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Synthetic utility of beta-keto sulfoxides

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SYNTHETIC UTILITY OF BETA-KETO SULFOXIDES

by

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INTRODUCTION

A survey of the literature reveals that intensive study of the chemistry of the sulfoxide group is a relatively new area of organic chemistry. The commercial availability of dimethyl sulfoxide has stimulated numerous programs aimed at utilizing the novel properties of this compound.

As a dipolar, aprotic solvent, it is especially useful as a medium for the generation of carbanions under relatively mild conditions. This property has been utilized in extensive studies on the sterochemistry of carbanions, acidity of hydrocarbons and oxidation of hydrocarbons via a carbanion intermediate. The solvent properties of dimethyl sulfoxide have also been used to advantage in synthetic procedures involving displacement reactions on saturated carbon atom.

Since the sulfoxide group is in an intermediate state of oxidation, it is easily oxidized or reduced. Numerous studies have demonstrated the ability of dimethyl sulfoxide to act as an oxidizing agent for halides, alcohols, and alcohol derivatives.

The present study was undertaken to find ways to incorporate the methylsulfinylmethylene group (CH_3SOCH_2-) into a variety of organic molecules such as nitriles, halides, epoxides, and esters. The initial products derived

from these reactions

$$RCN \longrightarrow RC(=NH)CH_2SOCH_3 \tag{i}$$

$$RX \longrightarrow RCH_2SOCH_3 \tag{ii}$$

$$RR'C\underset{O}{\overset{}{\diagup\!\!\!\diagdown}}CR''R''' \longrightarrow RR'C(OH)C(CH_2SOCH_3)R''R'' \tag{iii}$$

$$RCO_2R' \longrightarrow RCOCH_2SOCH_3 \tag{iv}$$
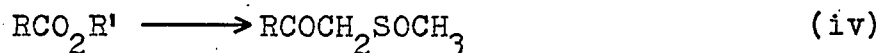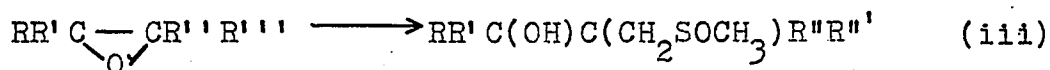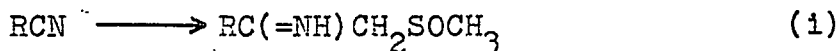
showed promise of being useful synthetic intermediates.

The β-keto sulfoxides, formed from aromatic esters, Equation 4, proved to be an interesting class of compounds. Efforts were then directed toward exploring the chemistry of these compounds. The bifunctional nature of β-keto sulfoxides was utilized in attempts to devise practical synthetic procedures for the formation of ketones, ketols, glyoxals, α-diketones, glyoxalic acids and esters, and glycols.

In the brief review which follows, some of the more important aspects of the chemistry of sulfoxide derivatives have been presented. The review is by no means complete since the reports of uses for, and studies on dimethyl sulfoxide, and sulfoxides in general, are legion.

The term, "dimsylsodium" has been coined for sodium (methylsulfinyl)-methide, CH_3SOCH_2Na (1). Similarly, the term, "dimsylpotassium" can be applied to the potassium salt. These terms will be used in the discussion that

follows. It is to be understood that "dimsylsodium" refers
to the salt generated from dimethyl sulfoxide and sodium
hydride, and "dimsylpotassium" refers to the salt generated
from dimethyl sulfoxide and potassium t-butoxide in t-butyl
alcohol. Exceptions to this will be pointed out.

LITERATURE REVIEW

The preparation of sulfoxides, their structure, and chemical behavior have been reviewed (2, 3, 4). Reviews with specific emphasis on the use of dimethyl sulfoxide as a reactant and a solvent are also available (5, 6, 7).

The Methylsulfinylcarbanion: Generation and Properties

The methylsulfinylcarbanion has been generated using sodium methoxide (8), or potassium t-butoxide (9, 10) in dimethyl sulfoxide. The carbanion is generated reversibly and in low concentration in these systems. The equilibrium shown in Equation 1 has been measured

$$CH_3SOCH_3 + t\text{-BuOK} \xrightleftharpoons{K_1} CH_3SOCH_2K + t\text{-BuOH} \qquad (1)$$

$$(Ph)_3CH + CH_3SOCH_2K \xrightleftharpoons{K_2} (Ph)_3CK + CH_3SOCH_3 \qquad (2)$$

$$(Ph)_3CH + t\text{-BuOK} \xrightleftharpoons{K_3} (Ph)_3CK + t\text{-BuOH} \qquad (3)$$

$$(Ph)_2CO + CH_3SOCH_2K \xrightleftharpoons{} (Ph)_2C(OH)CH_2SOCH_3 \qquad (4)$$
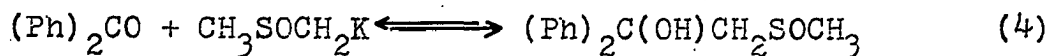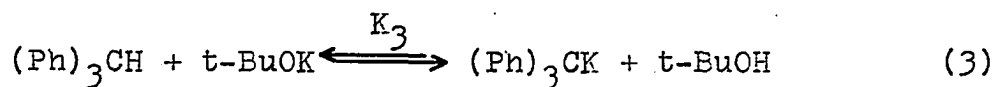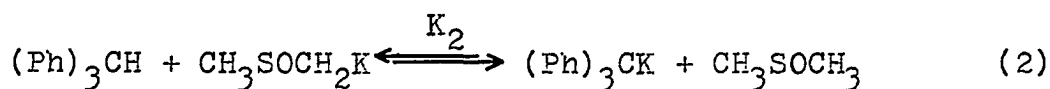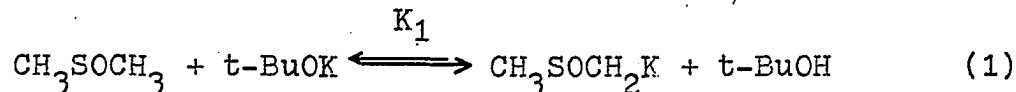
to be $1.5 \pm 0.5 \times 10^{-7}$ at $25^\circ C$. (11). The rapid and nearly quantitative formation of an adduct with benzophenone at room temperature (12, 13), as shown in Equation 4,

has been cited as evidence that the equilibrium shown in Equation 1 is rapidly established (14). Measurement of the equilibrium of Equation 3 and calculation of K_2 from the data gave the values, $K_2 = 8 \times 10^3$ and $K_3 = 1.2 \times 10^{-3}$. Thus, in this system, the methylsulfinylcarbanion is about eight thousand times more basic than the triphenylmethyl anion.

As Equation 4 shows, the methylsulfinylcarbanion forms adducts with carbonyl compounds, forcing the equilibrium of reactions 1 and 4 to the right. A similar situation prevails when sodium methoxide, an even weaker base, was advantageously used to effect condensation of dimethyl sulfoxide with diethyl phthalate (8). The basicity, H_-, of a dimethyl sulfoxide-methanol-sodium methoxide system has been shown to vary from 12 to 19 as the solvent was changed from pure methanol to 5% methanol-95% dimethyl sulfoxide (15). The effect of alcohol on the basicity of the medium is dramatically illustrated by comparison with a more recent study in the same system which indicates that dimunition of the alcohol content to 0.02% raises the basicity to $H_- \approx 27$ (16).

The methylsulfinylcarbanion has also been generated using sodium hydride, sodium amide, lithium hydride, or butyllithium (8, 17, 18). This results in the irreversible formation of the anion as an extremely reactive, non-

hydrogen bonded carbanion. In contrast to the dimethyl

sulfoxide methanol-sodium methoxide system, the basicity

of a two molar solution of dimsylsodium corresponds to an

alkaline solution with H_- = 31-33 (1). In a solution of

dimsylpotassium in alcohol-free dimethyl sulfoxide, the

acidity of triphenylmethane has been placed at pK_a 27.2 and

that of dimethyl sulfoxide, at pK_a 31.3 (16). This is in

good agreement with a recent report which indicates that

dimsylsodium in dimethyl sulfoxide-tetrahydrofuran mixtures

is about two to three powers of ten more basic than the

triphenylmethide ion (18), and verifies the value for

dimsylpotassium obtained from measurements in dimethyl

sulfoxide-t-butyl alcohol (11).

The differences in the reactivity of these two basic

systems are not usually evident in the reactions with

carbonyl compounds. However, the reaction of 1,2,5,6-

tetrabromocyclooctane with dimsylsodium and dimsylpotassium

reveals interesting differences (19). As shown in Equation

5a, dimsylsodium effects debromination and does not cause

isomerization of the 1,5-diene to the more stable 1,3-

diene. Dimsylpotassium, on the other hand, causes dehydro-

halogenation and is known to rapidly isomerize the 1,5-

diene (20). Debromination was also observed in the re-

action of 3β-chloro-5α-bromo-6β-bromocholestane (19). The

α,β-unsaturated chloride could be recovered in 82% yield

when subjected to the reaction conditions.
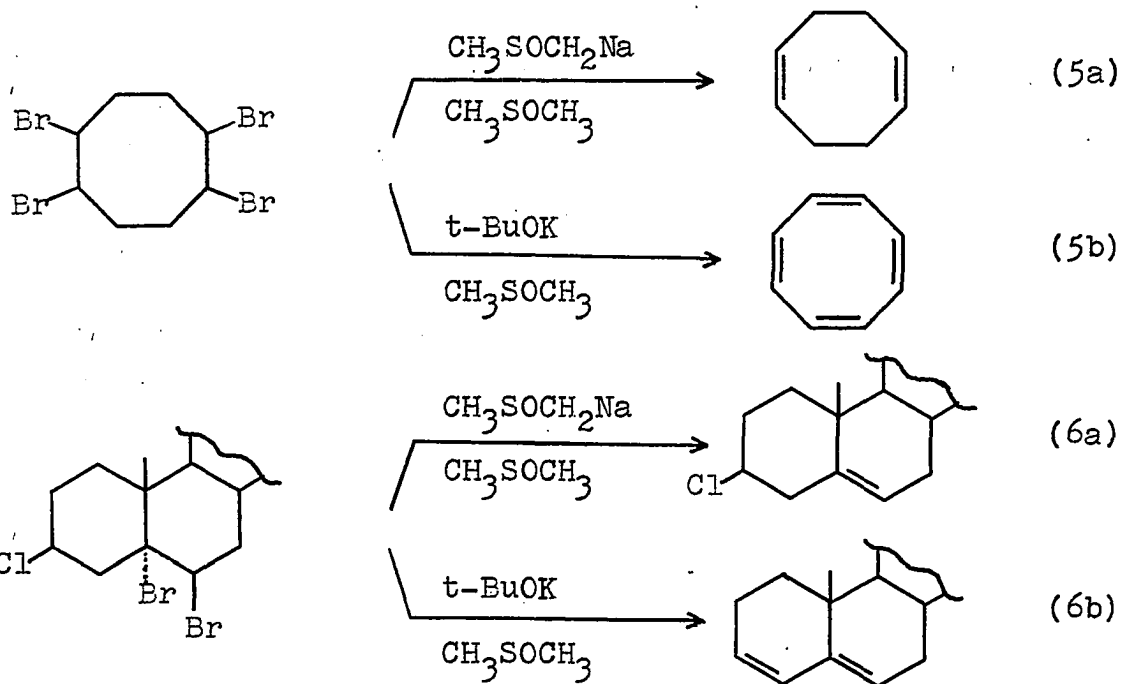
These differences can be attributed to the fact that the predominant basic species in reaction 5b is potassium t-butoxide for which O-H bond formation, leading to dehydrohalogenation is more favorable than O-Br bond formation, leading to dehalogenation.

Though no comparison with dimsylpotassium is available, it is interesting to note that dimsylsodium acts as a nucleophile in the reaction of normal C_{12} to C_{16} alkyl bromides and tosylates. The sulfoxides were formed in 70-85% yield and no olefinic products were reported (21).

The addition product of benzophenone, Equation 4, is formed with dimsylpotassium (13, 9, 14) or dimsylsodium

(12, 22). The cleavage of a tertiary alcohol into a ketone and a carbanion is a known reaction, and has been studied extensively in aprotic solvents containing alkoxide bases (23). Thus the benzophenone adduct should be, and is, formed reversibly. When reaction 4 was quenched after 30 minutes at room temperature, an 80% yield of the adduct was obtained. However, when the reaction was carried out at 65°C., or when the adduct was added to the basic solution at this temperature, an 80% yield of benzophenone was obtained (14). The analogous adduct with dimethyl sulfone cleaves in the same manner at room temperature in the presence of dimsylpotassium (9).

