)pro-

panone (Ib), identified by comparison to an authentic sample

(2). Analytical tlc reveal, as major components, two spots

with ΔR_f = 0.02, cyclohexane (50%)-hexane (50%) optimum solvent.

The small difference in R_f values prevent separation by chroma-

tography technique, which included numerous attempts by gpc.

Attempted distillation resulted in rapid elimination of hydro-

gen   chloride and polymerization. The crude mass spectrum

is consistent with XXII: (16 eV) $\underline{m/e}$ (relative intensity) = 214

(12) [$M+2^+$= 36% of M^+, indicative of chlorine], 178 (28), 105

(100).

Preparation of 1-phenyl-2,3-di(methylmercapto)propane (XXIIa)

from XXII

To a freshly, in situ generated chloroform solution of XXII,

prepared from 1.96 g (10 mmol) of Ia, was added 15 ml of methyl-

mercaptan and 0.75 ml of triethylamine base catalyst. The re-

action was allowed to stir for 3 hrs under a nitrogen atmosphere;

solvents were evaporated under vacuum and taken up in 100 ml

of ether. The ether was washed with two 100 ml portions of dilute aqueous bicarbonate, dried (MgSO₄) and concentrated to yield a yellow semi-solid residue. The residue was eluted eight times on preparative tlc plates with cyclohexane (50%)-pentane (50%). From the plate was recovered 0.14 g (~7.7%) of Ib and 1.87 g (83%) of 1-phenyl-2,3-di(methylmercapto)propanone (XXIIa), which was recrystallized from pentane to yield 1.80 g of colorless needles, mp = 44-45°. The nmr (CDCl₃) was consistent with XXIIa: 1.97δ (s, 3, SC$\underline{H}_3$); 2.13δ (s, 3, SC$\underline{H}_3$); (major feature of spectrum was an ABX pattern, 3, due to C$\underline{H}$(SCH₃)C$\underline{H}_2$(SCH₃), $\delta A = 3.26$, $\delta B = 2.87$, $\delta X = 4.41$; $\underline{J}_{AX} = 8.1$ Hz, $\underline{J}_{BX} = 6.9$ Hz, $\underline{J}_{AB} = 13.5$ Hz); (m, 3, 7.3-7.55δ); (m, 2, 7.94-8.12δ), mass spectrum (70 eV) $\underline{m}/\underline{e}$ (relative intensity) 226 (50), 179 (90), 163 (15), 121 (75), 105 (100), $\underline{m}^* = 142$ (226 → 179$^+$ + 47·).

$\underline{\text{Anal}}$. Calcd. for C₁₁H₁₄OS₂: C, 58.40; H, 6.24; S, 28.29. Found: C, 58.36; H, 6.23; S, 28.25.

Alternative method for the preparation of 1-phenyl-2,3-di-(methylmercapto)propanone (XXIIa); Reaction of methyl mercaptal of phenylglyoxal (XII) with diazomethane

By an analogous procedure to that devised by Schoenberg and Praefike (145) for reaction of diazomethane with orthothio-esters, 3.18 g (15 mmol) of XII was dissolved in 150 ml of ether and cooled to 0°. To the solution was added diazomethane, prepared as a 80 ml distillate in ether from 1.4 equivalents

of diazald, and 10 drops of boron trifluoride etherate cata-
lyst. After 1 hr at 0°, the diazomethane color disappeared;
3 ml of acetic acid was added and the ether washed with 100
ml of saturated aqueous sodium bicarbonate. After drying
(MgSO₄), the ether was evaporated to yield a yellow oil residue.
The residue was chromatographed on a column of silica gel with
hexane (98%)-ethyl acetate (2%) to yield 1.83 g (55%) of XXIIa,
1.19 g (37.5%) of recovered XII, and a trace of phenylglyoxal.
Immobile polymer was not recovered.

Conversion of XII into 1-phenyl-2,2-di(methylmercapto)ethanol
(XXIVa)

To 1.4 g of sodium borohydride, dissolved in 200 ml of
water, was added 10.6 g (50 mmol) of the methyl mercaptal of
phenylglyoxal (XII). The reaction was stirred for 6 hrs at
room temperature, neutralized with an excess of ammonium
chloride and extracted with three 200 ml portions of ether.
After drying (MgSO₄), the ether was evaporated to yield 10.65 g
of a colorless oil that contained a single component by tlc.
An analytical sample was prepared by distillation, bp 78-80°
(0.2 Torr). The nmr (CDCl₃) was consistent with XXIVa: (AB
quartet with $\delta A = 3.56$, $\delta B = 4.55$, 2; $J_{AB} = 9.0$ Hz, C(OH)$\underline{H}$-C$\underline{H}$);
1.88δ and 1.98δ(d, 6, SC$\underline{H}_3$); 3.36δ (s, 1, O$\underline{H}$).

Anal. Calcd. for $C_{10}H_{14}OS_2$: C, 56.07; H, 6.59; S, 29.88.
Found: C, 55.99; H, 6.73; S, 29.88.

In identical fashion, XII was reduced with sodium boro-
deuteride to afford a quantitative conversion into 1-phenyl-1-

deuterio-2,2-di(methylmercapto)ethanol (XXIVe).

Preparation of 1,1-di(methylmercapto)-2-phenyl-2-propanol (XXIVb)

To methylmagnesium iodide, prepared from 1.7 g of magnesium and 21.3 g of methyl iodide in 200 ml of ether, was added 10.6 g (50 mmol) of the methyl mercaptal of phenylglyoxal (XII). The product was isolated as a pale yellow oil after neutralization with ammonium chloride and further extraction with ether, bp 130-133° (0.7 Torr) (69%) or by column chromatography on silica gel with hexane (95%)-ethyl acetate (5%) to yield 93% of the product (XXIVc). The crude product was pure by nmr (CDCl$_3$) analysis: 1.78δ and 1.95δ (d, 6, SC$\underline{H}_3$); 1.64δ (s, 3, C(OH)C$\underline{H}_3$); 3.30δ (s, 1, O$\underline{H}$); 3.72δ (s, 1, C$\underline{H}{<}^S_S$).

<u>Anal.</u> Calcd. for C$_{11}$H$_{16}$OS$_2$: C, 57.88; H, 7.07; S, 28.04. Found: C, 57.78; H, 7.04; S, 28.28.

Preparation of 1,1-di(methylmercapto)2-phenyl-2-butanol (XXIVc)

The ethyl Grignard reaction, following the procedure described for 1,1-di(methylmercapto)-2-phenyl-2-propanol (XXIVc), yielded a product isolated as an oil in 89% yield by chromatography and 71% by distillation at 137-138° (0.7 Torr); nmr (CDCl$_3$): 0.78δ and 2.08δ (t, 2; q, 3; $\underline{J}$ = 7.5 Hz, C$\underline{H}_2$C$\underline{H}_3$); 3.16δ (s, 1, O$\underline{H}$); 3.79δ (s, 1, C$\underline{H}{<}^S_S$); 1.80δ and 1.97δ (d, 6, SC$\underline{H}_3$).

<u>Anal.</u> Calcd. for C$_{12}$H$_{18}$OS$_2$: C, 59.49; H, 7.49; S, 26.42. Found: C, 59.27; H, 7.48; S, 26.41.

Preparation of 1,1-diphenyl-2,2-di(methylmercapto)ethanol (XXIVd)

Addition of 50 mmol of methyl mercaptan of phenylglyoxal (XII) to 70 mmol of phenyl magnesium bromide yielded the product as an oil (86%) by chromatography on silica gel with hexane (95%)-ethyl acetate (5%), and by distillation at 155-158° at 0.7 Torr (66%); nmr (CDCl$_3$): 1.81δ (s, 6, SC$\underline{H}_3$); 3.53δ (s, 1, O$\underline{H}$); 4.22δ (s, 1, C$\underline{H}\underset{S}{\overset{S}{<}}$); (m, 10, 7.10-7.65$\delta$).

Anal. Calcd. for C$_{16}$H$_{18}$OS$_2$: C, 66.19; H, 6.25; S, 22.05. Found: C, 66.42; H, 6.23; S, 21.93.

Conversion of XVIII into 2-(α-hydroxybenzyl)-m-dithiane (XVIIIa)

By a modification of the procedure utilized for the preparation of XXIVa, 1.90 g (8.5 mmol) of XVIII was dissolved in 80 ml of 95% ethanol and treated with 6.3 mmol of sodium borohydride. After 9 hrs the reaction was neutralized with ammonium chloride, diluted with 100 ml of water and extracted with three 50 ml portions of ether. The ether was dried (MgSO$_4$) and concentrated to a colorless oil, which solidified on standing. Recrystallization of the residue from ethyl acetate (10%)-hexane (90%) yielded 1.88 g (98.5%) of fine colorless plates, mp 70-72° (lit (137), mp 70.5-71.6°).

Conversion of XIX into 2-(α-hydroxybenzyl)-1,3-dithiolane (XIXa)

In identical fashion to the preparation of XVIIIa, 2.1 g (10 mmol) of XIX was reduced with sodium borohydride. The crude product was purified by column chromatography on silica gel with ethyl acetate (5%)-hexane (95%) to yield 1.83 g (86%) of color-

less oil. All attempts to crystallize the product failed. Attempted distillation resulted in pyrolysis at 170° (0.2 Torr) into multiple unidentified products. The nmr (CDCl$_3$) spectrum was consistent with XIXa: 1.92-7.02δ (m, 2); 2.48-2.57δ (m, 7); (AB quartet with δA = 2.63, δB = 3.95, 2, J_{AB} = 6.1 Hz); 3.50δ (s, 1, O$\underline{H}$); 7.19δ (s, 5).

Anal. Calcd. for C$_{10}$H$_{12}$OS$_2$: C, 56.60; H, 5.70; S, 30.16. Found: C, 56.76; H, 5.82; S, 30.11.

Conversion of XX into 1-phenyl-2,2-dimethoxy ethanol (XXa)

By the identical procedure utilized for the preparation of XXIVa, 2.2 g (12.2 mmol) of acetal (XX) was reduced with sodium borohydride to yield on distillation 2.05 g (98%) of α-hydroxy-acetal (XXa), bp 75-78° (0.25 Torr); nmr (CDCl$_3$) 3.20δ (s, 6, OC$\underline{H}_3$); 4.24-4.59δ (m, 3, deuterium exchange simplified the spectrum to an AB quartet, δA = 4.19, δB = 4.54, J_{AB} = 6.7 Hz, C$\underline{H}$(OD)-C$\underline{H}\langle^O_O$); (m, 5, 7.15-7.47δ).

Anal. Calcd. for C$_{10}$H$_{14}$O$_3$: C, 65.91; H, 7.74. Found: C, 65.87; H, 7.58.

Preparation of mandelaldehyde (XXVa)

To 80 ml of dioxane solution containing 6.42 g (30 mmol) of 1-phenyl-2,2-di(methylmercapto)ethanol (XXIVa) was added 80 ml of water, 9.8 g (38.5 mmol) of iodine and 3.5 g of sodium bicarbonate. After stirring for 3 hrs at 25°, a 2nd portion of iodine, 5.1 g (20 mmol), and sodium bicarbonate, 2.5 g, was added. In 1.5 hrs the solution was colorless, at which time it

was diluted with 100 ml of saturated aqueous sodium chloride.
Extraction of the solution with four 50 ml portions of chloro-
form, drying (MgSO$_4$), and evaporation of solvent left an oil
which crystallized from hexane to yield 3.60 g (88%) of the
dimeric mandelaldehyde, mp 137-138° (lit (70, 71) 134-137°).
The material gave no carbonyl absorption in the infrared;
nmr (d$_6$-DMSO) 4.5δ and 5.6δ (m, 2, C$\underline{H}$-C$\underline{H}$); 3.2δ, 6.2δ and 6.8δ
(broad singlets, 1 total, O$\underline{H}$). The nmr spectrum suggested a
mixture of <u>cis</u>-<u>trans</u> isomers of the 1,4-dioxane structure, by
comparison to an authentic sample (Aldrich) of <u>cis</u>-<u>trans</u> isomer
mixture of glycolaldehyde dimer. The infrared of the dimer
contained the following diagnostic bands: ν KBr (cm^{-1}) (relative
intensity) 3380 (s), 1455 (m), 1136 (s), 1070 (s), 1021 (s)
cm^{-1}. The mass spectrum at either 70 eV or 16 eV contained no
peaks higher than monomer: $\underline{m/e}$ (relative intensity) 136 (35),
107 (90), 105 (100), 77 (80). The deuterio derivative pre-
pared from XXIVe gave similar peaks of comparable intensity at
$\underline{m/e}$: 137, 138, 106 and 78.

<u>Anal</u>. Calcd. for C$_8$H$_8$O$_2$: C, 70.57; H, 5.92. Found: C,
70.70; H, 6.02.

When the preparation of XXVa was attempted in 50% aqueous
ethanol by iodine oxidative hydrolysis, the reaction required
13 hrs for an identical molar scale to consume all added
iodine. In addition to XXVa, the reaction yielded 1.74 g of
the ethyl hemiacetal of mandelaldehyde (PhCH(OH)CH(OH)OEt),

which was isolated by column chromatography on silica gel on elution with ethyl acetate (3%)-hexane (97%). On standing the hemiacetal rearranged to ω-(hydroxy)acetophenone (XXVI), mp 86-87° (lit (58) 85-86°). However, the hemiacetal was characterized by its nmr (CDCl$_3$) spectrum and was consistent with a mixture of diastereomeric epimers: (AB quartet, δA = 4.22, δB = 4.47, J_{AB} = 7.2 Hz, 2, C$\underline{H}$ (OH)C$\underline{H}$(OH)OEt); 3.1δ and 3.8δ (broad singlets, 2, O$\underline{H}$); 1.00δ and 3.58δ (t, 3; q, 2, J = 8.0 Hz, C$\underline{H}_2$C$\underline{H}_3$).