The methylsulfinylcarbanion also adds to benzaldehyde (12, 18) and other aromatic aldehydes (24) as illustrated by Equation 7. This addition

$$ArCHO + CH_3SOCH_2M \longrightarrow ArCH(OM)CH_2SOCH_3$$

$$(M = Na \text{ or } K) \tag{7}$$
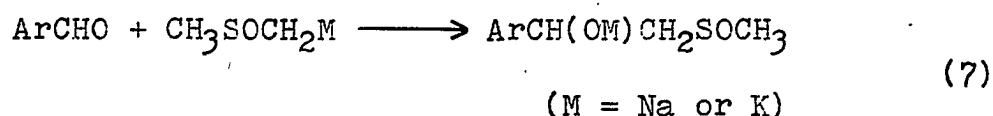
is also reversible as indicated by the formation of benzaldehyde when the adduct was treated with sodium hydride in tetrahydrofuran solution.[a]

In the presence of substances with hydrogens that are

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[a]E. T. Sabourin, Dept. of Chemistry, Iowa State University, Ames, Iowa. Reversible addition. Private communication, February, 1966.

more acidic than those of dimethyl sulfoxide, such as acti-
vated toluene derivatives, the reaction was found to take
a different course. The reaction of p-tolylsulfone or
methyl toluate with a variety of substituted benzaldehydes
was found to result in the formation of stilbene deriva-
tives (13, 24).

The addition of the methylsulfinylcarbanion to the
carbon-carbon double bond of olefins has also been reported
(14, 22, 25, 26), and recently, additions to aromatic
carbon-carbon double bonds have been effected (26, 27).
There is no evidence for the reversibility of these addi-
tions though, in the addition to aromatic compounds, they
might reasonably be postulated as such.

Dimsylsodium adds to the triple bond of diphenyl-
acetylene and 1,4-diphenylbutadiyne (28). A mono-adduct
was formed in the latter case. The mono-adduct with
diphenylacetylene undergoes a second addition to the ole-
finic double bond, followed by beta-elimination of the
methylsulfinyl groups to form 1,3-diphenyl-1,3-butadiene.

Ketones of the type $ArCOCH_2S(O)_nR$ have been prepared
by a variety of methods. Reaction of aryl halomethyl
ketones with methyl mercaptan in sodium ethoxide-ethanol
solution yielded the beta-keto sulfide (n=0) (29, 30). The
beta-keto sulfone (n=2) was prepared from the sulfide by
oxidation of the sulfide with ortho-monoperphthalic acid

(29). Beta-keto sulfones were also prepared by the chromic acid oxidation (31) of beta-hydroxy sulfones (31, 32). Condensation of dimethyl sulfone with aromatic esters has been found to be an efficient method for the synthesis of beta-keto sulfones (33).

Beta-keto Sulfoxides

Preparation of beta-keto sulfoxides (n=1) by oxidation of the sulfide has not been reported, presumably due to the difficulty in stopping the oxidation at the intermediate oxidation state, and the ease with which beta-keto sulfoxides rearrange under acidic conditions. The classical hydrogen peroxide-acetic acid oxidation was attempted with aryl or alkyl phenacyl sulfides. Only the phenyl phenacyl sulfoxide could be isolated; the other compounds (R = CH_3, C_2H_5, n-C_4H_9) led to rearranged products (34).

Reagents for effecting specific oxidation of sulfides to sulfoxides are known (2). Many of these oxidation procedures take advantage of the fact that, for a given series of sulfides, the second oxidation to the sulfone is slower than the oxidation from the sulfide to the sulfoxide. The ease of oxidation of different types of sulfides and sulfoxides is dependent on the nature of the substituents (2). A good rho-sigma correlation was found in the oxidation of substituted diphenyl sulfoxides with perbenzoic

acid, indicating that the ease of oxidation is related to the electron density at sulfur (35).

The beta-keto sulfoxide, ω-(methylsulfinyl)-p-methoxyacetophenone (Ic, Ar = p-MeOPh) was first prepared by manganese dioxide oxidation of the β-hydroxy sulfoxide formed by addition of dimsylpotassium to anisaldehyde (24). It was found to be more readily prepared by the reaction of ethyl anisate with dimsylpotassium, as depicted by Equation 8. This method was applied to a variety of aromatic esters and gave the keto sulfoxide in high yield (10).

$$ArCO_2R + CH_3SOCH_3 + B^- \longrightarrow \underset{I}{ARCOCH_2SOCH_3} + RC^- + BH \qquad (8)$$
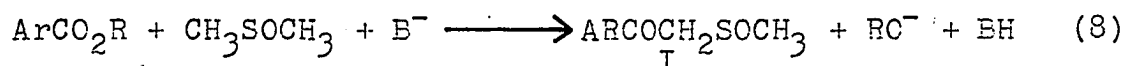
An alternate procedure using dimsylsodium was later reported (17, 18). This latter procedure is also applicable to alkyl esters.

Air oxidation of a mixture of styrene and mercaptans was reported to yield the beta-alkylsulfinyl alpha-phenylethanol. The oxidation was studied using n-propyl, t-butyl and p-anisyl mercaptan (36), Equation 9a. The yields were moderate and only the thiophenol oxidized at a reasonable rate without added initiator. No keto sulfoxide was found although reduction of the hydroxy sulfoxide yielded both acetophenone and alpha-phenethanol. In view of the extensive purification of the oxidation product, it must be assumed that the ketone was formed by dehydrogenation of the alcohol by the Raney nickel catalyst. A beta-

hydroxy sulfoxide, derived from styrene and beta-phenethyl
mercaptan was formed in the distillation of a substance
believed to be beta-phenethyl disulfide (37).

Phenylacetylene reacts in a similar manner when ox-
idized in the presence of mercaptans. The intermediate in
this case is a vinyl hydroperoxide which decomposes to a
hemimercaptal, presumably through the intermediate forma-
tion of a beta-keto sulfoxide, Equation 9b (34). The

$$PhC=CH_2 + RSH + O_2 \longrightarrow$$

(9a)

$$[PhCH(OOH)CH_2SR] \longrightarrow PhCH(OH)CH_2SOR$$

$$PhC\equiv CH + RSH + O_2 \longrightarrow PhC(OOH)=CHSR \longrightarrow$$

(9b)

$$[PhCOCH_2SOR] \longrightarrow PhCOCH(OH)SR$$
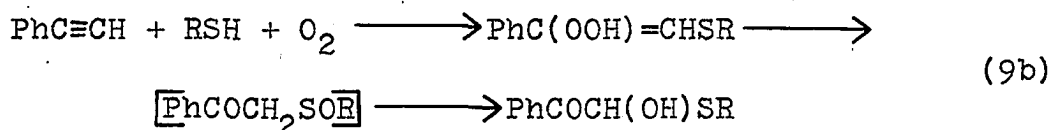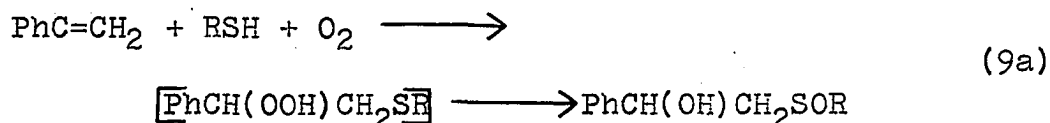
vinyl hydroperoxide with R = phenyl could be isolated, but
none of the keto sulfoxides were isolated.

Asymmetry of the Sulfoxide Group

The beta-keto and beta-hydroxy sulfoxides prepared by
these reactions are racemic mixtures since the sulfoxide
group is an asymmetric center. The structure of the
sulfoxide group had been compared to the carbonyl group,
and in fact, many of the early studies on the chemical re-
activity of sulfoxides gave results which were analogous to
known reactions of ketones (38).

However, the preparation and resolution of ethyl
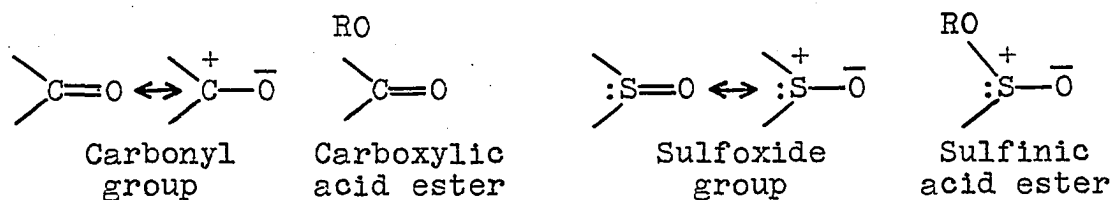
Figure 1. Structure of the carbonyl and sulfoxide group

p-toluenesulfinate into optically active forms showed that the SO group was structurally different from the CO group in that the presence of a -COOR group is not a sufficient condition for observing optical activity (39). Elucidation of the structure of sulfinic acid esters suggested the dipolar representation of the S-O bond was more consistent with the chemical and physical properties. This formulation would suggest a tetrahedral or pyramidal configuration about the sulfur atom rather than a planar structure, and would provide a basis for the differences of the optical properties of the CO and SO groups. Since this type of structure could also be written for sulfoxides, it was reasoned that they too should show optical activity. The successful synthesis and resolution of the d- and l-isomers of 4-amino-4'-methyldiphenyl sulfoxide and methyl p-carboxyphenyl sulfoxide established this in fact (40).

The asymmetry of the sulfoxide group manifests itself in the pmr spectra of sulfoxides of the type, RCH_2SOR'. The methylene protons of the beta-keto sulfoxides, I, in

deuterochloroform or carbon tetrachloride appear as AB

quartets, J_{AB} = 13-14 c.p.s. (10, 18). The unsubstituted

and p-chloro derivatives of ω-(phenylsulfinyl)-acetophenone

also have this pattern, J_{AB} = 14 c.p.s. (34). The methyl-

ene protons of diethyl sulfoxide, and ethyl iso-propyl

sulfoxide (41), 2-thiaindan-2-oxide (42), and a number of

alpha-(alkylsulfinyl)-cinnamic acid derivatives (43) also

give AB patterns, J_{AB} = 13-16 c.p.s. That the presence of

a sulfoxide group in a molecule of this type is a pre-

requisite, but not a sufficient condition, for observing

the non-equivalence of the methylene group has been demon-

strated by studying the effect of solvent on the N.M.R.

spectra of a number of sulfoxides (43). A typical example

is that of benzyl phenacyl sulfoxide, $PhCH_aH_bSOCH_cH_dCOPh$.

In deuterochloroform the ab protons appear as a singlet and

the cd protons appear as an AB quartet, J_{cd} = 14.0 c.p.s.

In acetone, the ab protons now appear as an AB quartet,

J_{ab} = 13.0 c.p.s., and the cd protons appear as a singlet.

Chemical Reduction of Sulfoxides

Since sulfoxides are in an oxidation state (+IV)

between that of the sulfide (+II) and the sulfone (+VI)

they can be readily reduced or oxidized to these valence

states. Reduction reactions, leading to the formation of

the sulfide or the hydrocarbon, are of the greatest value

from a synthetic viewpoint.

Reduction of the sulfoxide group to the sulfide can be accomplished with zinc in acetic acid (2, 17). The C-S bond in unactivated molecules is not readily cleaved by this reagent. The use of sodium metabisulfite, $Na_2S_2O_5$, in aqueous solution is reported to reduce methionine sulfoxide and 1-alpha-(ethylsulfinyl)-2,3,4,6,-tetra-O-acetyl glucose to the sulfide (44). (Since the metabisulfite is formed by thermal dehydration of sodium bisulfite, presumably in aqueous solution, the active reducing agent is the bisulfite ion).

Triphenylphosphine cleanly reduces sulfoxides to the sulfide in high yield. This type of reduction generally requires acid catalysis but can be carried out in neutral solution if carbon tetrachloride is used as the solvent (45). It is interesting to note that the reaction is postulated as proceeding via transfer of a dichloromethylene from $(Ph)_3PCCl_2$ to the sulfoxide with subsequent formation of $(Ph)_3PO$, in analogy to the reaction with ketones.

Reduction of the sulfoxide moiety with metal hydrides has not been widely studied. Lithium aluminium hydride in ether effects reduction of a sulfoxide to the sulfide without cleavage of the C-S bond (46, 47). Sodium borohydride in aqueous or ethanolic solution reduces the carbonyl group

of the beta-keto sulfoxides, but the sulfoxide portion is not reduced under these conditions (48).

However, sodium borohydride-boron trifluoride, which generates diborane, is reported to react slowly with dimethyl sulfoxide though the nature of the product from this reaction was not disclosed (49). This reagent reduces 2-carboxy-3-(phenylsulfinyl)-bicyclo 2.2.1 heptane to the corresponding 2-hydroxymethyl-3-thiophenoxy derivative (50). Diborane is cleaved by dimethyl sulfoxide in a unsymmetrical manner to give an adduct, Equation 10,

$$B_2H_6 + 2CH_3SOCH_3 \xrightarrow{-78^\circ C} BH_2[\bar{O}S(CH_3)_2]_2^+ BH_4^-$$

(10)

$$\xrightarrow{0^\circ C} 2H_2 + \tfrac{1}{3}B_2H_6 + \tfrac{2}{3}B_2O_3 + 2CH_3SCH_3$$
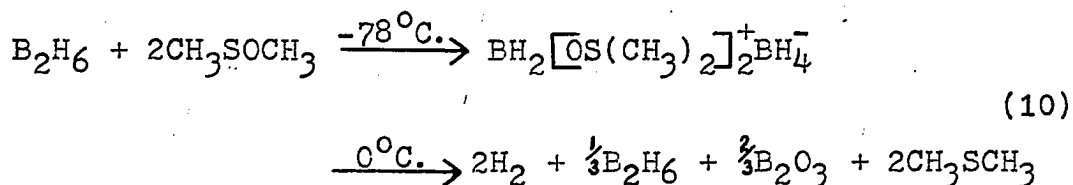
which decomposes violently at temperatures above $-6^\circ C$. (51). Reaction of decahydrodecaborate and dodecahydrododecaborate anions in the presence of acid also reduce dimethyl sulfoxide to the sulfide (52).

These differences in reactivity of sodium borohydride compared to the borane derivatives can be rationalized on the basis of their basic and acidic nature. Sodium borohydride, a base, reacts at an electron deficient center, the carbonyl carbon. The diborane is a strong Lewis acid and reacts at a position of high electron density, the sulfoxide oxygen atom (49, 53).

Reduction with cleavage of the C-S bond can be effected by use of Raney nickel (54). There are very few recorded instances of reduction of sulfoxides, but since sulfoxides are readily reduced to the sulfides, and these can be desulfurized by Raney nickel (54, 55), the method should be generally applicable.

The mercaptan and the symmetrical disulfide, sulfide, and sulfoxide in the series, p-CH$_3$PhS- can be reduced to toluene in ethanol solution by reaction with nickel chloride with sodium borohydride. An active nickel catalyst and hydrogen gas is generated _in situ_ by use of these reagents. The nickel catalyst generated in this manner, in contrast to Raney nickel W-2, does not reduce sulfones (56).

In the beta-keto sulfoxide system, reduction to the ketone was accomplished by use of an aluminum amalgam in tetrahydrofuran-water mixtures (17, 18). This facile cleavage of the C-S bond must be attributed to the ease of reduction of alpha-substituted ketones, rather than to the nature of the reducing agent.

The reduction product of ω-(methylsulfinyl)-acetophenone with sodium borohydride, the β-hydroxy sulfoxide, was pyrolyzed to acetophenone (57). In the strict sense this is not a reduction but rather an oxidation since the pyrolysis is believed to involve beta-elimination of CH$_3$SOH to form an olefin. The "olefin"

formed in this case, however, is the enol of acetophenone which immediately tautomerizes to the ketone. However, the net effect of the two step reaction is a reduction of the keto sulfoxide, with carbon-sulfur bond cleavage, to the ketone.

The reaction of organomagnesium halides with sulfoxides generally results in reduction of the sulfoxide to the sulfide, though more complex reactions can occur concurrently with reduction. The original reaction scheme proposed by Grignard (58), Equations 11a-c, has been verified to some extent by later studies.

$$RMgX + R_2SO \longrightarrow R_3SOMgX \longrightarrow R_3SOH + Mg(OH)X \quad (11a)$$

$$R_3SOMgX \longrightarrow R_2S + ROMgX \longrightarrow R_2S + ROH + Mg(OH)X \quad (11b)$$

$$R_2S \begin{matrix} {}^{C_2H_{2n+1}} \\ {}_{OMgX} \end{matrix} \longrightarrow R_2S + C_nH_{2n} + Mg(OH)X \quad (11c)$$
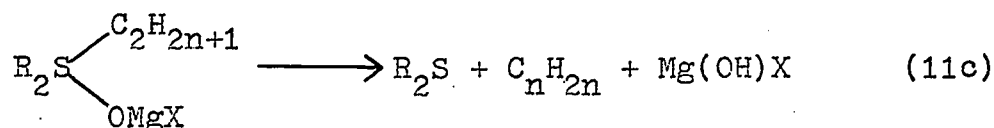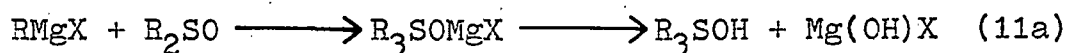
Grignard reported that reactions 11a-c do not occur if R is an aryl group. With isoamylmagnesium bromide and diisoamyl sulfoxide, reactions 11a and 11b occur, whereas diethyl sulfoxide and ethylmagnesium bromide react via reactions 11a and 11c.

Methylmagnesium iodide reduced diisoamyl, diphenyl, and benzyl phenyl sulfoxides to the sulfides (59), but no attempt was made to obtain a mass balance on the reaction,

so the postulate of Grignard regarding alcohol formation can not be checked.

While aryl sulfoxides do not react under Grignard's conditions, the reaction of diphenyl sulfoxide with arylmagnesium bromides in refluxing benzene or di-n-butyl ether results in formation of triarylsulfonium salts (reaction 11a) in 12-49% yields (60). Another departure from the original scheme was noted in the reaction of aryl-, alkyl- and aralkylmagnesium bromides with dimethyl sulfoxide. Reduction of the sulfoxide portion with concomitant incorporation of the organic moiety was found to be the general course of the reaction, Equation 12a (61). The yields were low (10-36%) even though an excess of Grignard reagent was used. Consistent with Grignard's postulate, ethyl-, n-propyl-, and n-butyl-magnesium bromide gave a large amount of ethylene, propene, and 1-butene.

The rearrangement noted with benzylmagnesium chloride, Equation 12b might be visualized as proceeding according to Equation 12a and then undergoing a Sommelet-Hauser type rearrangement (62) in the presence of the strong base to give the observed product. Alternatively, the addition of formaldehyde, benzaldehyde, and the pseudohalogens at the ortho position of benzylmagnesium halides is well established (63). An analogous reaction via the same exo-methylenecyclohexadiene intermediate could occur at the

C=S of the complexed ylid intermediate shown in Equation
12a.

$$ArMgX + CH_3SOCH_3 \longrightarrow \underset{+}{CH_3-\overset{\overset{\overset{X}{\vdots}}{Ar^-Mg\cdots O}}{\underset{}{S}}-CH_3} \xrightarrow{B^-}$$

(12a)

$$\left[\begin{array}{c} \text{CH}_2 \\ \end{array} \right] \qquad \left[\begin{array}{c} X \\ Ar^-\!Mg\cdots O \\ CH_2=\overset{}{S}-CH_3 \end{array} \right] \longrightarrow \begin{array}{c} ArCH_2SCH_3 \\ + \\ Mg(OH)X \end{array}$$

$$PhCH_2MgCl + CH_3SOCH_3 \longrightarrow PhCH_2-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{S}}-OMgX$$

(12b)

$$\longrightarrow \qquad \qquad \qquad \downarrow \qquad \begin{array}{c} CH_3 \\ \end{array}\!\!CH_2SCH_3$$

$$o\text{-}CH_3PhMgBr + CH_3SOCH_3 \longrightarrow$$

(12c)
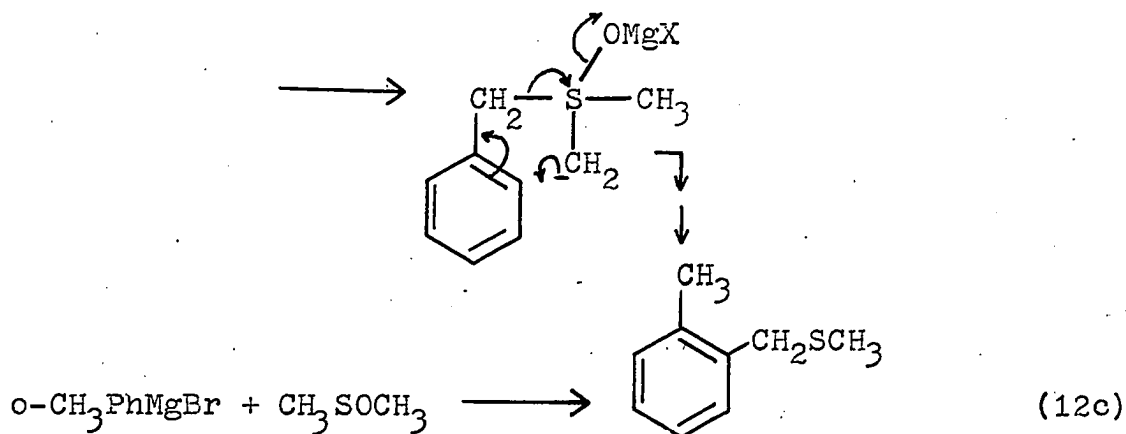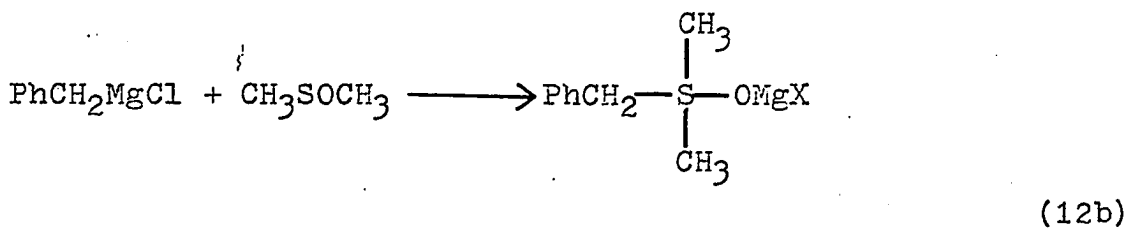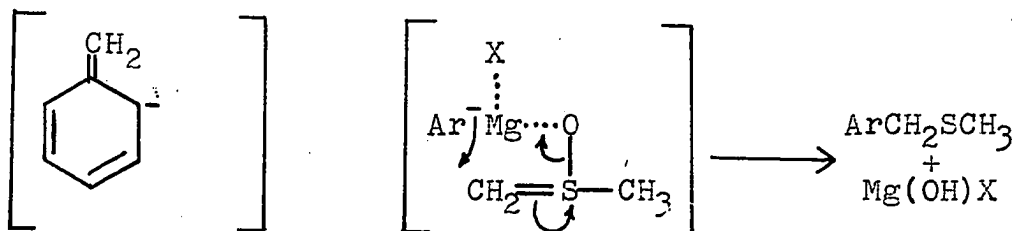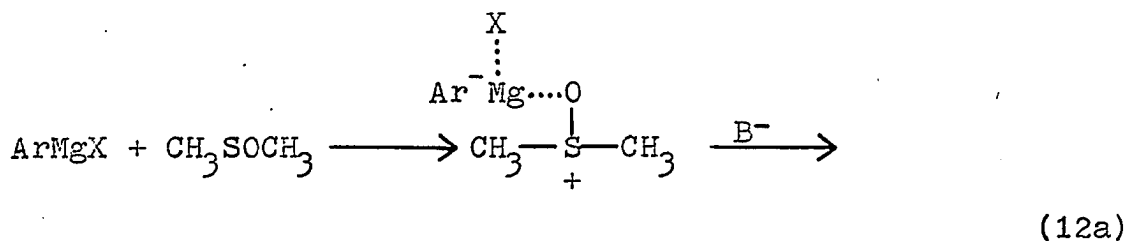
Reaction of the α,β-unsaturated sulfoxide, β-styryl
p-tolyl sulfoxide, with ethyl- or phenyl-magnesium bromide
leads to the formation of 1,4-diphenyl-1,3-butadiene and

the alkyl or aryl p-tolyl sulfide. In addition, phenyl-
magnesium bromide gives a small amount of β,β,β-
triphenylmethyl p-tolyl sulfide (64). Since the un-
saturated sulfide does not react under the reaction condi-
tions, the sulfoxide must eliminate the PhCH=CH- group
prior to reduction.

Pummerer Rearrangement

Treatment of sulfoxides with organic and mineral
acids, and inorganic and organic acid halides or anhydrides
leads to a product in which the sulfoxide has been reduced
to the sulfide and the alpha carbon, providing it contains
at least one hydrogen, is substituted with a nucleophile
(N) usually derived from the acid, as depicted in Equation
13.

$$RSOCH_3 + AN \longrightarrow RSCH_2N + AOH \qquad (13)$$
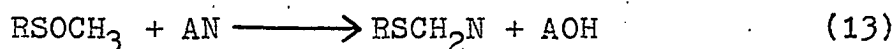
This type of reaction between dibenzyl sulfoxide and
hydrogen chloride was first reported by Smythe in 1909
(65). The chemical properties of the sulfoxide and the
reaction products (benzaldehyde, benzyl mercaptan, dibenzyl
disulfide, benzyl sulfide, and benzyl benzylthiolsulfonate)
were rationalized as being derived from one or both of the
"tautomeric" forms of the sulfoxide (Equation 14):

$$\overset{\quad\quad\quad\quad\quad OH}{PhCH_2SOCH_2Ph \Longleftrightarrow PhCHSCH_2Ph} \qquad (14)$$

"keto" form   "enol" form
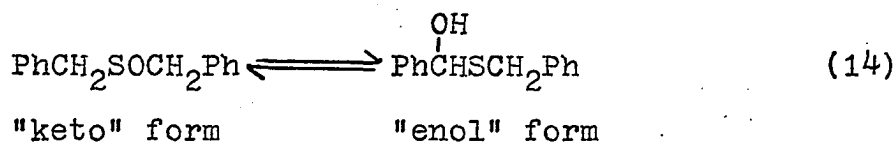
The vigorous reaction with acetic anydride or benzoyl chloride was attributed to the ready production of the "enolic" form in the presence of dehydrating agents.