Preparation of atrolacetaldehyde (XXVb)

The reaction between 72 mmol of iodine and 40 mmol of 1,1-di(methylmercapto)-2-phenyl-2-propanol (XXIVb) was performed in the manner employed for the preparation of mandelaldehyde (XXVa). Vacuum distillation yielded 94% of the monomeric atrolactaldehyde, bp 116-120° (0.7 Torr). The structure was confirmed by infrared and nmr spectroscopy: νCCl$_4$ (1719 (C=O)cm^{-1}; nmr (CDCl$_3$) 1.57δ(s, 3, C$\underline{H}_3$); 4.08δ (s, 1, O$\underline{H}$); 9.43δ (s, 1, C$\underline{H}$O).

Addition of a drop of concentrated hydrochloric acid followed by evacuation at 2 Torr for 12 hrs led to a waxy solid, mp <27°, identified as pure dimer. The infrared (CCl$_4$) was void of carbonyl absorption: νCCl$_4$ (cm^{-1}) (relative intensity) 3395 (s), 2968 (m), 2940 (m), 1600 (w), 1037 (s), 1026 cm^{-1} (s). The nmr (CDCl$_3$) was consistent with the 1,4-dioxane structure: 1.30δ (s, 3, C$\underline{H}_3$); 3.42δ (broad singlet, 1, C$\underline{H}$(OH)); 3.93δ (broad singlet, 1, O$\underline{H}$, deuterium oxide exchangeable). The mass spectrum contained both monomer and dimer parent ions: $\underline{m/e}$ (170 eV) (relative intensity) 300 (65), 268 (50), 236 (55), 167 (15),

150 (70), 136 (30), 134 (15), 120 (10), 105 (100), 91 (90), 77 (60).

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.20; H, 6.46.

Preparation of 2-phenyl-2-ethylglycoaldehyde (XXVc)

Iodine oxidative hydrolysis of 50 mmol of XXIVa yield XXVc in 80% yield as the monomeric oil by distillation, bp 65-68° (0.7 Torr); ν·CCl$_4$ 1719 cm^{-1} (C=O); nmr (CDCl$_3$) 0.81δ and 1.97δ (t, 3; q, 2, J = 7.5 Hz, C$\underline{H_2}$C$\underline{H_3}$); 4.04δ (s, 1, O$\underline{H}$); 9.50δ (s, 1, C$\underline{H}$O).

Treatment of the monomer with a drop of hydrochloric acid and evacuation at 2 Torr for 12 hrs resulted in an increased viscosity of the oil. However, the nmr revealed that dimer was not formed, but rather a mixture of monomeric and polymeric forms. The mass spectrum of this material contained no dimer molecular ion: $\underline{m}$/$\underline{e}$ (16 eV, same pattern observed at 70 eV), (relative intensity) 223 (5), 210 (2), 194 (7), 180 (5), 164 (30), 146 (50), 134 (43), 105 (100), 77 (80).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.24; H, 7.24.

Preparation of benzilaldehyde (XXVd)

Treatment of XXIVd in identical fashion to the preparation of XXVa yielded from 16.4 mmol of XXIVd, 2.94 g (94%) of XXVd as an oily residue on work-up, which solidified on standing, mp 160-162° (lit (156, 157) 162-165); recrystallization from methanol

raised the mp 164-166°. Neither the crude oil product, nor the purified material gave evidence for carbonyl absorption: ν KBr (cm^{-1}) (relative intensity) 3360 (s), 3040 (w), 1595 (vw), 1492 (s), 1446 (s), 1139 (s), 1086 (s), 1035 (s), 1002(s), cm^{-1}. The molecular weight in tetrahydrofuran was found to be 406, indicating the material to be dimeric (Table 7). The nmr ($\underline{d}_6$-DMSO spectrum was consistent with a cis-trans mixture of 1,4-dioxane isomers: 3.60δ (broad singlet, 1, O$\underline{H}$); 5.9δ and 5.97δ (broad singlets, 1, C$\underline{H}$(OH)); 7.1-7.65δ (m, 10, Ph$_2$). The mass spectrum contained no molecular ions greater than monomer: $\underline{m}/\underline{e}$ (16 or 70 eV) (relative intensity) 212 (40), 107 (68), 105 (100), 77 (95).

Anal. Calcd. for C$_{14}$H$_{12}$O$_2$: C, 79.22; H, 5.70. Found: C, 79.19; H, 5.60.

Preparation of 1,1,3,3-tetraphenylglycerol (XXVII); condensation of disodiobenzophenone with dimethylformamide in liquid ammonia

Liquid ammonia (250 ml) was maintained under a Dry Ice condenser and a positive nitrogen pressure. Sodium, 2.30 g (100 mmol) was dissolved in the ammonia and 9.11 g (50 mmol) of benzophenone in 30 ml of ether added. After 20 min, 20 ml of dimethylformamide and 40 ml of ether was added slowly. The blue-black color of disodiobenzophenone slowly faded and was discharged completely in 15 min. The reaction mixture was stirred for an additional hour and then neutralized by the addition of 7 g of ammonium chloride. After evaporation of the ammonia, the residue was treated with 200 ml of water and extracted three times with 100 ml portions of ether. The solution

was dried (MgSO$_4$) and evaporated under vacuum to yield a residue that was purified by column chromatography on silica gel. Elution with hexane gave a trace of diphenylmethane, 0.83 g of benzophenone and 0.37 of benzhydrol. Elution with ethyl acetate (50%)—hexane (50%) yielded 8.25 g (83%) of the glycerol which could be crystallized from heptane, mp 195-197°; ν CHCl$_3$, 3450, 3550 cm^{-1} (OH); mass spectrum (70 eV), m/e = 396. The nmr (d$_6$-DMSO) was consistent with the structure of XXVII: 4.42δ (d, 1, J = 9.0 Hz, CH(OH), deuterium exchangeable); 5.85δ (d, 1, J = 9.0 Hz, CH(OH)), 6.55δ (broad singlet, 2, Ph$_2$COH, deuterium exchangeable); (m, 10, 6.70-6.95δ); (m, 10, 7.05-7.45δ).

<u>Anal</u>. Calcd. for C$_{27}$H$_{24}$O$_3$: C, 81.79; H, 6.10. Found: C, 82.01; H, 6.24.

The above procedure was repeated using fluorenone, xanthone, thioxanthone, and acridone in place of the benzophenone. Fluorenone yielded a mixture of fluorene and fluorenol while acridone gave mainly acridane. Xanthone and thioxanthone also gave mainly products of reduction, but the glycerols were also isolated in low yields.

<u>Preparation of β,β-di(methylmercapto)-α-methoxystyrene (XXVIII);</u>
<u>methylation phenylglyoxal methylmercaptal anion</u>

To a dispersion of 1.1 g of sodium hydride in 150 ml of tetrahydrofuran was added 5.3 g (25 mmol) of the methyl mercaptal of phenylglyoxal (XII). The reaction was maintained under a nitrogen atmosphere. After the conversion of the mercaptal to the sodium salt, 3.25 g of methyl sulfate was added dropwise.

The solution was stirred for 2 hrs, filtered, concentrated under vacuum and the residue dissolved in 200 ml of ether. The ether solution was washed twice with 50 ml of water and dried (MgSO$_4$). Removal of ether left a pale yellow oil that showed only one component by nmr and tlc. Distillation at 100° (0.2 Torr) gave 4.8 g (85%) product; nmr (CDCl$_3$) 2.09δ (s, 3, SC$\underline{H}_3$); 2.34δ (s, 3, SC$\underline{H}_3$); 3.40δ (s, 3, OC$\underline{H}_3$); 7.33δ (s, 5, Ph).

Anal. Calcd. for C$_{11}$H$_{14}$OS$_2$: C, 58.40; H, 6.24; S, 28.29. Found: C, 58.38; H, 6.05; S, 28.28.

Preparation of β,β-di(methylmercapto)-α-acetoxystyrene (XXIXa)

In a similar fashion to the preparation of XXVIII, reaction of 50 mmol of the enolate of ω,ω-di(methylmercapto)acetophenone with 3.9 ml of acetyl chloride yielded 10.4 g (82%) of a nearly colorless oil that distilled at 127-129° (0.35 Torr); nmr (CDCl$_3$) 2.03δ(s, 3); 2.16δ (s, 3), 2.30δ (s, 3), (m, 5, 7.16-7.60δ).

Anal. Calcd. for C$_{12}$H$_{14}$O$_2$S$_2$: C, 56.69; H, 5.55; S, 25.17. Found: C, 56.44; H, 5.71; S, 25.25.

Preparation of β,β-di(methylmercapto)-α-benzoylstyrene (XXIXb)

The sodium salt from 21.2 g (100 mmol) of ω,ω-di(methyl-mercapto)acetophenone (XII) was reacted in tetrahydrofuran solution with 13.4 ml of benzoyl chloride. After 25 min the solution was filtered, concentrated under vacuum, the residue dissolved in 200 ml chloroform and washed with 100 ml of aqueous saturated sodium bicarbonate. Removal of solvent left a yellow oil that crystallized from 95% ethanol to yield 29.4 g (93%) of

product as colorless crystals, mp 75°C; nmr (CDCl$_3$) 2.19δ (s,3, SC$\underline{H}_3$); 2.28δ (s,3,SC$\underline{H}_3$); (m, 8, 7.10-7.65δ); (m, 2, 7.97-8.18δ, o-benzoyl protons).

Anal. Calcd. for C$_{17}$H$_{16}$O$_2$S$_2$: C, 64.55; H, 5.10; S, 20.63. Found: C, 64.66; H, 5.01; S, 20.44.

Preparation of ω,ω,ω-tri(methylmercapto)acetophenone (XXX); reaction of phenylglyoxal methyl mercaptal anion with methane-sulfenyl chloride (166)

The methyl mercaptal of phenylglyoxal (XII), 42.4 g (200 mmol) in 200 ml of tetrahydrofuran, was added to 10 g of sodium hydride suspended in 1 liter of ether. After the evolution of hydrogen had ceased the solution was cooled to 0° and 19 g (230 mmol) of methanesulfenyl chloride in 50 ml of ether was added. The reaction mixture was stirred and allowed to come to room temperature and then poured into 500 ml of 0.01 $\underline{N}$ hydrochloric acid. The ether fraction was washed, dried (MgSO$_4$) and concentrated. Distillation yielded 36.8 g (71%) of the desired product, bp 129-130° (0.05 Torr); nmr (CDCl$_3$) 2.01δ (s, 9, SC$\underline{H}_3$), (m, 3, 7.17-7.55δ); (m, 2, 8.30-8.50δ). The mass spectrum contained a M+2 of 15% relative to the parent peak: $\underline{m/e}$ (70 eV) (relative intensity) 258 (37), 153 (100), 105 (100).

Anal. Calcd. for C$_{11}$H$_{14}$OS$_3$: C, 51.16; H, 5.47; S, 37.17. Found: C, 51.24; H, 5.67; S, 37.14.

Preparation of ω,ω-di(methylmercapto)-ω-succiniminoacetophenone

(XXXII); reaction of phenylglyoxal methyl mercaptal anion with

N-bromosuccinimide

The methyl mercaptal of phenylglyoxal (XII), 5.3 g (25 mmol)

was converted to the anion with one equivalent of sodium hydride

in 250 ml of THF. To this solution was added 4.45 g of N-

bromosuccinimide dispersed in 50 ml of tetrahydrofuran at 0°.

The reaction mixture was stirred for 3 hrs under a nitrogen

atmosphere, poured into 300 ml of water and the aqueous solution

extracted with four 100 ml portions of ether. The ether extracts

were washed, dried (MgSO$_4$), and concentrated to a residue that

crystallized from hexane (50%)—ethyl acetate (50%) to give 6.8 g

(87.5%) of product, mp 154-155°; nmr (CDCl$_3$) 2.08δ (s, 6, SC$\underline{H}_3$);

2.64δ (s, 4, N$\overset{CO-CH_2}{\underset{CO-CH_2}{}}$); (m, 3, 7.28-7.56$\delta$); (m, 2, 7.98-8.18$\delta$);

mass spectrum (70 eV) $\underline{m/e}$ (relative intensity) 309 (16), 262

(28), 204 (150), 158 (20), 105 (95).

$\underline{Anal}$. Calcd. for C$_{14}$H$_{15}$O$_3$S$_2$N (309.27): C, 54.37; H, 4.89;

S, 20.70. Found: C, 54.21; H, 4.81; S, 20.63.

Reduction of XXX into methyl orthotrithiomandelate (XXXIII)

Methyl orthophenyltrithioglyoxylate (XXX), 1.58 g (6.1 mmol),

was dissolved in 50 ml of 95% ethanol. To this solution was

added 5 ml of water and 0.24 g of sodium borohydride. After 7

hrs the reaction mixture was treated with 100 ml of saturated

aqueous ammonium chloride and extracted with three 50 ml portions

of ether, dried (MgSO$_4$), and the solvent removed under vacuum

to yield 1.54 g (96%) of the thiomandelate ester on chromato-graphic purification by elution with hexane (80%)—cyclohexane (10%)-ethylacetate (10%) from a silica gel column. Attempted distillation of the purified material resulted in pyrolysis at 150° (0.2 Torr). The nmr (CDCl$_3$) was consistent with the mandelate ester: 2.00δ (s, 9, SC$\underline{H}_3$); (AB quartet, δA = 3.50, O$\underline{H}$, deuterium oxide exchangeable, δB = 4.84, C$\underline{H}$(O$\underline{H}$), $\underline{J}_{AB}$ = 4.2 Hz); (m, 5, 7.19-7.68δ).

An analytical sample of XXXIII was prepared by evacuation of a chromatographed aliquot for 18 hrs (0.2 Torr).

<u>Anal</u>. Calcd. for C$_{11}$H$_{16}$OS$_3$: C, 50.77; H, 6.20; S, 36.89. Found: C, 50.49; H, 6.42; S, 36.97.