This type of reaction was also noted by Pummerer later that year when he treated phenylsulfinylacetic acid with dilute mineral acids and observed the formation of thiophenol and glyoxalic acid. The reactions observed by Pummerer are summarized in Equations 15a-c (66, 67).

$$PhSOCH_2CO_2R \begin{cases} + H_2O + HCl \longrightarrow PhSCH(OH)CO_2R \longrightarrow & (15a) \\ \quad PhSH + RO_2C\text{-}CHO \quad (R = H) \\ + HCl \longrightarrow PhSCH(Cl)CO_2R \quad (R = H) & (15b) \\ + (CH_3CO)_2O \longrightarrow PhSCH(OCOCH_3)CO_2R & \\ \quad + CH_3CO_2H \quad (R = C_2H_5) & (15c) \end{cases}$$
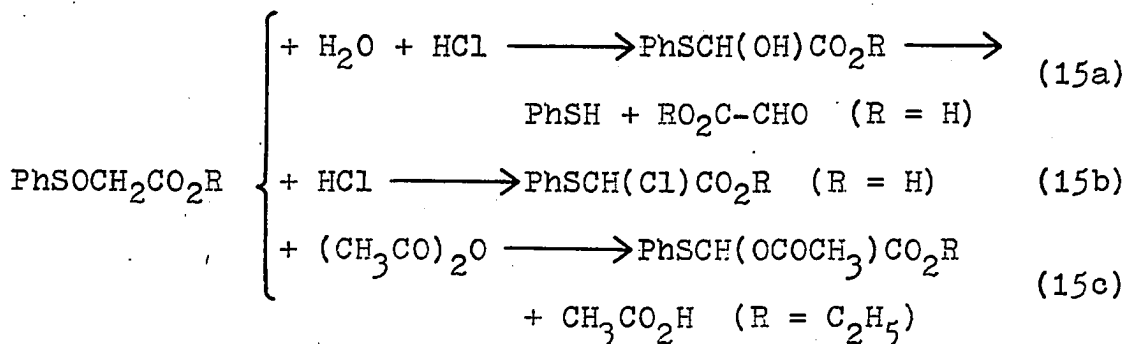
The reaction of sulfoxides with acetic anhydride was later developed as a method for the synthesis of acyclic (68) and cyclic (69) α,β-unsaturated sulfides by pyrolysis of the resultant α-acetoxy sulfide (Equation 16).

$$RSOCH_2CH_2R + (CH_3CO)_2O \longrightarrow RSCH(OCOCH)CH_2R$$
$$\xrightarrow{\Delta} RSCH=CHR + 2CH_3CO_2H' \qquad (16)$$

$$RSOCH_2R + SOCl_2 \longrightarrow RSCH(Cl)R + SO_2 + HCl \qquad (17)$$
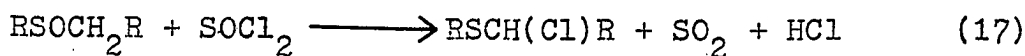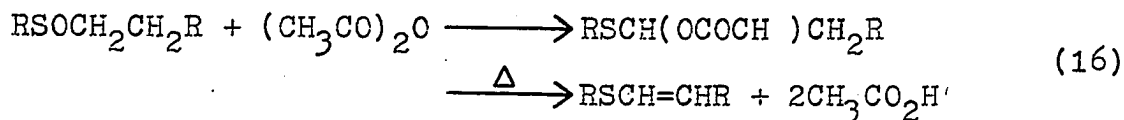
An analogous reaction with thionyl chloride, shown in Equation 17, was investigated as a means of preparing α-chlorosulfides (70). Most sulfoxides, with the exception of tetramethylene sulfoxide and ethyl phenyl sulfoxide,

reacted readily to give the chlorosulfide in good yield.

The mechanism of this type of reaction has been debated for many years. Pummerer originally suggested the sequence shown in Equation 18a and 18b (66). The postulated sulfonium salt intermediate could rearrange by a 1,2 shift of "X" (X = Cl), or could be hydrolyzed to the aldehyde and thiophenol. The latter reaction has an analogy in the hydrolysis of immonium salts, $(R_2N=CHR_2')^+X^-$.

$$PhSOCH_2CO_2H \longrightarrow Ph\overset{\overset{X}{|}}{S}=CHCO_2H \begin{cases} \longrightarrow PhSCH(X)CO_2H & (18a) \\ \\ \longrightarrow PhSH + OHC-CO_2H & (18b) \end{cases}$$
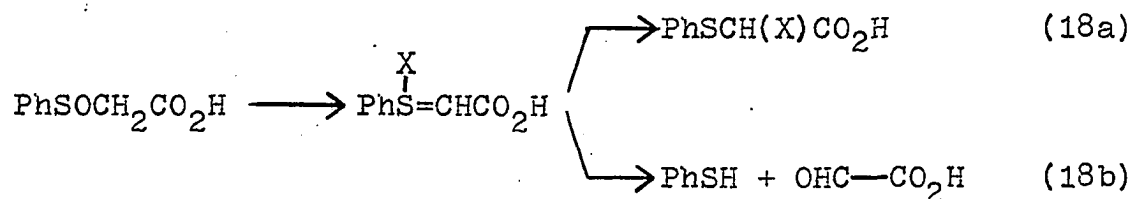
Further study of the decomposition of phenylsulfinyl-acetic acid with (71) or without (72) added acid catalysts, has shown that dithiophenoxyacetic acid is produced in addition to the thiophenol and glyoxalic acid. This has been rationalized in terms of a cleavage-recombination mechanism (71) shown in path A, Figure 2, and an intra-molecular rearrangement (72), shown in path B, Figure 2. The actual cleavage recombination mechanism shown can be discounted as unlikely since the most basic site of the sulfoxide is the oxygen atom and hence, protonation at the sulfur atom does not seem reasonable. Also, the reaction was carried out under conditions (11 hour reflux in acetic acid) which would favor cleavage of the hemimercaptal, 2h.

Figure 2. Possible mechanism for the Pummerer Rearrangement

Path A: cleavage-recombination mechanism

Path B: intramolecular or "external nucleo-
phile" mechanism
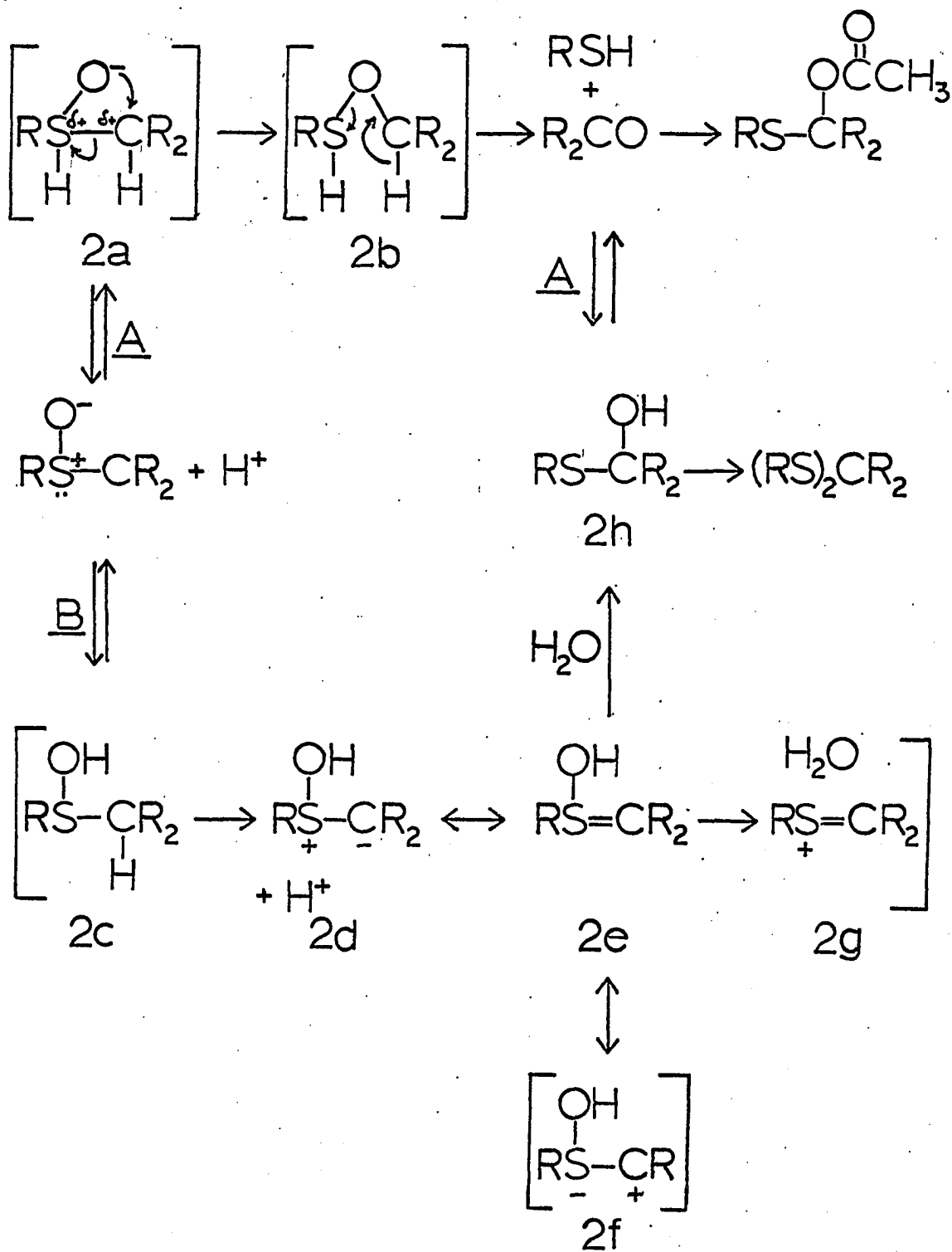
While the protonated sulfenate ester, 2b, is a reasonable formulation for a short lived intermediate, the polarization of the C-S bond indicated in 2a would not be especially favorable in this particular case in which one of the R groups is a carboxyl group.

When the reaction is carried out under milder conditions (refluxing benzene for four hours with no added acid catalyst), the hemimercaptal could be isolated along with the aldehyde, mercaptan and mercaptal (72). It is significant that a 32% yield of the mercaptal, 2j, was obtained in the presence of hydrazine sulfate, even though an independent experiment showed that the hydrazine reacted with the aldehyde faster than the mercaptan reacted to form the mercaptal. Thus, if the free aldehyde were an intermediate it should have been scavenged by the hydrazine.

The rearrangement of ω-(methylsulfinyl)-acetophenone, Ia, occurs at room temperature under the influence of mineral acid catalysts. Under these mild conditions the product of the reaction is the methyl hemimercaptal of phenylglyoxal, formed without any evident intervention of the free glyoxal as an intermediate species (10).

The intramolecular rearrangement, path B, Figure 2, is more consistent with these observations that free carbonyl compounds are not formed in the reaction. Moreover, the reaction of dimethyl sulfoxide with O^{18}-acetic

anhydride (73) established that the intermediate 3a, Figure 3 (analogous to 2e, Figure 2) reacts with an external nucleophile, path A, rather than by an intramolecular transfer of the acetoxy group from sulfur to carbon, path B, as has been proposed (68, 69, 70).

Gentle heating of the pyrimidothiazine, Figure 4a (74) or the indandione, Figure 4b (75) with nucleophilic solvents such as ethanol, methanol, water, and acetic acid, results in rearrangement with incorporation of the "acid" anion into the rearranged product. When rearrangement of the indandione is effected in concentrated hydrochloric acid, the chloride is substituted in the 2-position of the sulfide. The 2-hydroxy derivative can not be converted to the 2-chloro derivative as had been proposed prior to the isolation of the intermediates (8).

These experiments would suggest that the formation of the hemimercaptal of glyoxalic acid, under anhydrous conditions was actually due to reaction of the intermediate 2e with adventitious water, or due to acid catalyzed dehydration of the intermediate to give the resonance stabilized carbonium ion, 2g, which is then converted to the hemimercaptal. Subsequent to this work a carbonium ion of this type was postulated to account for skeletal rearrangements in a Pummerer reaction (76).