<u>Preparation of S-methyl phenylthioglyoxylate (XXXIV) by iodine oxidative hydrolysis of XXX</u>

To 6.4 g (24.8 mmol) of XXX, dissolved in 150 ml of ether, was added 5 g of sodium bicarbonate, 50 ml of water and 6.3 g, 1 equivalent, of iodine. The mixture was stirred for 7 hrs, until the iodine color disappeared. The cooled ethereal solution was washed with 100 ml of 0.5% sodium bisulfite, dried (MgSO$_4$) and concentrated to yield a yellow oil residue, which was dis-tilled to yield 4.21 g (94.5%) of XXXIV, bp 92-94° (0.1 Torr). The distillate solidified on standing and was recrystallized from 80% ethanol to yield 3.66 g of fine yellow needles, mp 39-40.5° (lit (58) mp 39.5-41°).

When the identical reaction was performed with the use of

3/2 equivalents of iodine, complete desulfurization and quanti-
tative yields of phenylglyoxalic acid (XXXV) were affected.
The anhydrous acid, dehydrated by heating at 150-160°, was
crystallized from benzene (50%)-carbon disulfide (50%), mp 65-
66° (lit (212) mp 62-65°).

Preparation of XXXIV by bromination and hydrolysis of phenyl-glyoxal methyl mercaptal anion

The methyl mercaptal of phenylglyoxal, 5.30 g (25 mmol), was
converted to the enolate salt by one equivalent of sodium hydride
in 250 ml of tetrahydrofuran under nitrogen. At 0°, 4 g (~1.4
ml) of bromine was injected by syringe directly into the stirred
solution, followed by the immediate addition of 20 ml of water.
After 30 mins the reaction mixture was diluted with 300 ml of
water and extracted with three 100 ml portions of ether. The
ether extracts were dried (MgSO₄), concentrated, and distilled
to yield 2.43 g (54%) of the thioester (XXXIV), bp 91-93° (0.1
Torr). The distillation residue contained 37% of XL.

Preparation of ethyl phenylglyoxylate (XXXVI) by iodine oxi-dative hydrolysis of XXX in ethanolic media

ω, ω, ω-Tri(methylmercapto)acetophenone (XXX), 4.40 g (17 mmol),
was dissolved in 100 ml of ether to which was added 6.55 g of
iodine (1.5 equivalents), 35 ml of ethanol, 50 ml of water and
5.5 g of sodium bicarbonate. After stirring and refluxing for 6
hrs, the iodine color disappeared. The cooled ethereal layer was
diluted with 100 ml of ether and washed with 100 ml of 0.5%

aqueous sodium bisulfite. After drying, distillation yielded 2.05 g (67.5%) of an oil, bp 71-72° (0.1 Torr), which was identical to an authentic sample of XXXVI (Aldrich) (lit (213) bp 160° (55 Torr)).

In identical fashion, methyl phenylthioglyoxylate was prepared in 52% yield, bp 70-72° (0.3 Torr), (lit (213) bp 246-248° (750 Torr)).

Preparation of S-methyl thiomandelate (XXXVII) by oxidative hydrolysis of XXXIII

Methyl orthotrithiomandelate (XXXIII), 6.5 g (25 mmol), was dissolved in 200 ml of water containing 5.35 g of ammonium chloride and 1 ml of concentrated hydrochloric acid. The solution was vigorously agitated by an air stream from a gas dispersion tube for 3 hrs at 70°. The cooled solution was extracted with two 100 ml portions of ether and washed with 100 ml of saturated aqueous sodium bicarbonate. After drying ($MgSO_4$), the ether was evaporated under vacuum to leave a colorless oil which crystallized upon standing. Recrystallization from ethyl acetate (10%)-hexane (90%) yielded 3.26 g (71.5%) of needles, mp 77-77.5°. The nmr ($CDCl_3$) spectrum was consistent with the structure of XXXVII: 2.17δ (s, 3, SCH₃); 4.08δ (s, 1, CH(OH)); 5.13δ (s, 1, CHOH, deuterium oxide exchangeable); (m, 5, 7.16-7.48δ).

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.33; H, 6.07; S, 17.57. Found: C, 59.29; H, 6.00; S, 17.61.

When oxidative hydrolysis was attempted by the use of iodine oxidant, only mandelic acid (XXXVIII) could be recovered from the reaction, even when a deficiency of iodine was employed, mp (from carbon tetrachloride) 115-117° (lit (58) mp 116-118°).

Preparation of ethyl mandelate (XXXIX) by iodine oxidative hydrolysis of XXXIII in ethanolic media

Methyl orthotrithiomandelate (XXXIII), 4.3 g (16.5 mmol), was dissolved in 50 ml of 90% ethanol. To this solution was added 2.8 g of sodium bicarbonate and 16.5 mmol of iodine which was added slowly in small portions. After 1 hr at 25° the reaction product was concentrated under vacuum, diluted with 100 ml of water and extracted twice with 100 ml of ether. The ether solution was dried (MgSO$_4$) and distilled to yield 1.74 g of ethyl mandelate (59%), bp 79-81° (0.25 Torr) (lit (214) bp 253-255° (760 Torr)); nmr (CDCl$_3$) 3.9δ (broad singlet, 1, O$\underline{H}$), 5.12δ (s, 1, C$\underline{H}$(OH); 1.13δ and 4.24δ (t, 3; q, 2, $\underline{J}$ = 7.3 Hz, C$\underline{H_2}$C$\underline{H_3}$), (m, 5, 7.17-7.55δ). The product was identical to an authentic sample independently synthesized (215).

Preparation of 1,2-di(methylmercapto)-1,2-dibenzoylethylene (XL) by bromine treatment of the methyl mercaptal of phenylglyoxal anion

The mercaptal (XII), 4.20 g (22 mmol) was converted to its anion with 1 equivalent of sodium hydride in 220 ml of tetrahydrofuran. After the evolution of hydrogen had ceased, the reaction product was cooled to 0° and 3.55 g of bromine added dropwise with vigorous stirring over a 5 min period. The

reaction product was stirred for 3 hrs at 25° and then quenched with 300 ml of water. Extraction with three 100 ml portions of ether yielded an oily residue that crystallized from hexane (95%)-ethyl acetate (5%) to yield 3.10 g of crystals (86%), mp 147-157°. Leaching the crystals with hexane left a crystalline residue that was crystallized from hexane (50%)-ethyl acetate (50%) to yield 0.54g of crystals, mp 168-171°, assigned the <u>cis</u> structure; nmr (CDCl$_3$) 1.98δ (s, 3, SC$\underline{H}_3$); mass spectrum (70 eV) $\underline{m/e}$ (relative intensity) = 328 (85); 313 (10), 223 (5), 105 (100), m* 298.1 (328→313).

<u>Anal</u>. Calcd. for C$_{18}$H$_{16}$O$_2$S$_2$: C, 65.85; H, 4.91; S, 19.30. Found C, 65.94; H, 5.02; S, 19.48.

The material, mp 168-171°, reacted readily with hydrazine in acetic acid (216) to yield the corresponding pyridazine, mp 150-152°; mass spectrum (70 eV) $\underline{m/e}$ = 324; nmr (CDCl$_3$) 2.26δ (s, 6, SC$\underline{H}_3$); (m, 10, 7.3-7.6δ).

The hexane extract from the original <u>cis</u>-<u>trans</u> mixture of XL was concentrated and crystallized from hexane to yield 2.30 g of bright yellow crystals, mp 69.0-70.5°. This product was assigned the <u>trans</u> structure of LX. It yielded only traces of the pyridazine after refluxing 4 days with hydrazine in acetic acid. The mass spectrum (70 eV) was identical to the <u>cis</u> isomer; nmr (CDCl$_3$) 2.13δ (s, 3, SC$\underline{H}_3$).

<u>Anal</u>. Calcd. for C$_{18}$H$_{16}$O$_2$S$_2$: C, 65.85; H, 4.91; S, 19.30. Found: C, 65.93; H, 5.10; S, 19.47.

Preparation of 1,2-di(methylmercapto)-1,2-dibenzoylethylene
(XL) by pyrolysis of ω-chloro-ω-(methylmercapto)acetophenone
(XLI)

The crude product resulting from the reaction of 4.55 g (20
mmol) of ω-(methylsulfinyl)acetophenone (I) with one equivalent
of thionyl chloride was heated in a 100 ml flask equipped with
a condenser and swept with nitrogen. After 12 hrs at 190-200°
the escaping nitrogen was free of acidic vapors. The residue
was cooled and dissolved in 100 ml of chloroform. The chloro-
form solution was washed with aqueous sodium bicarbonate, dried
(MgSO₄) and concentrated. The residue was crystallized from
hexane (50%)-ethyl acetate (50%) to yield 2.94 g (72%) of bright
yellow crystals, mp 152-158°, which were fractionated as de-
scribed previously to give 1.69g of the cis isomer, mp 168-170°,
and 0.98 g of the trans product, mp 66-67°.

Preparation of β-hydroxy-β-phenethyl methyl sulfide (XLIa) and
its dehydration to acid-catalyzed dehydration to β-(methyl-
mercapto)styrene (XLII)

Preparation of XLIa by lithium aluminum hydride reduction
of ω-(methylsulfinyl)acetophenone (I) and its subsequent de-
hydration by distillation of XLII from potassium hydrogen
sulfate has been previously described (60). An alternate route
to XLII involves the O-methylation of β-hydroxy-β-phenethyl
methyl sulfoxide, followed by base-catalyzed methanol elimina-
tion to yield β-(methylsulfinyl)styrene (LXIIIa) (60). The

sulfoxide is then reduced to XLII with sodium metabisulfite
(91). Both routes led to the <u>trans</u> isomer of XLII.

<u>Preparation of 1-phenyl-2-(methylmercapto)propanol (LXIb), and</u>

<u>its treatment with hydrogen bromide in benzene to yield XLVII</u>

The preparation of XLIb involves a three step reaction
series, such that I is methylated to Ia, which in turn is re-
duced in two steps by sodium borohydride and sodium metabisul-
fite into XLIb (60, 91). Alternatively, XLIb can be prepared
by treatment of α-bromopropiophenone with an excess of methyl
mercaptan in the presence of triethylamine to yield Ib, followed
by sodium borohydride reduction to XLIb.

The hydrogen bromide-benzene solution for dehydration of
XLIb was prepared by equilibrating 30 ml of 48% hydrobromic
acid with 250 ml of benzene in a separatory funnel. The aqueous
phase was discarded, and 8.83 g (48.5 mmol) of XLIb was dissolved
in the benzene phase and transferred to a 500 ml reaction flask
equipped with a Dean Stark trap. After 15 hrs of dehydration
under reflux in a nitrogen atmosphere, the solvent was removed
under vacuum and the yellow oil residue was chromatographed on
a silica gel column. Elution with hexane yielded 4.75 g (60%)
of β-methyl-β-(methylmercapto)styrene (XLVII) as a single stereo-
isomer. XLVII was identical to an authentic sample prepared by
the potassium <u>t</u>-butoxide elimination of methanol from 1-phenyl-1-
methoxy-2-(methylmercapto)propane (91); nmr (CDCl$_3$) 2.04δ (d, 3,
<u>J</u> = 1 Hz, C<u>H</u>$_3$); 2.26δ (s, 3, SC<u>H</u>$_3$); 6.75δ (q, 1, <u>J</u> = 1 Hz, C<u>H</u>=C);
(m, 5, 7.2-7.5δ).

Further elution with ethyl acetate (5%)-hexane (95%) yielded 1.03 g (15%) of a cis-trans mixture of β-methylstyrene oxide, which was reduced with sodium borohydride to yield 1-phenyl-propanol, identical with an authentic sample (Aldrich). From the column, 1.39 g of unreacted XLIb was recovered as the final mobile component.

Preparation of α,β-di(methylmercapto)styrene (XLIIIa) by thermolysis of XXIVa

2,2-Di(methylmercapto)-1-phenethanol (XXIVa), 10.1 g (50 mmol) was heated with stirring at 80° in an oil bath for 48 hrs, at which time tlc analysis indicated complete conversion to a single new component. The oil was distilled to yield 9.1 g (93%) of XLIIIa, bp 125-127° (1 Torr). A 58:42 mixture of trans:cis olefin was indicated by nmr (CDCl$_3$): (trans XLIIIa) 2.02δ and 2.34δ (s, 3; s, 3, SC$\underline{H}_3$); 6.37δ (s, 1, C$\underline{H}$=); (cis XLIIIa) 2.08δ and 2.20δ (s, 3; s, 3, SC$\underline{H}_3$); 6.27 (s, 1, C$\underline{H}$=). The olefinic mixture could be isomerized to >95% of the trans isomer by re-fluxing 8 hrs in benzene solution, containing a trace of hydrogen chloride catalyst.

Anal. Calcd. for C$_{10}$H$_{12}$S$_2$: C, 61.21; H, 6.17; S, 32.62. Found: C, 61.38; H, 6.37; S, 32.66.

Preparation of XLIIIa by reaction of XXIVa or XXIVe under basic conditions with thionyl chloride

Treatment of 5.73 g (26.7 mmol) of (XXIVa) in 30 ml of pyridine with 2.94 g of thionyl chloride resulted in a highly

exothermic reaction which refluxed from the heat of reaction for 20 min. After stirring for 1 hr at 25° the mixture was poured into 150 ml of water and 15 ml of concentrated hydrochloric acid was added. The solution was extracted with three 100 ml portions of chloroform and the dry (MgSO$_4$) extract concentrated and purified by column chromatography on silica gel with hexane to yield 4.24 g (81%) of (XLIIIa) in a trans/cis ratio of 70/30.

In identical fashion, the deuterio alcohol (XXIVe), which was prepared by sodium borohydride-d$_4$ reduction of XII in deuterium oxide solution, yielded XLIIIa as a 70/30 ratio of trans/cis isomers. Both the nmr and mass spectrum indicated the product was completely free of deuterium.

An alternative route to the conversion of XXIVa under basic condition into XLIIIa in >75% yield involves conversion of XXIVa to its alkoxide in tetrahydrofuran and subsequent reaction with tosyl chloride. The procedure is outlined for the preparation of XLIIId.

Conversion of XXIVa by treatment with thionyl chloride in methylene chloride solution into β-(methylmercapto)-α-chloro-styrene (XLIV)

To 7.6 g (52 mmol) of XXIVa in 100 ml of methylene chloride at 0° under a nitrogen atmosphere, there was added 7.15 g of thionyl chloride in a dropwise fashion with efficient stirring. The exothermic reaction was maintained at 25° for 2 hrs, and the solvent removed under vacuum to leave a red residue. The residue

was dissolved in 50 ml of chloroform, washed with a 100 ml of saturated aqueous sodium bicarbonate, dried (MgSO$_4$), and concentrated. The neutralized residue was chromatographed on a silica gel column with hexane eluent to yield 4.2 g (44%) of XLIV, identical to the <u>trans</u> (E) isomer previously reported (60). Trace of XLII and XLIIIa were also eluted as more mobile components. Considerable polymer, immobile in (100%) ethyl acetate was not recovered.

Conversion of XXIVb into α-methyl-β-(methylmercapto)styrene (XLIIIb)

In identical fashion to the preparation of XLIIIa, 4.55 g (20 mmol) of 1,1-di(methylmercapto)-2-phenyl-2-propanol (XXIVb) was treated with 1 equivalent of thionyl chloride. The crude product was chromatographed on a column of silica gel with hexane eluent to yield 2.74 g (83.5%) of XLIIIb. The nmr (CDCl$_3$) of the chromatographed material was consistent with 90/10 ratio of <u>cis</u>/<u>trans</u> isomers (where <u>cis</u> (Z) refers to the phenyl and methylmercapto groups); (<u>cis</u> XLIIIb) 6.21δ (q, 0.9, J = 0.4 Hz, C<u>H</u>=); (<u>trans</u> XLIIIb) 5.85δ (q, 0.1, J = 0.6 Hz, C<u>H</u>=); <u>cis</u> and <u>trans</u>, 2.05δ (d, 3, J = 0.5 Hz, C<u>H</u>$_3$); 2.16δ (s, 3, SC<u>H</u>$_3$); (m, 5, 7.00-7.41δ). The pure <u>cis</u> isomer was crystallized from pentane as colorless needles, mp 29-30.5°.

<u>Anal</u>. Calcd. for C$_{10}$H$_{12}$S: C, 73.14; H, 7.37; S, 19.49. Found: C, 73.09; H, 7.43; S, 19.65.

Detection of methanesulfenyl chloride as a reaction by-product
on treatment of XXIVb with thionyl chloride

To 2.49 g (10.9 mmol) of (XXIVb) in 50 ml of methylene
chloride at 0° there was added 0.9 ml of cyclohexene (~10.9
mmol) and 0.80 ml of thionyl chloride. After stirring for 2
hrs at 0° the solvent was removed under vacuum at ~10°. The
residue was developed with four elutions of pentane on a 20 x
60 x 0.3 cm preparative tlc plate, prepared by using a mixture
of Merck Silica Gel P_{254} (CaSO$_4$) (80%) and Merck Silica Gel-H
(20%). The chromatogram contained two major components, $R_f \cong$
0.35 was eluted with chloroform to yield 1.55 g (86.5%) of
(XLIIIb). The band with $R_f \cong$ 0.8 was eluted with chloroform to
yield 1.18 g (66%) of a yellow oil identical with an authentic
sample of trans-1-(methylmercapto)-2-chlorocyclohexene prepared
by the direct addition of methanesulfenyl chloride to cyclohexene
by infrared and nmr comparison. The mass spectrum of the
methanesulfenyl chloride adduct was consistent with the assigned
structure; m/e (70 eV) (relative intensity) 164 (15) (M+2, 166
= 33% of M$^+$), 131 (2), 129 (28), 118 (12), 116 (36), 81 (100),
80 (95).

Conversion of XXIVc into α-ethyl-β-(methylmercapto)styrene
(XLIIIc)

The alcohol (XXIVc), 4.83 g (20 mmol) was treated with
thionyl chloride in pyridine in identical fashion to the prep-
aration of XLIIIa,b. In a similar fashion, chromatography with

hexane eluent yielded 2.76 g (78%) of XLIIIc, bp 70-72° (0.2

Torr). Nmr (CDCl$_3$) analysis indicated a mixture of cis/trans

isomers in a 80/20 ratio: (cis (Z) refers to the phenyl and

methylmercapto groups); (cis XLIIIc) 1.04δ and 2.60δ (t, 3; q,

2, J = 7.5 Hz, CH$_2$CH$_3$); 2.25δ (s, 3, SCH$_3$); 6.07δ (s, 1, J → 0,

CH=):(trans XLIIIc) 2.12δ (s, 3, SCH$_3$); 5.82δ (t, 1, J = 0.4 Hz,

CH=).

Anal. Calcd. for C$_{11}$H$_{14}$S: C, 74.13; H, 7.92; S, 17.96.

Found: C, 73.91; H, 7.85; S, 17.90.

Conversion of XXIVc into 1-(methylmercapto)-2,2-diphenylethyl-
ene (XLIIId) with thionyl chloride in pyridine

Alcohol (XXIVc), 6.15 g (21.2 mmol) was dissolved in 50 ml of

pyridine and 1.8 ml of thionyl chloride was added dropwise at 0°

with stirring. After 2 hr the reaction mixture was poured into

200 ml of saturated aqueous sodium bicarbonate solution and

extracted with three 100 ml portions of chloroform. The chloro-

form extract was dried (MgSO$_4$), and the concentrated residue

chromatographed on silica gel with petroleum ether to yield 3.4

g (72%) of XLIIId that was recrystallized from pentane, mp 70

(lit (217) mp 70.0-71.5°); nmr (CDCl$_3$) 2.23δ (s, 3, SCH$_3$);

6.37δ (s, 1, CH=); 7.13δ and 7.25δ (d, 10, Ph$_2$).

Anal. Calcd. for C$_{15}$H$_{14}$S: C, 79.60; H, 6.24; S, 14.26.

Found: C, 79.64; H, 6.33; S, 14.42.

Reaction of XXIVd with tosyl chloride, alternative preparation
of XLIIId

The alcohol (XXIVd), 7.0 g (24 mmol) was converted to the
alkoxide in 200 ml of tetrahydrofuran by 1 equivalent of sodium
hydride under a nitrogen atmosphere. Tosyl chloride, 4.6 g,
dissolved in 60 ml of tetrahydrofuran was added dropwise at
room temperature. After 1 hr, the solution was filtered, con-
centrated under vacuum, and the residue dissolved in 100 ml of
chloroform. The chloroform extract was washed with 100 ml of
saturated aqueous sodium bicarbonate solution, dried (MgSO$_4$)
and the solvent removed under vacuum. Column chromatography on
silica gel with hexane yielded 3.9 g (71%) of the styrene
(XLIIId).

Comparable results were obtained under identical reaction
conditions when benzoyl chloride was utilized as the electro-
philic halide.

Reaction of XXIVd with hydrogen bromide in benzene

To 4.50 g (15.5 mmol) of the alcohol (XXIVd) in 150 ml of
benzene was added 20 ml of 48% aqueous hydrobromic acid. The
mixture was refluxed for 10 hrs and the water removed by a Dean
Stark trap. The benzene was removed under vacuum and the crude
residue was chromatographed with hexane on silica gel to yield
2.3 g (63%) of the styrene (XLIIId) and 1.0 g (31%) of benzil
(153).

Conversion of XXIVc into α-(methylmercapto)-α-phenylbutyraldehyde

(XLVIIIa)

The alcohol (XXIVc), 9.66 g (40 mmol) was converted to the alkoxide with 1 equivalent of sodium hydride in 125 ml of tetrahydrofuran. At -5°, 1 equivalent of acetal chloride was added. After 30 min at -5°, the solution was filtered and diluted with 30 ml of water. After refluxing for 15 min, the solvent was removed under vacuum and the residue taken up in 200 ml of ether. The ether solution was washed with three 100 ml portions of 1N sodium hydroxide, dried (MgSO$_4$), concentrated and chromatographed on a silica gel column with hexane as eluent to yield 2.70 g (38%) of the styrene (XLIIIc) and 3.63 g (46%) of the butyraldehyde (XLVIIIa). An analytical sample was prepared by distillation, bp 112-114° (0.25 Torr); nmr (CDCl$_3$) 0.75δ and 1.90δ (t, 3; q, 2, J = 7.2 Hz, CH$_2$CH$_3$); 1.73δ (s, 3, SCH$_3$); 9.13δ (s, 1, CHO); (m, 5, 7.20-7.35δ).

Anal. Calcd. for C$_{11}$H$_{14}$OS: C, 68.02; H, 7.27; S, 16.46. Found: C, 68.19; H, 7.20; S, 16.55.

Conversion of XXIVd into α-(methylmercapto)-α,α-diphenylacetaldehyde (XLVIIIb)

In an identical fashion to the preparation of XLVIIIa, 8.85 g (30.5 mmol) of XXIVd yielded 1.40 g (20%) of the styrene (XLIIId), 2.65 g of recovered starting material, and 3.20 g (43%) of the aldehyde (XLVIIIb). The aldehyde was recrystallized from ether (5%)-hexane (95%) to yield colorless plates, mp 70-71°;

ν_{CCl_4} 1720 cm^{-1} (C=O); nmr (CDCl$_3$) 1.75δ (s, 3, SC$\underline{H}_3$); 9.44δ (s, 1, C$\underline{H}$O).

Anal. Calcd. for C$_{15}$H$_{14}$OS: C, 74.36; H, 5.83; S, 13.20. Found: C, 74.47; H, 5.91; S, 13.35.

Conversion of XXXIII into 2,2,2-tri(methylmercapto)-1-phenethyl benzoate (LXVI)

The alcohol (XXXIII), 6.20 g (23.8 mmol) was converted to the alkoxide with 1.2 g of sodium hydride in 100 ml of tetra-hydrofuran. The reaction was cooled to 0° and 3.5 ml of benzoyl chloride added. After stirring for 1 hr, 20 ml of water was added and the mixture poured into 30 ml of ice water. The aqueous solution was extracted with three 100 ml portions of ether and the ether extract washed twice with 50 ml of 0.5 $\underline{N}$ aqueous sodium hydroxide. Drying (MgSO$_4$) and concentration left a colorless oil which did not crystallize. Chromatography from a silica gel column with ethyl acetate (10%)-cyclohexane (10%)-hexane (80%) yielded 7.40 g (85.6%) of product which could not be distilled under vacuum without pyrolysis; nmr (CDCl$_3$) 2.12δ (s, 9, SC$\underline{H}_3$); 6.37δ (s, 1, C$\underline{H}$); (m, 8, 7.18-7.80δ); (m, 2, 8.00-8.22δ); mass spectrum (70 eV) (relative intensity) 364 (trace, 322 (trace), 317 (1), 259 (14), 242 (70), 227 (7), 212 (5), 196 (95), 180 (68), 153 (15), 134 (65), 105 (100)

Anal. Calcd. for C$_{18}$H$_{20}$S$_3$O$_2$: C, 59.33; H, 5.53; S, 26.35. Found: C, 59.56; H, 5.67; S, 26.05.

Conversion of XXXIII into α,β,β-tri(methylmercapto)styrene (XLV)

The alcohol (XXXIII), 2.60 g (10 mmol) was converted to the alkoxide with 1 equivalent of sodium hydride in 150 ml of tetrahydrofuran. At 0°, 1.2 g of thionyl chloride was added and the reaction stirred for 6 hrs at 25°. The reaction was concentrated under vacuum to ~50 ml, diluted with 200 ml of water, and extracted with three 80 ml portions of ether. The dried ethereal extract (MgSO$_4$) was concentrated to yield a light yellow oily residue. Chromatography on a silica gel column with hexane eluent yielded a colorless oil which crystallized on standing. Recrystallization from pentane gave 1.96 g (81%) of the olefin (XLV), mp 59.5-61°; nmr (CDCl$_3$) 1.82, 2.14 and 2.43δ (three singlets, 9, SC$\underline{H}_3$); 7.05-7.45δ (m, 5, Ph).

Anal. Calcd. for C$_{11}$H$_{14}$S$_3$: C, 54.54; H, 5.83; S, 39.63. Found: C, 54.78; H, 5.97; S, 39.46.

Preparation of α,β,β-tri(methylmercapto)styrene by thermolysis (XLVI)

Thermolysis of 4.65 g (17 mmol) of the benzoate (LXVI) for 8 hrs at 170° (0.3 Torr) in a flask fitted with a reflux condenser led to formation of a sublimate in the condenser. At the end of the reaction, products were washed back into the flask with ~50 ml of chloroform. The reaction mixture was diluted with 200 ml of ether and extracted with three 100 ml portions of 0.2$\underline{N}$ aqueous sodium hydroxide. The ether extracts were dried (MgSO$_4$) and concentrated under vacuum. Chromatography on silica gel with

hexane yielded 3.1 g (73.8%) of the styrene (XLV); mp 59.0-
60.0° from pentane and 0.89 g (19%) of recovered starting
material.

Reaction of β,β-di(methylmercapto)-α-benzoylstyrene (XXIXb)
and β,β-di(methylmercapto)-α-acetoxystyrene (XXIXa) with N-bromo-
succinimide; conversion to ω-(acyloxy)acetophenone derivatives
(VIII and VIIIa)

Styrene (XXIXb), 11.0 g (35 mmol) was suspended in 200 ml
of 50% aqueous ethanol and 8 g of sodium bicarbonate was added.
The solution was warmed to 60° and 6.85 g (38.5 mmol) of NBS
was added slowly. Each addition of NBS resulted in the rapid
evolution of carbon dioxide. The reaction was complete in 20
minutes and was diluted to 300 ml with water and extracted with
three 100 ml portions of ether. The ethereal extract was dried
(MgSO$_4$), concentrated, and distilled under vacuum to yield 8.1 g
(81%) of material, bp 108-110° (0.05 Torr). The oil crystal-
lized from hexane to give a product, mp 53-55°, which was identi-
cal to ω-benzoyloxy-ω-(methylmercapto)acetophenone (VIIIa), inde-
pendently synthesized from the reaction of the methyl hemi-
captal of phenylglyoxal (XI) with benzoyl chloride in pyridine,
or by the reaction of benzoyl chloride with the anion of
ω-(methylsulfinyl)acetophenone (I) in tetrahydrofuran solution
(2). The nmr (CDCl$_3$) was consistent with the presence of two
benzoyl functions: 2.21δ (s, 3, SCH$_3$); 6.22δ (s, 1, CH$\overset{O}{\underset{S}{\diagdown}}$);
(m, 5, 7.20-7.65δ); (m, 5, 8.00-8.21δ).