General base catalysis of the conversion of 2c to 2d

Figure 3. Mechanism of the reaction of acetic anhydride-O^{18} with dimethyl sulfoxide

Path A: $O^a = O^b = O^{18}$,
    calc., 0.49 atom-% excess O^{18}

Path B: $O^a = O^{18}$, $O^b = O^{16}$,
    calc., 0.28 atom-% excess O^{18}

Found, 0.50 atom-% excess O^{18}

Figure 4. Pummerer Rearrangement involving incorporation of solvent into the product

4a. 1-propyl-3-ethyl-1H-pyrimido[5,4-b][1,4]
     thiazine-2,4,7-(3H, 6H, 8H)-trione 5-oxide

4b. 2-(methylsulfinyl)-1,3-indandione
     HA = CH_3OH, C_2H_5OH, H_2O, CH_3CO_2H, HCl
     (gaseous)

$$CH_3SCH_3 \quad CH_3\overset{O}{\overset{*}{C}}\text{-O-}\overset{O^*}{\overset{*}{C}}CH_3 \xrightarrow[+CHCOO^{*-}]{-H^+} CH_3\overset{+}{S}=CH_2$$

$$\xrightarrow{3a} \overset{O^*}{\overset{}{O}}\overset{}{C}CH_3$$

$$CH_3\overset{+}{S}=CH_2 \quad \overset{O^*}{\underset{}{C}}\text{-}O\overset{CH_3}{\overset{}{C}}\overset{}{\underset{O^*}{}}$$

$$\xrightarrow{\Delta} \overset{O^*}{\underset{}{C}}CH_3$$

$$CH_3\overset{+}{S}=CH_2 \xleftarrow{B} CH_3SCH_2\overset{O}{\overset{}{O}}CCH_3$$

4a

HA / −H⁺

4b

HA / −H⁺
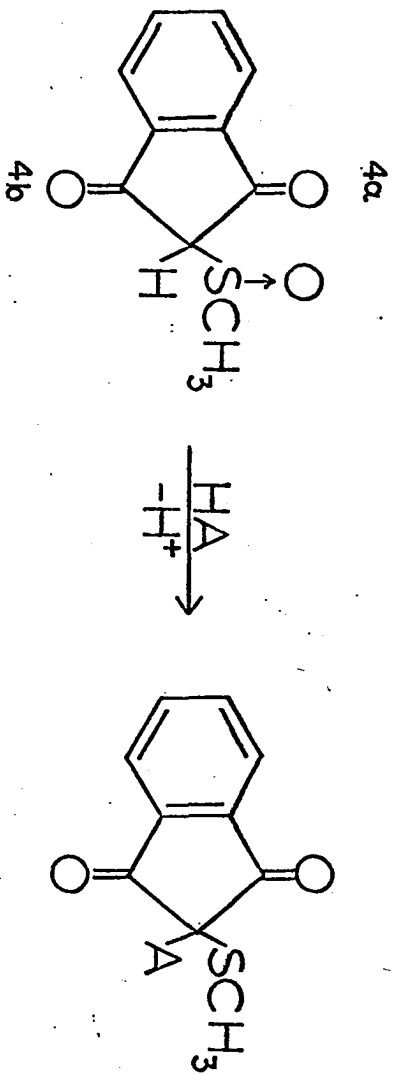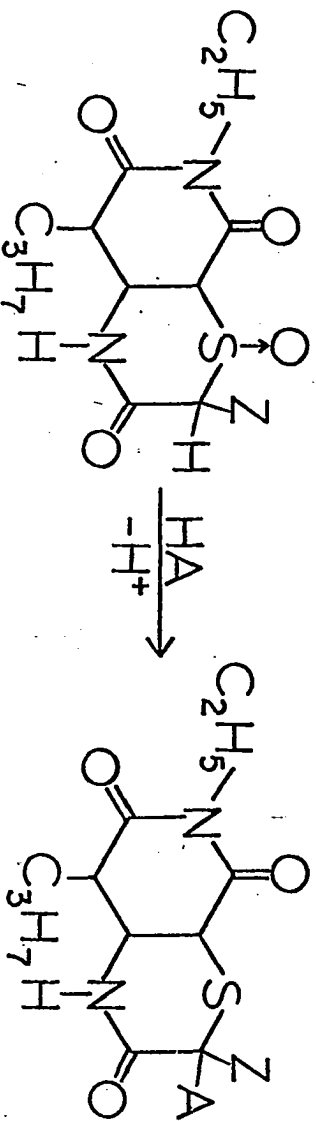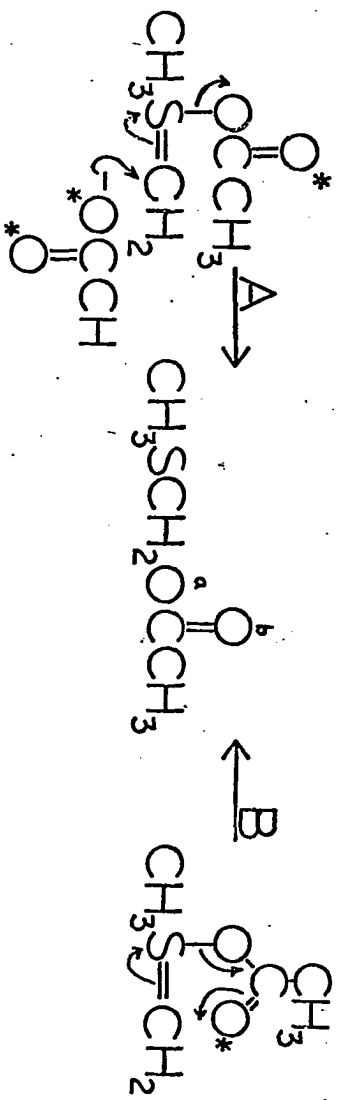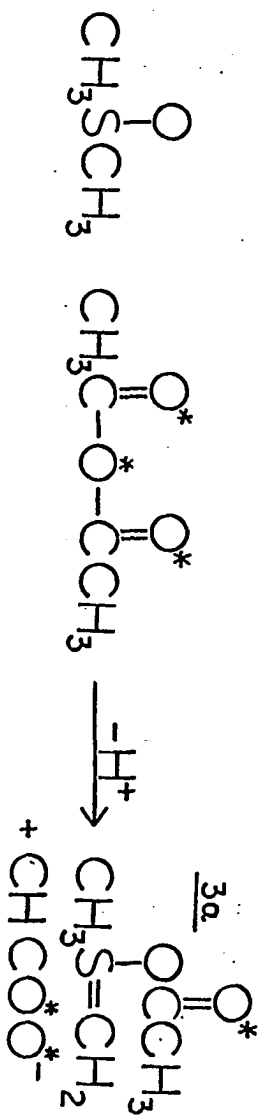
is suggested by the observation that maleic, ortho-
phthalic, and succinic anhydrides do not react with sul-
foxides (68).

As shown in Equations 19 and 20, this same mechanism
can be used

$$RSCH_3 + Cl_2 \longrightarrow \left[RSCl_2CH_3 \longrightarrow \begin{array}{c} RS\overset{O}{=}CH_2 \\ Cl \quad ClH^+ \end{array}\right] \tag{19}$$

$$\longrightarrow RSCH_2Cl + HCl$$

$$RSOCH_3 + ACl \longrightarrow \left[\begin{array}{c} RS\overset{O}{=}CH_2 \\ AO \quad ClH^+ \end{array}\right] \rightarrow RSCH_2Cl + HOA \tag{20}$$
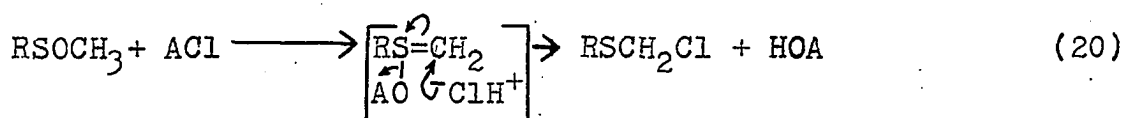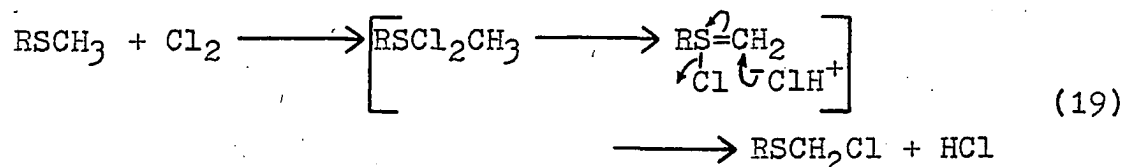
to account for the formation of alpha-chlorosulfides in the
chlorination of alkyl sulfides (70, 77, 78) or in the re-
action of sulfoxides with organic and inorganic acid
halides (70, 79, 80, 81, 82).

It has been suggested (71) that the copper ion cata-
lyzed reaction of sulfides with peroxy esters (83) proceeds
by oxidation to the sulfoxide and subsequent rearrangement
of the sulfoxide catalyzed by the acid formed in the re-
action. There was speculation in this regard concerning a
similar reaction with diacyl peroxides (68). The analogous
reaction of peroxy esters with ethers is known and is
believed to proceed by abstraction of the alpha-hydrogen
atom and radical coupling (84). A similar reaction
sequence could be operative in the reaction with thio-
ethers.

It is interesting to note that according to a proposed mechanism for oxidation of sulfides with hydroperoxides (85), an intermediate sulfonium salt would be formed as shown in Figure 5. This intermediate, identical

$$
\begin{array}{c}
\overset{\uparrow OCOR}{RCOO} \longleftarrow \underset{}{:S(R)CH_2R} \\
RSOCH_2R + (RCO)_2O
\end{array}
\searrow
\begin{bmatrix}
OCOR \\
\underset{+}{RSCH_2R} + RCO_2^-
\end{bmatrix}
\longrightarrow \longrightarrow
\begin{array}{c}
OCOR \\
RSCHR + RCO_2H
\end{array}
$$
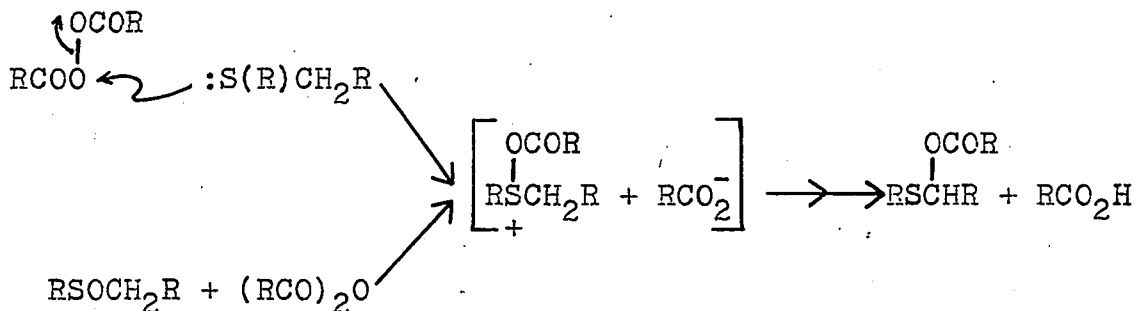
Figure 5. Diacyl peroxide oxidation of sulfides

to the intermediate formed in the reaction of sulfoxides with acid anhydrides (73), could rearrange directly to the observed products. This reaction sequence is less tenable for the reaction of peroxy esters.

Dimethyl Sulfoxide as an Oxidizing Agent

The fact that formation of alkoxysulfonium salts generally results in reduction of the sulfoxide has been utilized in reactions which involve sulfoxides, especially dimethyl sulfoxide, as oxidizing agents. Late in 1957, Kornblum reported that gentle heating of phenacyl halides with dimethyl sulfoxide resulted in formation of dimethyl sulfide and the dicarbonyl compound in yields in excess of

70% (86). The reaction of alpha-bromocarbonyl compounds
with dimethyl sulfoxide was later reported to give low
yields of the dicarbonyl compound and 45-50% yields of
trimethylsulfonium bromide (87).

Sulfoxides have been shown to undergo both O- and S-
alkylation when treated with halides and tosylates (88).
While methyl iodide gives only S-alkylated product, methyl
tosylate, brosylate, and nitrate give O-alkylated products
which can be isolated. The O-alkyl derivatives are quite
unstable and can be easily hydrolyzed to form dimethyl
sulfoxide and an alcohol.

Benzyl tosylate in dimethyl sulfoxide yielded an O-
alkyl salt which was converted to an S-alkyl salt with
longer reaction times. The tendency toward isomerization
in which the kinetically controlled product (O-alkyl) is
converted to the thermodynamically controlled product
(S-alkyl) decreases with change in the anion in the order,
$I^- > NO_3^- > OTs^-$ (88).

Trimethylsulfoxonium iodide (S-alkyl) is formed
readily from methyl iodide and dimethyl sulfoxide. This
salt, which can be converted to the chloride or hydroxide
with silver chloride or silver oxide, was shown to be a
good methylating agent for pyridine, quinoline and p-
nitrophenol (89). In the presence of acidic substances,
dimethylsulfoxonium methylide is converted to a trimethyl-

sulfoxonium salt and methylates the anion of the acid, Equation 21.

$$AH + CH_2SO(CH_3)_2 \longrightarrow A^- + CH_3\overset{+}{S}O(CH_3)_2 \longrightarrow$$

$$ACH_3 + SO(CH_3)_2 \qquad (21)$$
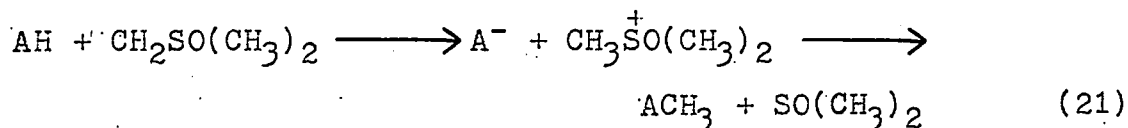
Phenol, benzaldehyde phenylhydrazone, carboxylic acids, and oximes react in this manner (90).