<u>Anal</u>. Calcd. for $C_{16}H_{14}O_3S$: C, 67.12; H, 4.93; S, 11.18.

Found: C, 66.91; H, 4.94; S, 11.37.

In identical fashion, XXIXa was reacted with 1 equivalent of NBS in a mixture of water (80%)-dioxane (20%) to yield 51% of ω-acetoxy-ω-(methylmercapto)acetophenone (VIII), bp 110-113° (2.0 Torr), identical to material described previously (91).

<u>Preparation of 2,2-di(methylmercapto)-1-phenethyl benzoate (XLIX)</u>

The alcohol (XXIVa), 8.93 g (4.16 mmol) was converted to the alkoxide with 1 equivalent of sodium hydride in 200 ml of tetra-hydrofuran. To the alkoxide was added dropwise 5.75 g of benzoyl chloride at 0° under a nitrogen atmosphere. After stirring for 3 hrs at 25°, the solution was filtered and concentrated under vacuum. To the residue was added 200 ml of ether and the ether-eal solution was washed with two 100 ml portions of 0.3<u>N</u> aqueous sodium hydroxide. The dried ether solution (MgSO₄) was con-centrated to yield a colorless oil which crystallized from hexane to yield 7.60 g (64%) of large crystals, mp 94.0-95.5°; nmr (CDCl₃) 2.04δ and 2.10δ (s, 3; s, 3, SCH₃); (AB quartet, δA = 4.10, δB = 6.20 J_AB = 9.0 Hz, CH-CH<S/S).

<u>Anal</u>. Calcd. for $C_{17}H_{18}O_2S_2$: C, 64.14; H, 5.70; S, 20.11.

Found: C, 64.29; H, 5.83; S, 19.98.

<u>Potassium t-butoxide elimination of benzoic acid from XLIX;</u>
<u>preparation of β,β-di(methylmercapto)styrene (LIa)</u>

The benzoate (XLIX), 5.73 g (20 ml) was dissolved in 60 ml of tetrahydrofuran and added to 3 g of potassium <u>t</u>-butoxide

suspended in 100 ml of tetrahydrofuran under nitrogen. The stirred solution was refluxed for 5 hrs. After cooling, 30 ml of water was added and the solution concentrated under vacuum before dilution with 200 ml of $0.1\underline{N}$ aqueous sodium hydroxide. The aqueous solution was extracted with two 100 ml portions of ether; the ethereal extract dried ($MgSO_4$), and concentrated under vacuum to yield a yellow oil that was chromatographed on a silica gel column by ethyl acetate (3%)-hexane (97:) to yield 2.53 g (64.5%) of the styrene (LIa) and 1.19 g (28%) of 2,2-di-(methylmercapto)phenethanol (XXIVa). An analytical sample of the styrene was prepared by distillation, bp 94-96° (0.25 Torr), (lit (172) 105-107° (0.5 Torr)); nmr ($CDCl_3$) 2.28δ and 2.32δ (s, 3; s, 3, $SC\underline{H}_3$); 6.78δ (s, 1, $C\underline{H}$=); (m, 5, 7.10-7.70δ).

<u>Anal</u>. Calcd. for $C_{10}H_{12}S_2$: C, 61.21; H, 6.17; S, 32.62. Found: C, 61.29; H, 6.22; S, 32.59.

<u>Preparation of 1,1-di(methylmercapto)-2-methoxy-2-phenylethane</u>
<u>(La) from XXIVa</u>

The alcohol (XXIVa) 8.0 g (37 mmol) was converted to the alkoxide with 1 equivalent of sodium hydride in 150 ml of tetrahydrofuran. To the alkoxide was added 7 g (1.3 equivalents) of methyl iodide. After 12 hrs stirring at 25° under nitrogen, the reaction was quenched with 20 ml of methanol and diluted with 200 ml of ether. The ethereal solution was washed with 300 ml of saturated aqueous ammonium chloride solution, dried ($MgSO_4$), and concentrated under vacuum to give a yellow oil that was

distilled to yield 7.40 g (87.6%) of colorless La, bp 99-100°

(0.25 Torr); nmr (CDCl$_3$) 2.02δ and 2.09δ (s, 3; s, 3, SC$\underline{H}_3$);

3.76δ (s, 3, OC$\underline{H}_3$); (AB quartet, δA = 3.79, δB = 4.39, $\underline{J}_{AB}$ =

6.0 Hz, C$\underline{H}$(OCH$_3$)–C$\underline{H}\langle^S_S$); 7.38δ (s, 5, Ph).

<u>Anal</u>. Calcd. for C$_{11}$H$_{16}$OS$_2$: C, 57.88; H, 7.07; S, 28.04.

Found: C, 57.75; H, 7.07; S, 27.90.

<u>Preparation of 1,1-di(methylmercapto)-2-methoxy-2-phenylpro-</u>

<u>pane (Lb)</u>

In identical fashion to the preparation of La, 15.4 g (67.5

mmol) of XXIVb was converted to 15.7 g (96.5%) of Lb, bp 123-

125°(0.5 Torr); nmr (CDCl$_3$) 1.73δ and 1.77δ (s, 3; s, 3, SC$\underline{H}_3$);

2.11δ (s, 3, C$\underline{H}_3$); 3.12δ(s, 3, OC$\underline{H}_3$); 3.73δ (s, 1, C$\underline{H}\langle^S_S$); (m,

5, 7.20-7.53δ).

<u>Anal</u>. Calcd. for C$_{12}$H$_{18}$OS$_2$: C, 59.79; H, 7.49; S, 26.42.

Found: C, 60.03; H, 7.44; S, 26.66.

<u>Preparation of 1,1-di(methylmercapto)-2-methoxy-2-phenylbutane</u>

<u>(Lc)</u>

In identical fashion to the preparation of La, 11.2 g (46.3

mmol) of XXIVc was converted to 10.1 g (91%) of Lc, bp 109-112°

(0.25 Torr); nmr (CDCl$_3$) 1.81δ and 1.90δ (s, 3; s, 3, SC$\underline{H}_3$);

0.93δ and 2.18δ (t, 3; q, 2; $\underline{J}$ = 7.3 Hz, C$\underline{H}_2$C$\underline{H}_3$); 3.20δ (s, 3,

OC$\underline{H}_3$); 3.96δ (s, 1, C$\underline{H}\langle^S_S$); (m, 5, 7.18-7.60δ).

<u>Anal</u>. Calcd for C$_{13}$H$_{20}$OS$_2$: C, 60.92; H, 7.87; S, 24.97.

Found: 60.90; H, 7.72; S, 24.88.

Preparation of 1,1-di(methylmercapto)-2-methoxy-2,2-diphenyl-
ethane (Ld)

In identical fashion to the preparation of La, 5.25 g (18
mmol) of XXIVd was converted to 5.12 g (93%) of Ld, bp 131-
135° (0.25 Torr); nmr (CDCl$_3$) 1.76δ (s, 6, SC$\underline{H}_3$); 2.98δ(s, 3,
OC$\underline{H}_3$); 4.60δ (s, 1, C$\underline{H}{<}^S_S$); (m, 10, 7.10-7.50δ).

Anal. Calcd. for C$_{17}$H$_{20}$OS$_2$:   C, 67.09; H, 6.62; S, 20.03.
Found: C, 66.95; H, 6.75; S, 19.96.

Conversion of La to β,β-di(methylmercapto)styrene (LIa) by
n-butyllithium elimination of methanol

The α-methoxy mercaptal (LIa), 7.00 g (30.7 mmol) was
treated in 150 ml of ether under nitrogen with the dropwise
addition at 0° of 1 equivalent of n-butyllithium, as a 1.6 M
solution in hexane. The reaction was allowed to come to room
temperature and stirred for 1 hr prior to neutralization with
excess solid ammonium chloride and 10 ml of methanol. After
washing with 100 ml of water, the ethereal solution was dried
(MgSO$_4$) and concentrated under vacuum. The colorless oil
residue was distilled under vacuum to yield 5.48 g (9.13%) of
the pure ketene mercaptal (LIa), which was identical to the
sample isolated from potassium t-butoxide treatment of XLIX.

Preparation of α-methyl-β,β-di(methylmercapto)styrene (LIb)
from Lb

In identical fashion to the preparation of LIa, treatment
of 13.60 g (56 mmol) of Lb with n-butyllithium yielded 9.20 g

(78.5%) of the ketene mercaptal (LIb), isolated by chromato-graphy on a silica gel column with cyclohexane (15%)-hexane (85%), bp 97-99° (0.25 Torr); nmr (CDCl$_3$) 2.35δ (d, $\Delta\delta$ = 0.2 Hz, 6, SC$\underline{H}_3$); 2.13δ (s, 3, CH$_3$); (m, 5, 7.15-7.37δ).

$\underline{\text{Anal}}$. Calcd. for C$_{11}$H$_{14}$S$_2$: C, 62.84; H, 6.71; S, 30.44. Found: C, 62.78; H, 6.76; S, 30.32.

Preparation of α-ethyl-β,β-di(methylmercapto)styrene (LIc) from Lc

In identical fashion to the preparation of LIa, treatment of 9.20 g (35.5 mmol) of Lc with $\underline{n}$-butyllithium yielded 6.70 g (84.5%) of the ketene mercaptal (LIc), isolated by chromato-graphy on a silica gel column with cyclohexane (5%)-hexane (95%), bp 94-95° (0.25 Torr); nmr (CDCl$_3$) 0.94δ and 2.78δ (t, 3; q, 2, $\underline{J}$ = 9.0 Hz, C$\underline{H}_2$C$\underline{H}_3$); 2.12δ and 2.33δ (s, 3; s, 3, SC$\underline{H}_3$); (m, 5, 7.0-7.45δ).

$\underline{\text{Anal}}$. Calcd. for C$_{12}$H$_{16}$S$_2$: C, 64.27; H, 7.19; S, 28.54. Found: C, 64.21; H, 7.14; S, 28.46.

Preparation of 1,1-di(methylmercapto)-2,2-diphenylethylene (LId) from Ld

In identical fashion to the preparation of LIa, 7.70 g (25 mmol) of Lc was treated with 1 equivalent of $\underline{n}$-butyllithium. The crude product was chromatographed on a silica gel column with hexane to yield 5.72 g (83.8%) of LId as a colorless oil, which crystallized on standing. Recrystallization from pentane yielded 5.60 g of LId as colorless needles, mp 83-84°; nmr (CDCl$_3$) 2.19δ (s, 6, SC$\underline{H}_3$); 7.26δ (s, 10, Ph$_2$).

Anal. Calcd. for $C_{16}H_{16}S_2$: C, 70.57; H, 5.92; S, 23.50.
Found: C, 70.72; H, 6.10; S, 23.41.

Hydration of LIa; preparation of S-methyl phenylthioacetate
(LIIa)

The ketene mercaptal (LIa), 2.94 g (15 mmol) was dispersed
in 150 ml of 30% aqueous ethanol and 12 ml of concentrated
sulfuric acid was added. The solution was stirred and heated
at 90° for 1 hr. After cooling to room temperature, the re-
action mixture was diluted with 200 ml of water and extracted
twice with 100 ml of ether. The ethereal extracts were washed
with 100 ml of dilute aqueous sodium bicarbonate, dried ($MgSO_4$),
and the ether removed under vacuum. The yellow oily residue
was chromatographed on a column of silica gel with hexane to
yield 2.06 g (83%) of LIIa; nmr ($CDCl_3$) 2.24δ (s, 3, SCH_3);
3.79δ (s, 2, CH_2); 7.26δ (s, 5, Ph). The product was identi-
cal to an authentic sample prepared by reaction of methyl-
mercaptan with phenylacetyl chloride.

Hydration of LIb; preparation of S-methyl α-phenylthiopro-
pionate (LIIb)

In identical fashion to the hydration of LIa, 2.0 g (9.5
mmol) of the ketene mercaptal (LIb) was heated in 30% alcoholic
sulfuric acid. The crude reaction residue was chromatographed
on a silica gel column with hexane to yield 1.51 g (88.5%) of
LIIb. An analytical sample was prepared by distillation, bp
83-85° (0.30 Torr); ν_{CCl_4} 1680 cm^{-1} (C=O); nmr ($CDCl_3$) 1.50δ

(d, 3, $\underline{J}$ = 8 Hz, C$\underline{H}_3$); 2.22δ (s, 3, SC$\underline{H}_3$); 3.95δ (q, 1, $\underline{J}$ = 8 Hz, C$\underline{H}$(CH$_3$)); 7.28δ (s, 5, Ph).

<u>Anal</u>. Calcd. for C$_{10}$H$_{12}$OS: C, 66.65; H, 6.71; S, 17.76. Found: C, 66.52; H, 6.91; S, 17.50.

<u>Hydration of LIc; preparation of S-methyl α-phenylthiobutyrate (LIIc)</u>

By the method described for the preparation of LIIa and LIIb, 2.0 g (8.9 mmol) of LIc was converted into 1.38 g (80%) of the butyrate (LIIc). The pure material was isolated by chromatography on a silica gel column with hexane, and distilled for the preparation of an analytical sample, bp 76-78° (0.30 Torr); ν_{CCl_4} 1695 cm^{-1} (C=O); nmr (CDCl$_3$) 2.25δ (s, 3, SC$\underline{H}_3$); 2.15δ and 1.92δ (q, 2; t, 3, $\underline{J}$ = 7.0 Hz, C$\underline{H}_2$C$\underline{H}_3$, the ethyl methylene protons are perturbed by the α-butyrate proton and $\underline{J}$ was measured for the ethyl triplet), 3.67δ (t, 1, $\underline{J}$ ≅ 9 Hz, C$\underline{H}$(Et)); 7.29δ (s, 5, Ph).

<u>Anal</u>. Calcd. for C$_{11}$H$_{14}$OS: C, 68.02; H, 7.27; S, 16.48. Found: C, 68.21; H, 7.24; S, 16.67.

<u>Hydration of LId</u>

The ketene mercaptal (LId), 1.50 g (5.5 mmol) was hydrated by the same method employed for the hydration of LIa-c. The crude semi-solid reaction product, 1.43 g, indicated the presence of three components by tlc. Due to unfavorable $\underline{R}_f$ values, separation could not be affected by column chromatographic technique. Analysis by nmr confirmed by intergration the presence of 1-(methylmercapto)-2,2-diphenylethylene (XLIIId)

(~68%), unreacted ketene mercaptal (LId) (~25%), and α-(methyl-mercapto)-α,α-diphenylacetaldehyde (XLVIIIb) (~5%). More vigorous reaction conditions resulted only in the further hydration of the intermediate 1-(methylmercapto)-2,2-diphenyl-ethylene (XLIIId) to the acetaldehyde derivative (XLVIIIb).

Hydration of XLV; preparation of S-methyl α-(methylmercapto)-α-(phenyl)thioacetate (LIII)

The styrene (XLV), 1.20 g (4.97 mmol) was suspended in 60 ml of 30% ethanol containing 4.5 ml of concentrated sulfuric acid and the stirred solution was refluxed for 2 hr. After cooling, the reaction was diluted with 100 ml of water and extracted with two 100 ml portions of ether. The ether extracts were washed with 100 ml of dilute aqueous sodium bicarbonate, dried (MgSO$_4$), and evaporated under vacuum. The residue was chromatographed with hexane on a 1.5 x 25 cm silica gel column to yield 0.12 g of starting material (XLV) and 0.76 g (71.6%) of LIII as a colorless oil, which solidified on standing. Recrystallization from ethyl acetate (15%)-hexane (85%) yielded fine colorless needles, mp 59°; ν_{CCl_4} 1685 cm^{-1} (C=O); nmr (CDCl$_3$) 2.14δ (s, 3, PhC(SC$\underline{H}_3$)); 2.30δ (s, 3, COSC$\underline{H}_3$); 4.66δ (s, 1, C$\underline{H}$-); (m, 5, 7.18-7.55δ).

Anal. Calcd. for C$_{10}$H$_{12}$OS$_2$: C, 56.60; H, 5.70; S, 30.16. Found: C, 56.61; H, 5.64; S, 29.94.

Hydration of XXVIII; conversion to the methylmercaptal of
phenylglyoxal (XII)

The α-methoxy-β,β-di(methylmercapto)styrene (XXVIII), 2.70
g (12 mmol) was hydrated by the procedure employed for the
hydration of the ketene mercaptals (LIa-c). The crude re-
action product was chromatographed on a silica gel column with
ethyl acetate (5%)-hexane (95%) to yield 2.33 g (91.6%) of
XII and 0.08 g (~5%) of phenylglyoxal, weighed as the anhydrous
material.

Hydration of XXIXb; conversion to the methyl mercaptal of
phenylglyoxal (XII)

The α-benzoyloxystyrene (XXIXb), 3.16 g (10 mmol) was
hydrated in identical fashion to the methoxy derivative (XXVIII).
The crude ether extracts, on work-up, were washed with 100 ml of
0.2$\underline{N}$ sodium hydroxide solution, dried (MgSO$_4$) and ether eva-
porated under vacuum. The yellow oil residue was chromatographed
on a silica gel column with ethyl acetate (5%)-hexane (95%)
to yield 1.51 g (71.3%) of XII, and 0.30 g (22.4%) of phenyl-
glyoxal, weighed as the anhydrous material.

Hydration of XLIIIa and XLIV; conversion to ω-(methylmercapto)-
acetophenone (LV)

The α,β-di(methylmercapto)styrene (XLIIIa), 2.94 g (15 mmol)
was hydrated by the method employed for the hydration of the
ketene mercaptals (LIa-c). The crude reaction product was
chromatographed on a silica gel column with hexane to yield a

trace, ~0.05 g, of unreacted starting material and 1.97 g (79%) of ω-(methylmercapto)acetophenone. Polymeric residue, immobile with ethyl acetate (50%)-hexane (50%) eluent, was not recovered from the column. LV was identical to an authentic sample independently synthesized by sodium metabisulfite reduction of ω-(methylsulfinyl)acetophenone (I) (91).

In identical fashion, α-chloro-β-(methylmercapto)styrene (XLIV), 2.76 g (15 mmol) was hydrated to yield 0.10 g (4.5%) of β-(methylmercapto)styrene (XLII), 0.61 g of starting material, and 1.58 g (63.5% of ω-(methylmercapto)acetophenone (LV).

Hydration of XLII; conversion to phenylacetaldehyde (LIVa)

The styrene (XLIII), 3.00 g (20 mmol) was dissolved in 200 ml of 50% aqueous ethanol to which was added 16 ml of concentrated sulfuric acid, effective 3N. The stirred reaction was heated at ~90° for 12 hrs, diluted with 200 ml of water and extracted with two 150 ml portions of chloroform. The chloroform extracts were dried (MgSO₄), concentrated, and the residue chromatographed on a column of silica gel with ethyl acetate (5%)-cyclohexane (5%)-hexane (90%). From the colum was recovered 1.94 g (64.6%) of starting material and 0.41 g (20.5%) of phenylacetaldehyde (LIVa), identical to an authentic sample (Aldrich).

An increase in the acid-catalyst or the reaction time failed to improve aldehyde yields. The use of Lewis acid-catalysts or heavy meal mercaptide scavengers likewise failed to give acceptable yields of aldehyde.

Hydration of XLIIIb-d; conversion to phenylacetaldehyde derivatives (LIVb-d)

The styrenes XLIIIb-d were hydrated and products isolated in identical fashion to the procedure employed for XLII. Thus, from 3.25 g (20 mmol) of XLIIIb was recovered 6.66 g (24.5%) of α-phenylpropionaldehyde, identical to an authentic sample (Aldrich). The styrene (XLIIIc) 3.56 g (20 mmol) was converted to 0.53 g (35%) of α-phenylbutyraldehyde, (LIVc) which was identical to an authentic sample independently prepared by reduction of α-phenylbutyryl chloride with tri-$\underline{t}$-butoxy lithium aluminum hydride (218). The styrene (XLIIId) 2.40 g (10.6 mmol) was converted to 1.02 g (44.5%) of diphenylacetaldehyde (LIVd), which was identical to an authentic sample (Aldrich).

Hydroboration and oxidation of the β-styrenyl sulfides (XLII, XLIIIb-d) to the phenethanol derivatives (LVIa-d)

A general hydroboration procedure, similar to that developed by H. C. Brown (190), was employed. The β-styrenyl sulfides (XLII, XLIIIb-d) (~25 mmol) were reacted at 0° in 35 ml of diglyme with the in situ generated diborane from 0.62 g of sodium borohydride and 3.39 ml of boron trifluoride etherate. After stirring for 3 hr, the solution was allowed to come to room temperature and excess hydride destroyed by 60 ml of water. A solution of 1.1 g of sodium hydroxide and 4.9 ml of 30% hydrogen peroxide in 40 ml of water was added and the reaction mixture stirred for 10 hr, after which 100 ml of water was added

and the aqueous solution was extracted twice with 100 ml of ether. The ether extracts were washed with water, dried ($MgSO_4$) and concentrated under vacuum. The residue was distilled or crystallized to yield the alcohols (LVIa-d).

The styrene (XLII) 4.00 g (26.7 mmol) yielded 2.90 g (88.7%) of LVIa by distillation, bp 50-53° (0.20 Torr). Analysis by nmr ($CDCl_3$) indicated the distilled product to consist of 23/77 ratio of 1-phenethanol/2-phenethanol, as previously observed for the hydroboration and oxidation of styrene (219). The isolated product was identical to an authentic mixture (Aldrich). The styrene (XLIIIb), 4.06 g (25 mmol) yielded 2.49 g (76.5%) of 2-phenylpropanol (LVIb) by distillation; 68-70° (0.70 Torr) (lit (220) bp 113-114° (14 Torr)). The product was identical to an authentic sample prepared by sodium borohydride reduction of LIVb.

The styrene (XLIIIc), 3.20 g (18 mmol) yielded 2.00 g (74.4%) of 2-phenylbutanol (LVIc) by distillation, bp 84-87° (0.70 Torr) (lit (221) bp 120-121° (14 Torr)).

The styrene (XLIIId), 5.65 g (25 mmol) yielded 3.92 g (79.3%) of 2,2-diphenylethanol (LVId) which was crystallized from ethylacetate (20%)-pentane (80%), mp 60-62°, (lit (221) mp 61-62°).

Hydroboration and chromic acid oxidation of styrenyl sulfides (XLII, XLIIIb-d), to phenyacetaldehyde derivatives (LIVa-d)

A modification of the general procedure developed by H. C. Brown (191) was employed. The β-styrenyl sulfides (XLII,

XLIIIb-d), (20-30 mmol) were reacted at 0° in 30 ml of diglyme with the in situ generated diborane from 0.5 g of sodium borohydride and 2.6 ml of borontrifluoride etherate. The reactions were stirred for 4 hr at 0° after which 10 ml of water and 100 ml of ether were added followed by oxidation with a 10% excess of chromonium trioxide. The heterogeneous reaction was stirred for 2 hr at 25°, after which 100 ml of water was added and the ethereal layer separated. The aqueous layer was extracted with 100 ml of ether and the combined ethereal extracts washed with 0.1 $\underline{N}$ sodium bicarbonate and dried ($MgSO_4$). After removal of the solvent under vacuum, the residue was distilled or chromatographed on silica gel with hexane as the eluent.

By the general procedure, styrene (XLIII), 4.50 g (30 mmol) yielded 0.50 g (14%) of acetophenone and 1.78 g (49.5%) of phenylacetaldehyde (LIVa), which were separated and isolated by chromatography with preparative tlc, cyclohexane (10%)-pentane (90%) as eluent.

Styrene (XLIIIb), 3.25 g (20 mmol) yielded 1.83 g (68.2%) of 2-phenylpropionaldehyde (LIVb) which was isolated by chromatography on a silica gel column with hexane.

Styrene (XLIIIc), 3.55 g (20 mmol) yielded 1.50 g (52%) of 2-phenylbutyraldehyde (LIVc) by distillation, 94-98° (10 Torr) (lit (222) bp 104-106° (15 Torr)).

Styrene (XLIIId), 4.52 g (20 mmol) yielded 2.35 g (61%) of diphenylacetaldehyde (LIVd) by distillation, bp 172-175° (10 Torr) (lit (222) bp 168-170° (10 Torr).

General procedure for sodium meta-periodate oxidations of

styrenyl and acetylenic sulfides to the corresponding sulfoxides

The sodium meta-periodate oxidations were performed by
mixing at -10°, 60 ml of a acetonitrile solution containing 25
mmol of the sulfide with 60 ml of a 0.5 M aqueous solution of
sodium meta-periodate. The solution was stirred in a refriger-
ator at -5 to -10° for 12 hr; the cold solution was filtered
and extracted with three 50 ml portions of chloroform. The
dry chloroform extract (MgSO₄) were concentrated under vacuum
to yield the crude sulfoxides that were purified by column
chromatography or crystallization. The yields of sulfoxides
isolated by this procedure are listed in Table 12.

General procedure for m-chloroperbenzoic acid oxidation of

styrenyl and acetylenic sulfides to the corresponding

sulfoxides

The m-chloroperbenzoic acid oxidation were preformed by
adding 1 equivalent of m-chloroperbenzoic acid, dissolved
50 ml of chloroform and cooled to -10°, to 25 mmol of the sulf-
ide in 100 ml of chloroform cooled to -10°. The reaction flask
was stoppered and allowed to stand at -23° in a refrigerator
for 12 hrs. The cool solution was filtered to remove m-chloro-
benzoic acid, washed twice with 100 ml of saturated aqueous
sodium bicarbonate, dried (MgSO₄), and the solvent removed
under vacuum to yield the crude sulfoxide, which were purified
by column chromatography or crystallization. Yields are re-
ported in Table 12.

Preparation of methyl phenethynyl sulfoxide (LVIII) by oxida-
tion of methyl phenethynyl sulfide (LVIII)

Methyl phenethynyl sulfide (XLII) was prepared as previous-
ly reported (60), and oxidized by the general procedures. The
product (LVIII) was eluted from a 2.5 x 50 cm silica gel column
with ethyl acetate (60%)-hexane (40%) as a colorless oil which
polymerized upon standing; ν_{CCl_4} 1060 cm^{-1} (S=O), 2210 cm^{-1}
(C≡); nmr (CDCl$_3$) 2.98δ (s, 3, SOC$\underline{H_3}$); (m, 5, 7.20-7.60δ). The
mass spectrum is reported in detail elsewhere (193).

<u>Anal</u>. Calcd. for C$_9$H$_8$SO: C, 65.58; H, 4.91; S, 19.49.
Found: C, 65.70; H, 5.03; S, 19.54.

Preparation of LVIII by dehydrochlorination of α-chloro-β-
(methylsulfinyl)styrene (LX)

Reaction of 2.0 g (10 mmol) of the chloro sulfoxide (LX)
with 2.3 g (200 mmol) of potassium <u>t</u>-butoxide in 100 ml of tetra-
hydrofuran for 15 hr at 25° led to 1.31 g (89.3%)of methyl
phenethynyl sulfoxide (LVIII). The acetylenic sulfoxide was
isolated by pouring the reaction mixture into 200 ml of ice
water followed by extraction with three 75 ml portions of chloro-
form. The chloroform extracts were washed with water, dried
(MgSO$_4$) and the solvent removed under vacuum. Chromatography
yielded the pure product (LVIII).