The other lower molecular weight (C_2-C_5) alkyl halides do not react readily with dimethyl sulfoxide. However, reaction of dimethyl sulfoxide with C_5-C_{12} primary and secondary alkyl halides and tosylates and with substituted benzyl halides and tosylates at elevated temperatures (100-120°C.) leads to the formation of aldehydes and ketones, generally in yields above 65% (91, 92, 93, 94). This method of oxidation has also been applied to tosylates (95) and alpha-bromoketones (96, 97) in the cholesterol series, generally without much success. The steric effects due to the bulk of the reagent and the rigid stereochemistry of the steroid system often prevent the S_N2 displacement of the tosylate or bromide which is necessary for the formation of the alkoxysulfonium salt.

The utility of the method is governed by the extent to which competing side reactions can be controlled. A base, usually sodium bicarbonate, was used to neutralize the acid formed in the reaction, and to aid in the removal

of the alpha-proton from the halide or tosylate (Figure 6).
The hydrohalic acids reduce dimethyl sulfoxide (98) and the
halogen and dimethyl sulfide formed can effect bromination
(99) and sulfonium salt formation on the substrate (100).
Methyl iodide and 1,2-epoxy-3-phenoxypropane have been used
effectively as scavengers for dimethyl sulfide and hydrogen
bromide respectively (100). With straight chain secondary
alkyl tosylates and the steroidal tosylates, elimination to
form olefins, often in quite high yields, is the predomi-
nant reaction (95, 101).

Alcohols can also be oxidized directly to the aldehydes
or ketones by dimethyl sulfoxide. Good yields of substi-
tuted benzaldehydes were obtained by heating the benzyl
alcohol in dimethyl sulfoxide at 190°C. for 24 hours (102).
The reaction does not occur in the absence of oxygen,
though no oxygen is consumed in the reaction. Anerobic
oxidation can be effected in the presence of di-t-butyl
peroxide.

Treatment of an alcohol with phosgene and decomposi-
tion of the crude chloroformate in dimethyl sulfoxide with
trimethylamine apparently proceeds by way of an alkoxy-
sulfonium salt intermediate (103). However, reaction by
base catalyzed elimination of hydrogen chloride and carbon
monoxide, in a manner similar to that reported for the
preparation of glyoxals by the decomposition of nitrate

esters in dimethyl sulfoxide (104), is also a possible mode of reaction.

Oxidation of alcohols using acetic anhydride (105) or dicyclohexylcarbodiimide (DCCD) with acid catalysis in the presence of dimethyl sulfoxide has been reported (106, 107, 108, 109, 110). The method has been restricted primarily to steroid alcohols and other complex molecules, but it would seem to be of general utility.

A rather extensive study of the reaction variables of the dimethyl sulfoxide-DCCD oxidation has been made (108). Using testosterone as the alcohol it has been shown that the acid catalyst, DCCD, and dimethyl sulfoxide are all necessary for the oxidation to occur to a significant extent. Phosphoric and phosphorous acids are effective but the strong inorganic acids and trifluoroacetic acid are not. The pyridinium salts, most notably, pyridinium trifluoroacetate, are quite efficient "neutral" catalysts. Optimum concentrations for the various components of the system were also determined.

A number of epimeric pairs of steroidal alcohols were oxidized (109). The C_3 and C_{17} epimers show minor differences in rate, with the equatorial alcohol being oxidized slightly faster throughout the reaction. The 11-alpha-hydroxyl (equatorial) is readily oxidized, whereas the beta-epimer is almost inert. This is to be contrasted with

the chromic acid oxidation of steroidal alcohols in which the axial epimer is oxidized more rapidly than the equatorial. Since both oxidations require abstraction of the alpha-proton, the rate determining step in the oxidations with dimethyl sulfoxide and DCCD would appear to be formation of the alkoxysulfonium salt.

Apparently the opposite situation prevails in the oxidations of yohimbine and methyl reserpate with acetic anhydride and dimethyl sulfoxide. In these oxidations the axial alcohols appear to oxidize faster than the equatorial alcohols (105). In view of the differences in bulk of the intermediate, 6c, from which the alkoxysulfonium salt is formed, these differences are not contradictory. The proposed mechanism for these oxidations is shown in Figure 6.

The oxidation of epoxides to alpha-hydroxy ketones (111, 112) is related to the oxidation of alcohols, halides and tosylates and can readily be accomodated within the mechanistic scheme given in Figure 6.

The scheme depicted for reaction with halides or tosylates shows an initial S_N2 displacement of X^-. This is consistent with the marked steric effects observed in the oxidation of steroidal tosylates (95, 96, 97) and with the observation that primary halides and tosylates react faster than the secondary isomers, even under forcing conditions (92). The variation of ease of oxidation with variation of

Figure 6. Mechanism of oxidations by dimethyl sulfoxide

$R, R' = $ hydrogen, alkyl, aryl

$R'' = C_6H_{11}$

$X = $ halide or tosylate

$Y = C_6H_{11}NHC=NC_6H_{11}$, or CH_3CO

$$R''N=C=NR'' + H^+ \longrightarrow \underset{(H_3C)_2\overset{+}{S}-\overset{-}{O}}{R''\overset{\overset{H}{|}}{N}-\overset{+}{C}=NR''} \longrightarrow \underset{(H_3C)_2\overset{+}{S}-O}{R''\overset{\overset{H}{|}}{N}-\overset{|}{C}=NR''}$$

$$\overset{\overset{O}{\|}}{CH_3C}-\overset{-}{O}-\overset{\overset{O}{\|}}{CCH_3} \longrightarrow \underset{+\;CH_3CO_2^-}{\overset{\overset{O\overset{\overset{O}{\|}}{C}CH_3}{|}}{CH_3\overset{+}{S}CH_3}} = \underset{}{\overset{OY}{CH_3\overset{+}{S}CH_3}}$$

$$\overset{}{R'RCH-X} \qquad\qquad R'RCH-\overset{..}{O}H$$
$$(H_3C)_2\overset{+}{S}-\overset{-}{O} \qquad\qquad CH_3\overset{+}{S}CH_3$$
$$\qquad\qquad\qquad\qquad\qquad OY$$

$$\searrow -X^- \qquad\qquad \nearrow \begin{array}{c}-YO^-\\-H^+\end{array}$$

$$R'R\overset{}{C}-O-\overset{+}{S}(CH_3)_2$$
$$B^-\overset{\curvearrowright H}{}$$

$$\Big\downarrow$$

$$R'RC=O \;+\; S(CH_3)_2 \;+\; BH$$

$$\underset{(H_3C)_2S-O}{\overset{\overset{OBF_3}{|}}{RHC-CHR}} = \underset{H}{R'R\overset{|}{C}-O-S(CH_3)_2}$$

$$\Big\uparrow$$

$$\underset{(H_3C)_2\overset{+}{S}-\overset{-}{O}}{\overset{\overset{+}{\underset{BF_3}{O}}}{RHC-CHR}} \longleftarrow \overset{\overset{O}{\triangle}}{RHC-CHR} + BF_3$$
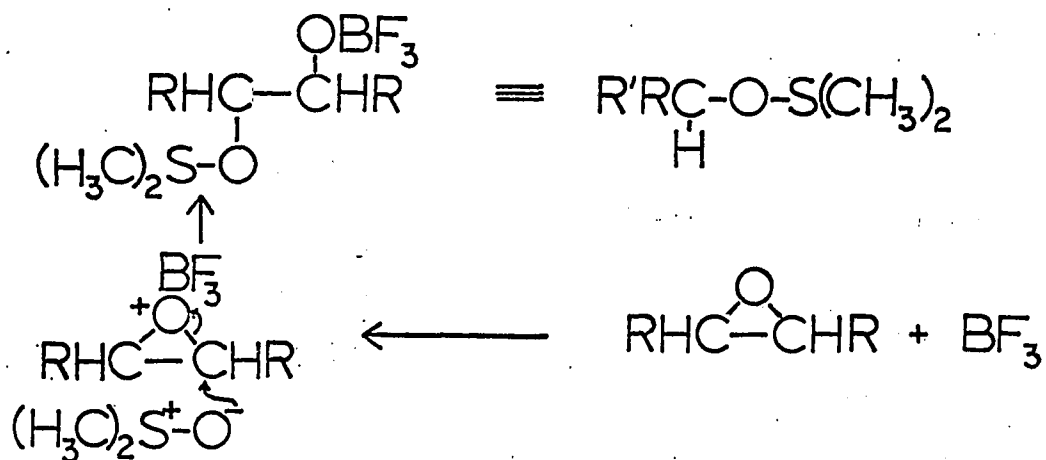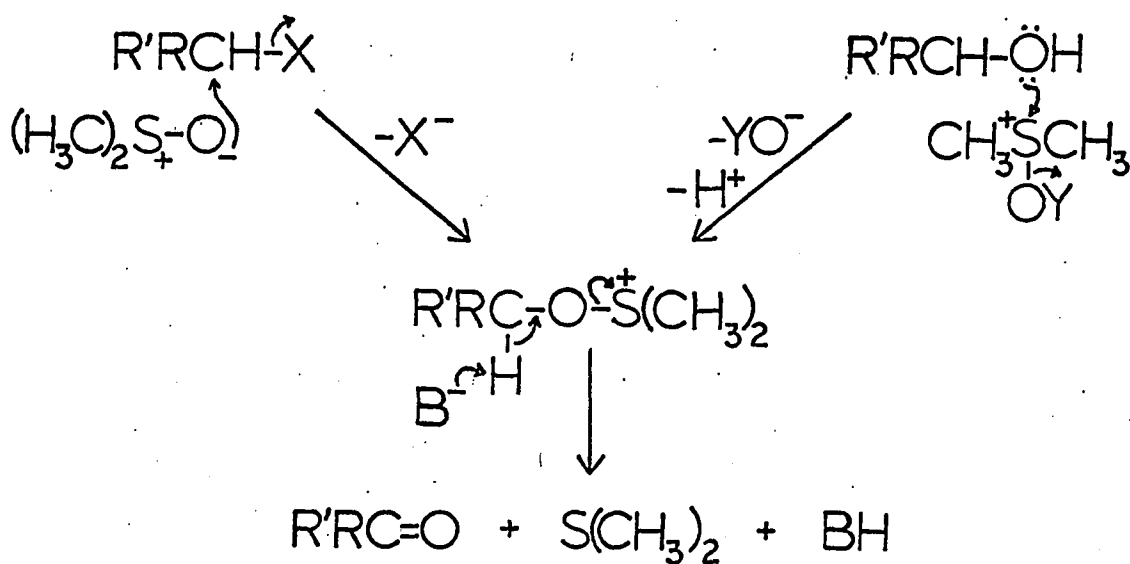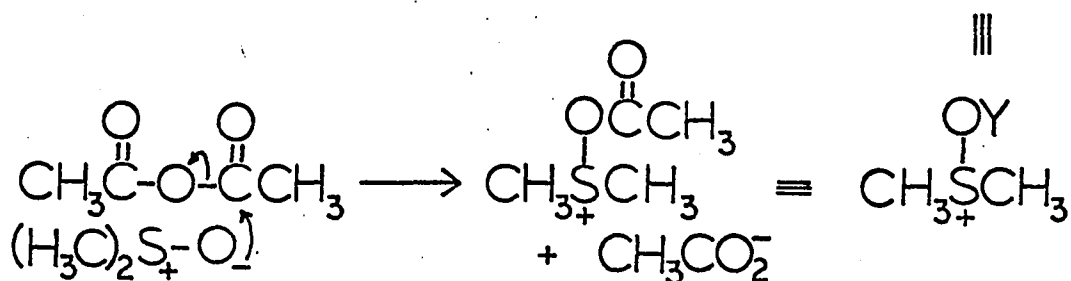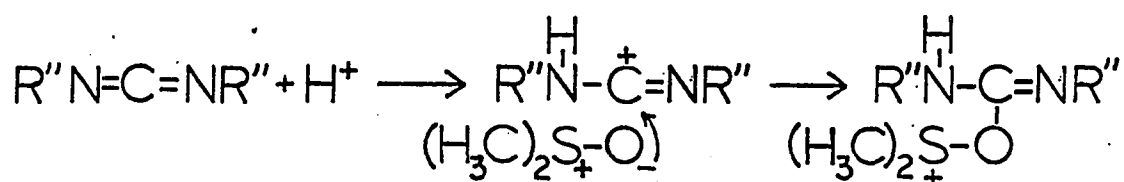
the leaving group TsO > I > Br > Cl (93, 100) is in the order expected for an S_N2 reaction. The effect of the anion on the stability of the intermediate, 6a, has been discussed earlier. The presence of electron withdrawing groups, R and R' also aids the reaction (93, 100) possibly due to polarization of the C-X bond making it more susceptible to nucleophilic attack, or by weakening the C-H bond, facilitating reaction A or D respectively.