Preparation of methyl phenethynyl sulfone (LIX) by oxidation
of LVII

Methyl phenethynyl sulfide (LVII) 2.96 g (20 mmol) was
dissolved in 100 ml of chloroform and cooled to -10°. A solution

of 7.9 g of 83% m-chloroperbenzoic acid in 100 ml of chloro-
form at -10° was added slowly to the sulfide and the mixture
allowed to stand for 4 days at -20°. The m-chlorobenzoic acid
was filtered from the cool solution and the chloroform solu-
tions washed twice with 100 ml of saturated sodium bicarbonate,
dried (MgSO$_4$), and the solvent removed under vacuum. The
residue was crystallized from ethyl acetate (20%)-ether (10%)-
hexane (70%) to yield 2.88 g (81%) of crystals, mp 59-60°.
Recrystallization from ether (50%)-hexane (50%) raised the mp
to 61-62°; ν_{KBr} 1308, 1145, 1125 cm^{-1} (SO$_2$), 2180 cm^{-1} (C≡C);
nmr (CDCl$_3$) 3.30δ (s, 3, SO$_2$CH$_3$); (m, 5, 7.25-7.75δ). The mass
spectrum is reported in detail elsewhere (193).

Anal. Calcd. for C$_9$H$_8$O$_2$S: C, 60.00; H, 4.48; S, 17.77.
Found: C, 60.11; H, 4.48; S, 17.58.

Preparation of α-chloro-β-(methylsulfinyl)styrene (LX)

Oxidation of XLIV by the general procedures yielded LX,
which was purified by column chromatography on silica gel.
Impurities were eluted by ethyl acetate and the sulfoxide was
recovered by elution with methanol. Evaporation of the methanol
gave a product that was recrystallized from ethyl acetate (50%)-
hexane (50%) to give the sulfoxide, mp 85-86°; nmr (CDCl$_3$)
2.80δ (s, 3, SOCH$_3$); 6.98δ (s, 1, CH=); (m, 5, 7.30-7.80δ).
The mass spectrum is reported in detail elsewhere (193).

Anal. Calcd. for C$_9$H$_9$ClOS: C, 53.86; H, 4.52; S, 15.97;
Cl, 17.66. Found: C, 54.01; H, 4.50; S, 16.02; Cl, 17.74.

Conversion of LX into α-ethoxy-β-(methylsulfinyl)styrene (LXI)

Treatment of 2.00 g (10 mmol) of $\underline{Z}$ (trans, chloro and methylsulfinyl) α-chloro-β-(methylsulfinyl)styrene (LX) (60) in 100 ml of tetrahydrofuran with 200 ml of sodium ethoxide yielded a crude oil, that was chromatographed on a silica gel column with ethyl acetate to 1.80 g (86%) of LXI. A single isomer, apparently the $\underline{Z}$ isomer (trans, ethoxy and methyl-sulfinyl groups) was formed; nmr (CDCl$_3$) 2.70δ (s, 1, SOC$\underline{H}_3$); 1.30δ and 3.97δ (t, 3; q, 2, $\underline{J}$ = 8.0 Hz, OC$\underline{H}_2$C$\underline{H}_3$); 6.02δ (s, 1, C$\underline{H}$=); (m, 5, 7.30-7.65δ).

Anal. Calcd. for C$_{11}$H$_{14}$O$_2$S: C, 62.84; H, 6.71; S, 15.22. Found: C, 62.62; H, 6.86; S, 15.13.

Reaction of methyl phenethynyl sulfoxide (LVIII) with thionyl chloride; preparation of α,β-dichloro-β-(methylmercapto)styrene (LXII)

The acetylenic sulfoxide (LVIII), 16.70 g (102 mmol) was dissolved in 100 ml of methylene chloride at 0° and maintained under a nitrogen atmosphere. To the solution was added, in a dropwise fashion over 30 min, 7.5 ml (1 equivalent) of thionyl chloride dissolved in 20 ml of methylene chloride. The re-action was stirred for 2 hrs at 0°, and solvent removed under vacuum. The crude residue was distilled under vacuum to yield 15.15 g (68%) of the dichlorostyrene (LXII), bp 84-86° (0.20 Torr). The nmr (CDCl$_3$) spectrum was consistent with a 50:50 mixture of the cis:trans product; 2.21δ and 2.35δ (s, 1.5, SC$\underline{H}_3$ and s, 1.5, SC$\underline{H}_3$); (m, 5, 7.15-7.50δ). The mass spectrum is

reported elsewhere (193).

Anal. Calcd. for $C_9H_8Cl_2S$: C, 49.32; H, 3.68; S, 14.63;
Cl, 32.36. Found: C, 49.08; H, 3.87; S, 14.84; Cl, 32.15.

Preparation of β-(methyl)-β-(methylsulfinyl)styrene (LXV)

Oxidation of XLVII by the general procedures yielded the
sulfoxide (LXV), which was crystallized from ethyl acetate (20%)-
hexane (80%), mp 103-104°; nmr (CDCl$_3$) 2.63 (s, 3, SOCH$_3$);
2.21 (d, 3, J = 2 Hz, CH$_3$); 7.10 (q, 1, J = 2 Hz, CH=);
7.32 (s, 5, Ph). The mass spectrum is reported elsewhere
(192).

Anal. Calcd. for $C_{10}H_{12}OS$: C, 66.65; H, 6.71; S, 17.76.
Found: C, 66.75; H, 6.60; S, 17.93.

Preparation of α-methyl-β-(methylmercapto)styrene (LXIIIb)

The sulfoxide (LXIIIb) was prepared by the general oxida-
tion procedure from a mixture of 9 parts of cis to 1 part of
trans α-methyl-β-(methylmercapto)styrene (XLIIIb) (wherein cis
and trans refer to the relationship of the phenyl and thio-
methyl groups). The crude product appeared to be a mixture of
the cis and trans sulfoxides in a 90/10 ratio. Column chroma-
tography on silica gel with ethyl acetate eluent gave material
that could be crystallized from hexane (80%)-ethyl acetate
(20%) to yield mp 28-34°; nmr (CDCl$_3$), (cis-isomer (90%)) 2.68δ
(s, 3, SOCH$_3$); 2.39δ (s, 3, J = 1.5 Hz, CH$_3$); 6.67δ (q, 1, J =
1.5 Hz, CH=); (trans-isomer (10%)) 2.61δ(s, 3, SOCH$_3$); 2.28δ
(d, 3, J = 2.5 Hz, CH$_3$); 6.40 (q, 1, J = 2.5 Hz, CH=). The
mass spectrum is reported elsewhere (192).

Anal. Calcd. for $C_{10}H_{12}OS$: C, 66.65; H, 6.71; S, 17.76.
Found: C, 66.83; H, 6.76; S, 17.88.

Preparation of α-ethyl-β-(methylsulfinyl)styrene (LXIIIc)

The sulfoxide (LXIIIc) was prepared by the general oxidation procedure from a mixture of 8 parts of cis and 2 parts of trans-α-ethyl-β-(methylmercapto)styrene (XLIIIc) (wherein cis and trans refer to the relationship of the phenyl and thiomethyl groups). The nearly pure crude product was chromatographed from silica gel by ethyl acetate to remove traces of more and less mobile impurities to give an oil containing approximately 80% of the cis sulfoxide and 20% of the trans sulfoxide; nmr (CDCl₃), (cis-isomer (80%)) 2.67δ (s, 3, SOCH₃); 6.46δ (s, 1, CH=); (trans-isomer (20%)) 2.58δ (s, 3, SOCH₃); 6.32δ (t, 1, J = 2 Hz, CH=). The ethyl groups and the aryl groups gave nmr multiplets centered at 1.07, 2.85 and 7.30δ. The mass spectrum is reported elsewhere (192).

Anal. Calcd. for $C_{11}H_{14}OS$: C, 68.02; H, 7.27; S, 16.47.
Found: C, 67.99; H, 7.43; S, 16.32.

Preparation of 1-(methylsulfinyl)-2,2-diphenylethylene (LXIIId)

The sulfoxide was prepared by the general oxidation procedures from XLIIId. The crude product was crystallized from hexane (50%)-ether (50%) to yield material, mp 106.0°; nmr (CDCl₃) 2.72δ (s, 3, SOCH₃); 6.81δ (s, 1, CH=); (m, 10, 7.15-7.55δ). The mass spectrum is reported elsewhere (192).

Anal. Calcd. for $C_{15}H_{14}OS$: C, 74.36; H, 5.83; S, 13.21.
Found: C, 74.10; H, 5.92; S, 13.21.

Preparation of β-methyl d₃-β-(deutereo)styrene (LXIIIe)

The deutereo sulfoxide was prepared from the proton deriva-
tive (LXIIIa) previously reported (60). To 10 ml of deuterium
oxide, in which 0.5 g of sodium had been dissolved, was added
1 g of LXIIIa, dissolved in 4 ml of dioxane. The reaction was
refluxed in an oil bath under nitrogen for 12 hrs. The cooled
solution was neutralized by saturation with ammonium chloride,
diluted with 50 ml of water and extracted with two 50 ml
portions of chloroform. The chloroform extracts were dried
(MgSO) and concentrated to yield 0.94 g of solid residue.
Recrystallization from ethyl acetate (20%)-hexane (80%) yielded
material, mp 62-63° (lit (60) mp 61-62°). The structure of
LXIIIe was unequivocally confirmed by mass spectroscopy (192).
Identical results were obtained by the use of sodium carbonate
as base catalyst; ν_{CCl_4} 1028 cm^{-1} (S=O).

Preparation of β-(methylsulfinyl)-β-(methylmercapto)-α-methyl-styrene (LXIVa)

The sulfoxide (LXIVa) was prepared by the general oxidation
procedures from the corresponding ketene mercaptal (LIb). The
crude product was recrystallized from hexane (80%)-ether (20%)
to give material, mp 101-102°, which is apparently a single
isomer; ν_{KBr} 1040 cm^{-1} (S=O); m/e (70 eV) 226; nmr (CDCl₃) 2.15δ
(s, 3, CH₃); 2.40δ (s, 3, SCH₃); 2.62δ (s, 3, SOCH₃); (m, 5,
7.00-7.45δ).

Anal. Calcd. for $C_{11}H_{14}OS_2$: C, 58.40; H, 6.24; S, 28.29.
Found: C, 58.56; H, 6.02; S, 28.30.

Preparation of β-(methylsulfinyl)β-(methylmercapto)-α-ethylstyrene (LXIVb)

The sulfoxide (LXIVb) was prepared by the general oxidation procedures from the corresponding ketene mercaptal (LIc). The crude product was crystallized from hexane (80%)-ether (20%) to give material, mp 82-84°, which apparently is a single isomer; ν_{KBr} 1035 cm^{-1} (S=O); m/e (70 eV) 240; nmr (CDCl$_3$) 0.99δ and 2.94δ (s, 3; q, 2, J = 7.5 Hz, CH$_2$CH$_3$); 2.58δ (broad singlet, 6, SCH$_3$, SOCH$_3$, Δδ = 0.8 Hz); (m, 5, 6.95-7.45δ).

Anal. Calcd. for C$_{12}$H$_{16}$OS$_2$: C, 59.99; H, 6.71; S, 26.64. Found: C, 60.00; H, 6.62; S, 26.62.

Preparation of 1-(methylsulfinyl)-1-(methylmercapto)-2,2-diphenylethylene (LXIVc)

The sulfoxide (LXIVc) was prepared by the general oxidation procedures from the corresponding ketene mercaptal (LId). The crude product was recrystallized from ethyl acetate (50%)-hexane (50%) to give material, mp 108-110°; ν_{KBr}1030 cm^{-1} (S=O); m/e (70 eV) 288; nmr (CDCl$_3$) 2.24δ (s, 3, SCH$_3$); 2.73δ (s, 3, SOCH$_3$); 7.15δ and 7.40δ (broad doublet, 10, Ph$_2$).

Anal. Calcd. for C$_{16}$H$_{26}$OS$_2$: C, 66.66; H, 5.59; S, 22.20. Found: C, 66.39; H, 5.41; S, 22.49.
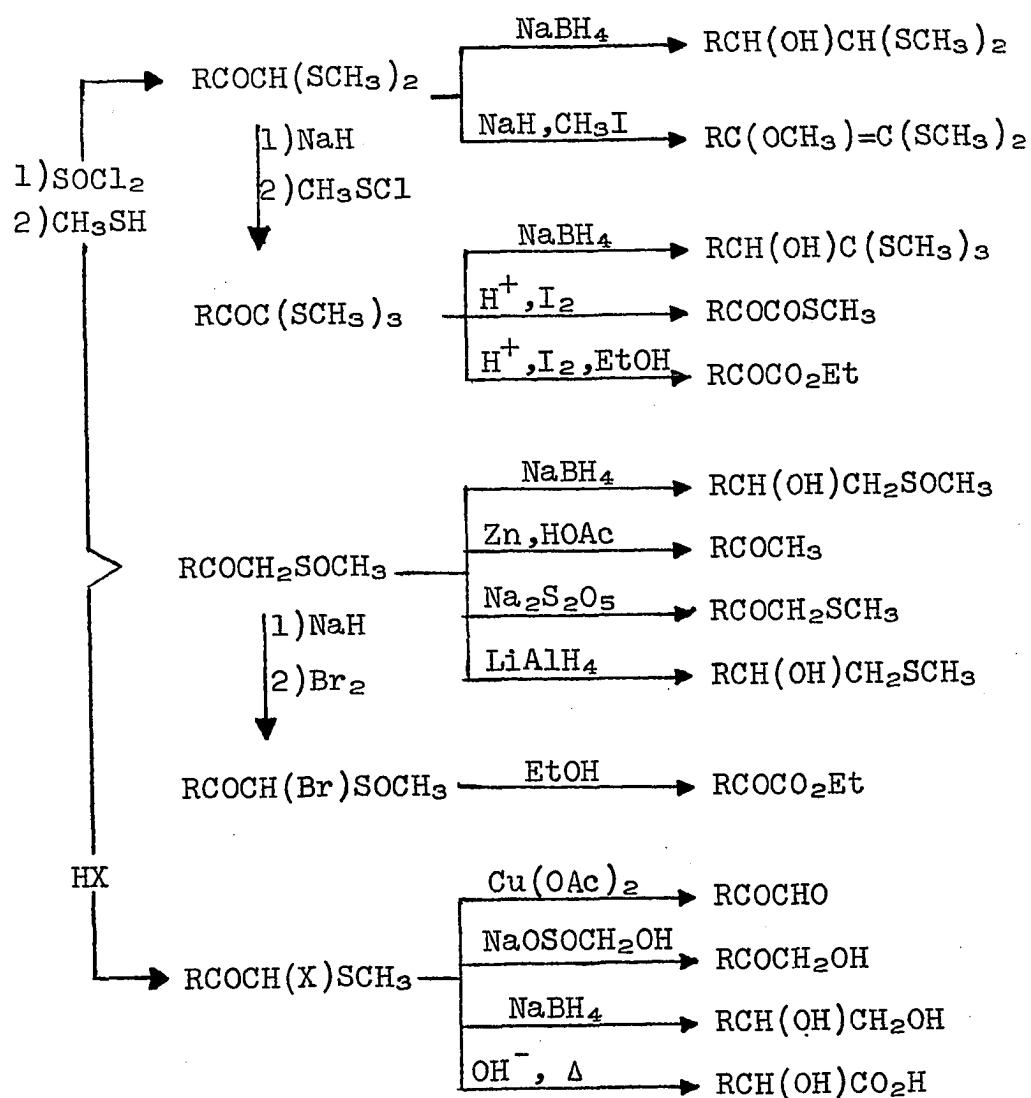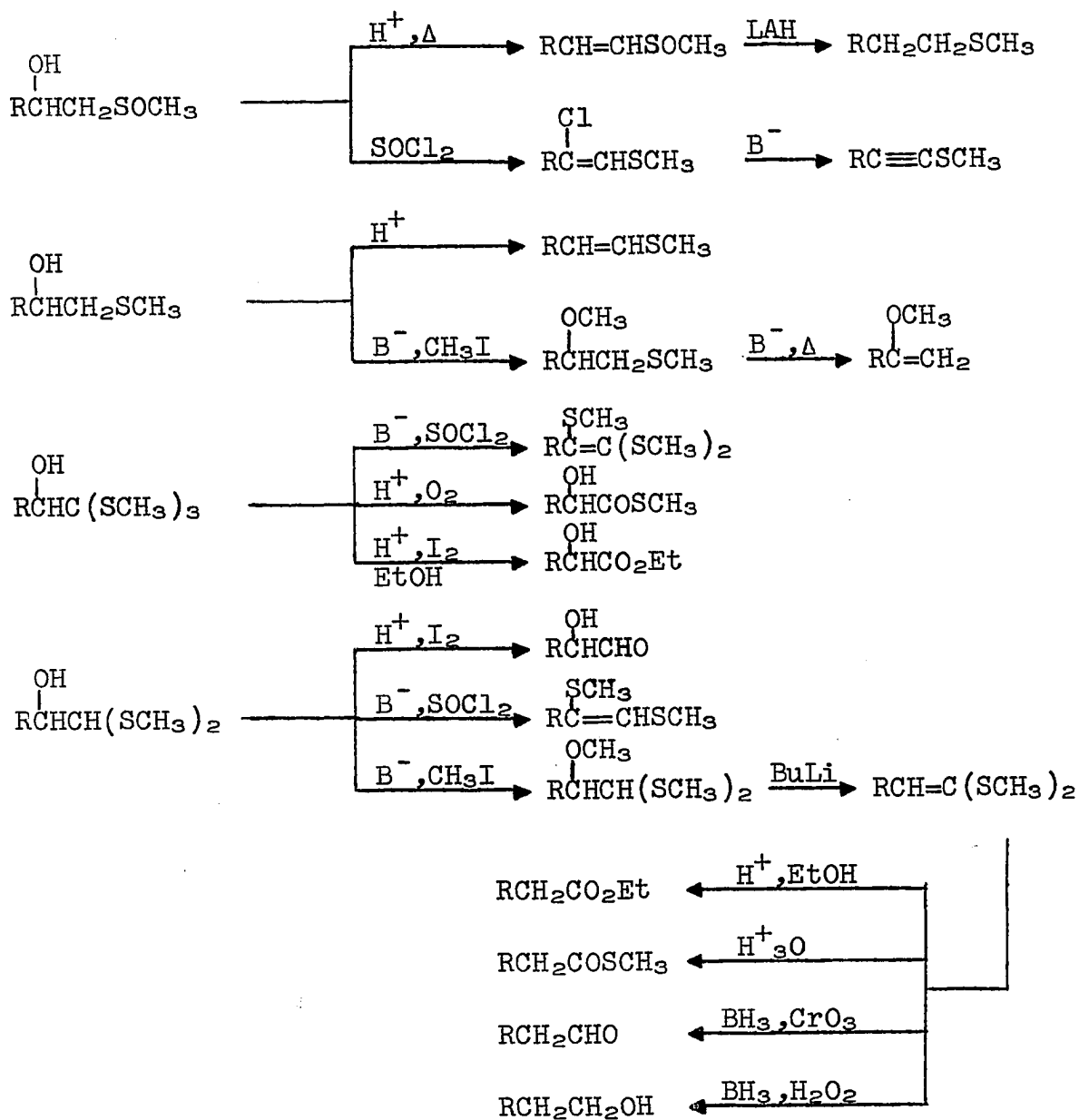
SUMMARY

The value of β-keto sulfoxides in organic synthesis has been demonstrated through the combined efforts of numerous researchers. A major and comprehensive contribution has been provided by Professor Russell and co-workers; Dr. Hans Dieter Becker, Dr. Gerard J. Mikol, Dr. Edward T. Sabourin, Dr. Gerhard Hamprecht, and in final supplement, the efforts of the present researcher. Thus, the conversions of β-keto sulfoxides ($RCOCH_2SOCH_3$) to the three classes of compounds listed in Chart 5 have now been documented (16, 20, 58). The individual reaction steps, and certain other useful intermediates are listed in

$RCOCH_3$ (1)

$RCOCH_2OH$ (1)	$RCH(OH)CH_2OH$ (1)	RCH_2CH_2OH (5)
$RCOCHO$ (1)	$RCH(OH)CHO$ (3)	RCH_2CHO (5)
$RCOCO_2H$ (1 or 3)	$RCH(OH)CO_2H$ (4)	RCH_2CO_2Et (5)

Chart 5. Sulfur-free products derived, in the number of reaction steps required, from β-keto sulfoxides.

Charts 6 and 7. In the first column of Chart 6 are collected a number of readily available compounds having the structural unit : R—CO—C—SCH$_3$. These substances are converted in high yields and in single-step reactions to the intermediates listed in the second column (58, 60, 91).

RCOCH(SCH₃)₂ → $\xrightarrow{\text{NaBH}_4}$ RCH(OH)CH(SCH₃)₂

$\xrightarrow{\text{NaH,CH}_3\text{I}}$ RC(OCH₃)=C(SCH₃)₂

1)SOCl₂
2)CH₃SH

1)NaH
2)CH₃SCl

RCOC(SCH₃)₃ → $\xrightarrow{\text{NaBH}_4}$ RCH(OH)C(SCH₃)₃

$\xrightarrow{\text{H}^+,\text{I}_2}$ RCOCOSCH₃

$\xrightarrow{\text{H}^+,\text{I}_2,\text{EtOH}}$ RCOCO₂Et

RCOCH₂SOCH₃ → $\xrightarrow{\text{NaBH}_4}$ RCH(OH)CH₂SOCH₃

$\xrightarrow{\text{Zn,HOAc}}$ RCOCH₃

$\xrightarrow{\text{Na}_2\text{S}_2\text{O}_5}$ RCOCH₂SCH₃

$\xrightarrow{\text{LiAlH}_4}$ RCH(OH)CH₂SCH₃

1)NaH
2)Br₂

RCOCH(Br)SOCH₃ → $\xrightarrow{\text{EtOH}}$ RCOCO₂Et

HX

RCOCH(X)SCH₃ → $\xrightarrow{\text{Cu(OAc)}_2}$ RCOCHO

$\xrightarrow{\text{NaOSOCH}_2\text{OH}}$ RCOCH₂OH

$\xrightarrow{\text{NaBH}_4}$ RCH(OH)CH₂OH

$\xrightarrow{\text{OH}^-, \Delta}$ RCH(OH)CO₂H

Chart 6. Reactions of primary β-keto sulfoxide derivatives.

$$\underset{\underset{RCHCH_2SOCH_3}{|}}{OH} \quad \xrightarrow{} \quad \begin{array}{l} \xrightarrow{H^+,\Delta} RCH=CHSOCH_3 \xrightarrow{LAH} RCH_2CH_2SCH_3 \\ \\ \xrightarrow{SOCl_2} \underset{RC=CHSCH_3}{\overset{Cl}{|}} \xrightarrow{B^-} RC\equiv CSCH_3 \end{array}$$

$$\underset{\underset{RCHCH_2SCH_3}{|}}{OH} \quad \xrightarrow{} \quad \begin{array}{l} \xrightarrow{H^+} RCH=CHSCH_3 \\ \\ \xrightarrow{B^-,CH_3I} \underset{RCHCH_2SCH_3}{\overset{OCH_3}{|}} \xrightarrow{B^-,\Delta} \underset{RC=CH_2}{\overset{OCH_3}{|}} \end{array}$$

$$\underset{\underset{RCHC(SCH_3)_3}{|}}{OH} \quad \xrightarrow{} \quad \begin{array}{l} \xrightarrow{B^-,SOCl_2} \underset{RC=C(SCH_3)_2}{\overset{SCH_3}{|}} \\ \xrightarrow{H^+,O_2} \underset{RCHCOSCH_3}{\overset{OH}{|}} \\ \xrightarrow[EtOH]{H^+,I_2} \underset{RCHCO_2Et}{\overset{OH}{|}} \end{array}$$

$$\underset{\underset{RCHCH(SCH_3)_2}{|}}{OH} \quad \xrightarrow{} \quad \begin{array}{l} \xrightarrow{H^+,I_2} \underset{RCHCHO}{\overset{OH}{|}} \\ \xrightarrow{B^-,SOCl_2} \underset{RC=CHSCH_3}{\overset{SCH_3}{|}} \\ \xrightarrow{B^-,CH_3I} \underset{RCHCH(SCH_3)_2}{\overset{OCH_3}{|}} \xrightarrow{BuLi} RCH=C(SCH_3)_2 \end{array}$$

$$\begin{array}{l} RCH_2CO_2Et \xleftarrow{H^+,EtOH} \\ RCH_2COSCH_3 \xleftarrow{H^+_3O} \\ RCH_2CHO \xleftarrow{BH_3,CrO_3} \\ RCH_2CH_2OH \xleftarrow{BH_3,H_2O_2} \end{array}$$

Chart 7. Reactions of secondary β-keto sulfoxide derivatives.

A wide variety of olefinic substances are depicted in Chart 7. These derivatives are collected in a more orderly manner in Chart 8.

$RCH = C(SCH_3)_2$ $RCH = CHSCH_3$ $RCH = CHSOCH_3$

$RC(OCH_3) = C(SCH_3)_2$ $RC(Cl) = CHSCH_3$ $RC \equiv CSCH_3$

$RC(SCH_3) = C(SCH_3)_2$ $RC(SCH_3) = CHSCH_3$ $RC(OCH_3) = CH_2$
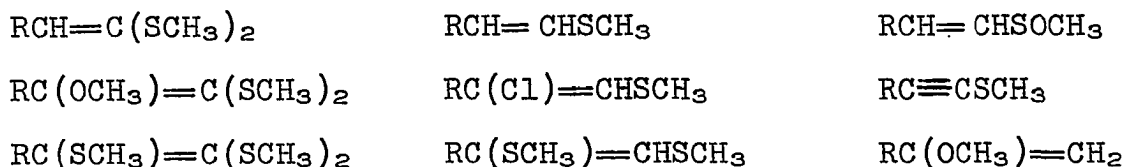
Chart 8.   Olefinic derivatives synthesized from β-keto sulfoxides.

The scope of β-keto sulfoxide utility in organic synthesis is considerably wider than that displayed in Charts 6 and 7. Thus, β-keto sulfoxides and the corresponding sulfides can be alkylated to give the mono- or dialkylated products: $RCOCHR'SOCH_3$, $RCOCR_2'SOCH_3$, $RCOCHR'SCH_3$, $RCOCR_2'SCH_3$ (58,59,62). Addition of Grignard reagents to the α-keto mercaptals allows for the synthesis of tertiary-β-hydroxy mercaptals $[RR'C(OH)CH(SCH_3)_2]$ and all the corresponding derivatives leading from the secondary alcohol derivative $[RCH(OH)CH(SCH_3)_2]$, Charts 6 and 7. Moreover, β-keto sulfoxides can be alkylated with boroacetic acid derivatives or undergo Michael additions to acrylate esters to yield two-and three-carbon-homologated derivatives: $RCOCH-(SOCH_3)CH_2CO_2Et$ and $RCOCH(SOCH_3)CH_2CH_2CO_2Et$ (61). These in turn can be converted to a wide variety of sulfur-free products.

gave to proof-read this manuscript.

I extend a special "thank you" to the Russell group and the whole organic section in general. I doubt if I shall ever have the privilege of working with a finer group. In particular, I am indebted to Dr. Roy King and Dr. Thomas Kinstle for invaluable aid and instruction in structure elucidation.

Somewhat removed from my graduate academic sphere, but without whose influence this venture would not have been undertaken and to whom, perhaps, my greatest debt is due are: my parents, to whom I dedicate this manuscript for their love, support and faith in the pursuit of my independent goals; my brothers, Boris and Orest, with whom I have shared my most memorable adventures; my undergraduate advisors, particularly Brother Ambrose Trusk, whose inspiration led me to graduate study; all my fellow classmates, whose high values and competitive examples were more than instrumental; George Lanik, Susan Howard, Bill Rose, and the whole Steffen and Shortridge families, to whom I am grateful for a lasting friendship and the development of my values.

Finally, but only by virtue of convention, I express my most sincere gratitude to Mrs. Louise Dayton, not only for her considerable effort in the typing of this manuscript, but also for the many favors and privileged friendship extended by the whole Dayton family.

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