This latter factor appears to be operative in the oxidation of alcohols by the radical (102) or the acid catalyzed (106, 109) reactions. The formation of 6a from 6c by displacement of YO^- from the alkoxysulfonium salt by an alcohol has been established by use of O^{18}-benzhydrol (105) and by studies with optically active sulfoxides and alkoxysulfonium salts (113). With crowded alcohols, some ether formation, as shown in Equation 22, occurs as a side reaction. Since it occurs to a significant extent only with alcohols which are difficult to oxidize, the Pummerer rearrangement

$$CH_3S(OY)CH \xrightarrow[-H^+]{} CH_2=S(OY)CH_3 \xrightarrow[-YOH]{ROH} ROCH_2SCH_3 \qquad (22)$$
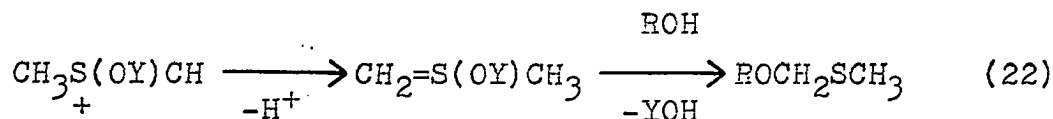
on dimethyl sulfoxide (proton loss to form the ylid) must be slower than the oxidation sequence (displacement on sulfur to form the alkoxysulfonium salt).

The reaction illustrated by Equation 22 is the pre-dominant reaction of carboxylic acids and hindered phenols with dimethyl sulfoxide and phosphorous pentoxide or DCCD (114, 115, 116). With these reagents there is no conjugate base of the acid catalyst and the carboxylic acid or phenol is the only available nucleophilic species available to react with the ylid.

EXPERIMENTAL

All melting points were determined on a Mel-Temp or Fischer-Johns melting point apparatus and are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, New York. Infrared spectra were taken on a Perkin-Elmer Model 21 double beam infrared spectrophotometer. Nuclear magnetic resonance spectra were obtained on Varian Associates HR-60 or A-60 spectrophotometers.

The chemicals employed were commercially available products. Sodium formaldehydesulfoxylate was obtained from Eastman Kodak Co. Ethyl benzoate was dried by stirring for four hours with calcium hydride; the suspended solids were removed by filtration. All other esters were used as received without drying or further purification.

Dimethyl sulfoxide was distilled from calcium hydride under reduced pressure and stored in tightly sealed glass containers. t-Butyl alcohol was stirred with calcium hydride for several hours, distilled at atmospheric pressure under a nitrogen atmosphere, and stored in tightly sealed containers. Tetrahydrofuran was distilled as needed from lithium aluminium hydride.

Sodium hydride was obtained as a 50-60% suspension in mineral oil from Metal Hydrides, Incorporated. The mineral

oil was removed by washing with light petroleum ether and decanting three times. The potassium oxide and hydroxide coating on the potassium must be removed, observing reasonable precautions, prior to dissolution in the t-butyl alcohol.

The infrared spectra are recorded in the text as the wavelength, in microns, of the significant absorptions. The letters after the numbers designate the intensity of the absorption: w = weak, m = medium, s = strong. A broad absorption is designated by the letter b after the intensity symbol.

<center>Preparation of Methylsulfinylmethyl Aryl
Ketones, I: Reaction of Aromatic Esters
with Dimethyl Sulfoxide and Potassium t-Butoxide</center>

The preparations, chemical properties and analytical data for compounds Ia-Ic have already been described elsewhere (10). The experimental procedure described below gives yields which are 10-15% higher than those previously reported.

ω-(Methylsulfinyl)-acetophenone, Ia

A 250 ml., three-necked flask was fitted with a mechanical stirrer, a small pressure equalizing addition funnel containing 9.6 ml. (67 mmoles) ethyl benzoate, and a Claisen distillation apparatus set up for vacuum distillation. The Claisen head was fitted with a pressure equal-

izing addition funnel containing 50 ml. of dry dimethyl sulfoxide. A mineral oil bubble trap served to close the system to the atmosphere.

Clean potassium, 2.7 g. (69.3 mmoles) and 50 ml. of dry t-butyl alcohol were placed in the flask and the mixture stirred and heated at 75-80°C. until the potassium had dissolved. The dimethyl sulfoxide was added, followed by dropwise addition of the ethyl benzoate. After 2 hours at room temperature, the solvent was removed by vacuum distillation until the residue became extremely viscous. The system was opened to the atmosphere and 40 ml. of cold water was added. The homogeneous solution obtained after rapid stirring for several minutes was transferred to a separatory funnel and the flask was rinsed with 10 ml. of water.

After extraction of the aqueous solution with three, 25 ml. portions of ethyl ether and acidification to pH 1-2 with 5-6 ml. of concentrated hydrochloric acid, the solution was quickly extracted with 25 ml. of chloroform and then vigorously extracted with an additional three, 25 ml. portions of chloroform. The combined chloroform extracts were extracted with 10 ml. of saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate and filtered. Removal of the solvent using a rotary evaporator left 10.9 g. of a pale yellow solid. This was

pulverized and air dried for twenty-four hours. The prod-
uct, Ia, 10.7 g. (88%), m.p. 85-86°C. (literature (10) m.p.
85-86°C.) can be obtained as white colorless crystals of
the same melting point after washing with ether or re-
crystallization from chloroform and ether.

Repetition of the above procedure using 8.4 ml. (67
mmoles) methyl benzoate instead of ethyl benzoate gave an
86% yield of the keto sulfoxide, Ia.

ω-(Methylsulfinyl)-p-methylacetophenone, Ib

The reaction of 8 ml. (56 mmoles) of methyl p-
methylbenzoate, according to the procedure described above,
yielded 9.6 g. (87.4%) of Ib as a pale yellow solid, m.p.
106-107°C. (literature (10) m.p. 105-106°C.).

Evaporation of the ether extract of the basic re-
action mixture yielded 0.19 g. (2.5%) of p-carbomethoxy-
benzyl p-tolyl ketone, XXVI, m.p. 123-125°C. The analyti-
cal and spectral data of this compound has already been
presented (10).

ω-(Methylsulfinyl)-p-methoxyacetophenone, Ic

The reaction of 11.1 g. (67 mmoles) of methyl p-
methoxybenzoate, according to the procedure described
above, yielded 13.4 g. (94.5%) of Ic as an off-white solid,
m.p. 101-103°C. (literature (10) m.p. 100-101°C.).

ω-(Methylsulfinyl)-p-bromoacetophenone, Id

Using the apparatus described above, 2.2 g. (56.6 mmoles) potassium was dissolved in 50 ml. t-butyl alcohol. After solution was effected, the excess alcohol was removed under reduced pressure until the white solid appeared to be dry. A solution of 12.9 g. (56 mmoles) of ethyl p-bromobenzoate in 45 ml. of dimethyl sulfoxide and 15 ml. of t-butyl alcohol was added to the base while cooling the reaction flask with a cold water bath (15°C.). After reacting for 5.5 hours at room temperature the flask was immersed in a 70°C. oil bath and the solvent was vacuum distilled (1 mm. Hg). The residue was dissolved in 300 ml. of ice water, extracted with 100 ml. of ether, and acidified with dilute hydrochloric acid to pH 1. The precipitate which formed was filtered and the filtrate was extracted with three, 50 ml. portions of chloroform. The solid obtained above was dissolved in the chloroform extract and this solution was extracted with two, 25 ml. portions of saturated sodium bicarbonate solution. Evaporation of the chloroform yielded 11.6 g. (79%) of a white solid, m.p. 128-131°C. Recrystallization from chloroform and ether gave white needles, m.p. 128-129.5°C.

ω-(Methylsulfinyl)-α-acetonaphtone, Ie

The reaction of 12 g. (60 mmoles) of ethyl α-naphthoate, according to the procedure described for the preparation of Ia, yielded 14.2 g. (103%) of a viscous, amber liquid. The yields on this preparation were consistently high and often above 100%. A very small amount of dimethyl sulfoxide could be detected in the N.M.R. of a sample from one preparation, even though the chloroform extract was washed with water. A purified sample gave a satisfactory analysis.

> Analysis Calc. for $C_{13}H_{12}O_2S$: C, 67.23; H, 5.21;
>
>   S, 13.28
>
>   Found: C, 67.02; H, 5.16; S, 13.55

> Infrared (chloroform) 3.33-3.43w, 6.02s, 6.27m, 6.36m,
>
>   6.67w, 6.85w, 7.15m, 7.35m, 7.83s, 9.23s,
>
>   9.72s, 10.3m, 10.61s, 11.6w (microns).

> N.M.R. (deuterochloroform) singlet (area 3) 2.75δ;
>
>   AB quartet (total area 2) 4.29, 4.59δ, J_{AB} =
>
>   14.7 c.p.s.; aromatic multiplet (total area
>
>   7) 7.28-8.10δ.

ω-(Methylsulfinyl)-β-acetonaphthone, If

Using the apparatus described above, in the preparation of Ia, 2.2 g. (56.5 mmoles) of potassium were dissolved in 50 ml. of t-butyl alcohol. After solution was effected the excess alcohol was removed under reduced pres-

sure. Forty milliliters of dimethyl sulfoxide were added to the white semi-solid mass. Distillation was continued until a precipitate began to form in the solution. A solution of 6.8 g. (34 mmoles) of ethyl β-naphthoate in 10 ml. of dimethyl sulfoxide was added. After reacting for four hours at room temperature, and distillation of the solvent under reduced pressure, the viscous residue was dissolved in 500 ml. of water and extracted twice with 75 ml. of ether. The aqueous solution was acidified to pH 6 and extracted with four, 100 ml. portions of chloroform. The chloroform extract was washed with 100 ml. of water, dried over magnesium sulfate, and filtered. Removal of the solvent by distillation yielded a red-brown oil. The oil was stirred with ether and a tan solid formed. This was pulverized, slurried with ether, filtered and air dried, yielding 6.2 g. (91%) of a solid, m.p. 91-94°C. The solid can be recrystallized from chloroform and ether to yield tan granules, m.p. 93-94°C.

Analysis Calc. for $C_{13}H_{12}O_2S$ C, 67.23; H, 5.21; S, 13.28

Found: C, 66.68; H, 5.00; 13.32

Infrared (KBr) 3.47w, 5.96s, 6.18m, 7.36s, 7.77m, 8.10m, 9.30s, 12.32m (microns).

N.M.R. (deuterochloroform) singlet (area 3) 2.73δ; AB quartet (total area 2) 4.3, 4.6δ, J_{AB} =

14.6 c.p.s.; complex multiplet (total area

6) 7.42-8.07δ; singlet (area 1) 8.47δ.

Preparation of Methyl Hemimercaptals of Arylglyoxals, II: Pummerer Rearrangement of Methylsulfinylmethyl Aryl Ketones, I

The preparations, chemical properties, analyses, and

N.M.R. spectra of compounds IIa-IIc have already been de-

scribed elsewhere (10). The experimental procedure de-

scribed below gives yields of IIa and IIb which are 20%

higher than those previously reported.

Methyl hemimercaptal of phenylglyoxal, IIa

Eighty-three grams (0.46 mole) of ω-(methylsulfinyl)-

acetophenone Ia, were dissolved in 166 ml. of dimethyl

sulfoxide. The solution was diluted with 166 ml. of con-

centrated hydrochloric acid and 1245 ml. of water and

allowed to stand at room temperature for twenty-four hours.

The white precipitate which formed was removed by suction

filtration and the filter cake was washed with 600 ml. of

water. The partially dry solid was pulverized and allowed

to dry for 24-36 hours at room temperature, or at 85-90°C.

for 8-12 hours. The product, 78.5 g. (94.6%), m.p. 104-

106°C., can be recrystalized from Skelly-B or ethanol-

water to yield colorless needles, m.p. 106-107°C., but this

was not routinely done since the product is in a high state

of purity as obtained from the reaction.

The material of melting point 106-107°C. has the same infrared spectrum as the material previously prepared and reported to have a melting point of 101°C. (10). Recrystallization from ethanol-water was generally found to give a product of slightly lower melting point than when recrystallized from non-aqueous solvents.

The preparation is efficient on any scale of reaction. The rearrangement can be carried out on a smaller scale than described using 2 ml. of dimethyl sulfoxide, 2 ml. of concentrated hydrochloric acid, and 15 ml. of water for every gram of the keto sulfoxide.

Methyl hemimercaptal of p-methylphenylglyoxal, IIb

Following the procedure described above, 46.1 g. (0.237 mole) of ω-(methylsulfinyl)-p-methylacetophenone, Ib, were converted to the methyl hemimercaptal, IIb. The product is obtained as pale yellow needles, m.p. 90-91°C. (literature (10) m.p. 90-91°C.) in 96.5% yield. Recrystallization from benzene-Skelly-B gives white needles, m.p. 91-92°C.

Methyl hemimercaptal of p-methoxyphenylglyoxal, IIc

Thirty grams of ω-(methylsulfinyl)-p-methoxy-acetophenone (0.141 mole), Ic, were dissolved in 150 ml. of

dimethyl sulfoxide. The solution was diluted with 240 ml. of water and 62 ml. of concentrated hydrochloric acid and allowed to react at room temperature for 60 hours. The pale yellow solid which formed was removed by filtration, washed with water and air dried. The product, IIc, was obtained in 87% yield, m.p. 85-87°C. Recrystallization from benzene-Skelly-B gave colorless crystals, m.p. 92-94°C. (literature (10) m.p. 89-91°C.).

Methyl hemimercaptal of p-bromophenylglyoxal, IId

Eleven grams of ω-(methylsulfinyl)-p-bromoacetophenone, Id, (42.2 mmoles) were dissolved in 50 ml. of dimethyl sulfoxide. The solution was heated to 50°C. and 5 ml. of concentrated hydrochloric acid and 25 ml. of hot water were added. The solution was cooled to room temperature and allowed to react for 48 hours. The solid which formed was removed by filtration and washed with 200 ml. of cold water and air dried to yield 6 g. (54.6%) of a very pale yellow solid, m.p. 86-88°C. The filtrate was diluted with 200 ml. of water and after 24 hours additional material had precipitated. After filtration, washing and drying this amounted to 2.46 g. (22.4%). Total yield, 77%.

Methyl hemimercaptal of α-naphthylglyoxal, IIe

A solution of 6 g. (25.8 mmoles) of ω-(methylsulfinyl)-α-acetonaphthone, Ie, in 10 ml. of dimethyl

sulfoxide was diluted with 6 ml. of water and acidified with 4.2 ml. of concentrated hydrochloric acid. The solution became milky and an oil precipitated. The mixture was stirred for 3 hours at 35°C. and then diluted with 100 ml. of water, and filtered. The solid was washed with 40 ml. of water and air dried to yield 3.74 g. (62.5%) of pale yellow flakes, m.p. 93-101°C. Recrystallization from benzene and Skelly-B gave tan crystals, m.p. 109-110°C. Another preparation of the compound produced tan crystals, m.p. 111-112.5°C.

> Analysis Calc. for $C_{13}H_{12}O_2S$: C, 67.25; H, 5.21;
> S, 13.77
>
> Found: C, 68.05; H, 5.29; S, 13.78
>
> Infrared (KBr) 2.98s, 3.27w, 3.42w, 5.97s, 6.28m,
> 6.64m, 6.97m, 7.88m, 8.07s, 8.30s, 8.51s,
> 8.79w, 8.97m., 9.30s, 9.47s, 9.80w, 10.31w,
> 10.46m, 10.62m, 11.0w, 11.55w, 11.74m,
> 12.28m, 12.69s, 12.98s, 13.18m, 13.50w
> (microns).
>
> N.M.R. (deuterochloroform) singlet (area 3) 2.06δ;
> broad absorption (area 1) 4.5δ; unresolved
> doublet (area 1) 6.2δ; aromatic multiplet
> (area 7) 7.25-8.20δ.

Methyl hemimercaptal of β-naphthylglyoxal, IIf

A solution of 5.6 g. (24.1 mmoles) of ω-(methyl-sulfinyl)-β-acetonaphthone in 30 ml. of dimethyl sulfoxide was diluted with 30 ml. of water and acidified with 5 ml. of concentrated hydrochloric acid. After one hour an oil had precipitated. The clear aqueous layer was decanted and kept at room temperature for 12 hours. The solid which formed was removed by filtration, washed with water and air dried to yield 3.5 g. (62.5%) of IIf. After two recrystallizations from Skelly-B, the product melted at 94-97°C.

Preparation of the Methyl Hemimercaptal of
Phenylglyoxal, IIa: Direct Rearrangement of
ω-(Methylsulfinyl)-acetophenone

The reaction apparatus was described in the procedure for the preparation of compound Ia. Clean potassium, 43 g. (1.1 moles), was dissolved in 800 ml. t-butyl alcohol by heating at 70-80°C. The excess alcohol was removed by distillation under reduced pressure. Dimethyl sulfoxide, 185 ml., was added and the distillation was continued until a precipitate began to form. The volume of the mixture was about 750 ml. at this point. After the dropwise addition of 155 ml. (1.08 moles) of ethyl benzoate the mixture was stirred and kept at room temperature for five hours. The solvent was removed by vacuum distillation until the reaction mixture was reduced to a volume of 325 ml. The

residue was dissolved in one liter of an ice-water slurry and extracted with 100 ml. of Skelly-B. The total volume of the solution was 1255 ml.

A portion of this solution (755 ml., containing the equivalent of 0.653 mole of the initial ester) was treated as described previously to yield 97.2 g. (0.534 mole, 82%) of the keto sulfoxide, Ia.

The remainder of the basic solution (500 ml., containing the equivalent of 0.432 mole of the initial ester) was diluted with 660 ml. of water. A solution of 178 ml. of concentrated hydrochloric acid and 100 ml. of dimethyl sulfoxide was added and this solution was allowed to react at room temperature for 24 hours. The solid which formed was removed by suction filtration, washed with 800 ml. of cold water, pulverized, and dried at room temperature for one hour and at 95°C. for three hours. The product, IIa, was obtained as a pale yellow powder, m.p. 104-106°C. The yield, based on the initial ester, was 79.5%. The yield, based on the amount of keto sulfoxide, Ia, formed in this reaction, is 95%.

Preparation of α-(Methylsulfinyl)-α-
alkylacetophenones, IIIa: Reaction of
ω-(Methylsulfinyl)-acetophenone, Ia, with Sodium
Hydride and an Alkyl Halide in Tetrahydrofuran

Preparation of 1-phenyl-2-(methylsulfinyl)-1-propanone, IIIa, R' = CH₃

An amount of a sodium hydride suspension in mineral oil
equivalent to 21.6 mmoles of sodium hydride was washed by
decantation three times with Skelly-B and suspended in 20
ml. of dry tetrahydrofuran. A solution of 3.64 g. (20
mmoles) of the keto sulfoxide, Ia, in 40 ml. of dry tetra-
hydrofuran was slowly added. After the hydrogen evolution
ceased, 2 ml. (32 mmoles) of methyl iodide was added and a
precipitate began to form. The mixture was stirred and
refluxed slowly for 23 hours. The sodium iodide was removed
by filtration and was washed with 25 ml. of chloroform. The
filtrate was concentrated under reduced pressure. The res-
idue was dissolved in 50 ml. of chloroform, extracted with
10 ml. of water, 10 ml. of a dilute sodium thiosulfate
solution, dried over magnesium sulfate, and filtered. Re-
moval of the solvent under reduced pressure yielded 4.07 g.
(106%) of a yellow-orange liquid. On attempted vacuum
distillation, some additional solvent was removed but the
keto sulfoxide decomposed. In a subsequent preparation,
the liquid formed a small amount of a pasty solid at the
top of a storage vial. This solid was mixed with the

liquid and after several hours a semi-solid mass had formed. This was filtered and the solid was recrystallized from chloroform and ether, giving colorless crystals, m.p. 75-76°C.

Analysis Calc. for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16; S, 16.34

Found: C, 61.23; H, 6.19; S, 16.19

Infrared (chloroform) 3.26w, 3.35w, 6.00s, 6.26m, 6.32w, 6.90m, 7.27m, 7.56m, 7.71m, 9.40s, 9.66s, 9.99m, 10.44s, 10.67s (microns).

N.M.R. (deuterochloroform) doublet (area 3) centered at 1.56δ, J_{AB} = 7 c.p.s; singlet (area 3) 2.52δ; quartet (area 1) centered at 4.73δ, J_{AB} = 7 c.p.s.; multiplet (total area 5) 7.25-8.25δ.

The alkylation product was reduced with zinc dust in acetic acid to yield a pale yellow liquid. Vacuum distillation of this liquid yielded 2.55 g. (95%, over-all yield, based on the keto sulfoxide, Ia) of propiophenone, VIIIa, R' = CH_3, identified by comparison of its infrared spectrum with that of an authentic sample (Matheson Coleman and Bell).

Attempted preparation of 1-phenyl-2-(methylsulfinyl)-1-butanone, IIIa, R' = C₂H₅

The reaction of the keto sulfoxide, Ia, with ethyl iodide according to the procedure described above, at room temperature for 32 hours yielded 95% of starting material.

Attempted preparation of 1,3-diphenyl-2-(methylsulfinyl)-1-propanone, IIIa, R' = CH₂Ph

The reaction of the keto sulfoxide, Ia with benzyl chloride according to the above procedure, refluxing for 12 hours yielded 93% of starting material.

Preparation of α-(Methylsulfinyl)-α-alkylacetophenones, IIIa: Reaction of ω-(Methylsulfinyl)-acetophenone, Ia, with Potassium t-Butoxide and an Alkyl Halide in Dimethyl Sulfoxide

Preparation of 1-phenyl-2-(methylsulfinyl)-1-propanone, IIIa, R' = CH₃

The apparatus and procedure utilized in this preparation is the same as that described for the preparation of the β-keto sulfoxides, I, except that a solution of 10.9 g. (60 mmoles) of the keto sulfoxide, Ia, in 45 ml. of dimethyl sulfoxide replaced the ethyl benzoate. The keto sulfoxide was added to a potassium t-butoxide-dimethyl sulfoxide slurry prepared from 2.34 g. (60 mmoles) of potassium, 45 ml. of t-butyl alcohol and 15 ml. of dimethyl sulfoxide.

After addition of the keto sulfoxide solution, the re-

action mixture was heated at 50-60°C. under vacuum for one hour. The solution was cooled and 8.5 g. (60 mmoles) of methyl iodide were added. After reacting for 2 hours at room temperature, the solution was poured into 300 ml. of water and acidified to pH 2 with 0.5 ml. of concentrated hydrochloric acid. The aqueous solution was extracted with two 50 ml. portions of chloroform. The combined chloroform extracts were washed with 50 ml. of water, dried over magnesium sulfate, and filtered. Removal of the solvent under reduced pressure yielded 12.1 g. (103%) of a yellow liquid. The infrared spectrum compares to the product obtained with the other method but appears to have dimethyl sulfoxide present also.

Preparation of 1-phenyl-2-(methylsulfinyl)-1-butanone, IIIa, R' = C_2H_5

The reaction of the keto sulfoxide with ethyl iodide according to the procedure described above yielded 18.5 g. (60%) of an orange liquid. Apparent gas evolution when ethyl iodide was added and low yield of butyrophenone after reduction with zinc and acetic acid suggests that ethylene was formed in considerable amounts. Purified product could not be obtained from this reaction and the course of the reaction is based on the conversion to the ketone.

Preparation of 1,3-diphenyl-2-(methylsulfinyl)-1-propanone, IIIa, R' = CH₂Ph

The reaction of 5.2 g. (28.5 mmoles) of the keto sulfoxide, Ia, with 3.8 g. (30 mmoles) of benzyl chloride according to the procedure described above yielded 8.6 g. (105%) of an orange liquid.

The liquid was reduced in 80% yield with zinc dust in acetic acid to 1,3-diphenyl-1-propanone, VIIIa, R' = CH₂Ph, m.p. 67-68°C. (literature (117) m.p. 70°C.).

Preparation of ω-Bromo-ω-(methylsulfinyl)-acetophenone, IVa: Reaction of ω-(Methylsulfinyl)-acetophenone with Bromine and Sodium Hydride

An amount of sodium hydride suspension in mineral oil equivalent to 52 mmoles of sodium hydride was washed by decantation with three 15 ml. portions of Skelly-B and slurried with 50 ml. of dry tetrahydrofuran.

A solution of 9.1 g. (50 mmoles) of the keto sulfoxide, Ia, in 75 ml. of tetrahydrofuran was added over a 0.75 hour period to the base. When hydrogen evolution ceased a solution of 8 g. (50 mmoles) of bromine in 10 ml. of carbon tetrachloride was added over a one hour period. The mixture began to turn yellow toward the end of the reaction. The solvent was removed at reduced pressure and the semi-solid mass was shaken with methylene chloride, and filtered. The sodium bromide was washed with methylene chloride. The

organic solutions were combined and evaporated to complete
dryness under reduced pressure and at low temperature (25-
35°C.). A tan solid, 13.34 g. (102%), m.p. 103-105°C.
remained. Recrystallization was accomplished by dissolu-
tion of the solid in 60 ml. of refluxing methylene chloride
followed by the slow addition of 60 ml. of ether. The
solution was allowed to stand at room temperature for sev-
eral hours, was cooled in an ice bath for one-half hour and
then filtered. The crystals were washed with ether and air
dried, yielding 6.3 g. of white solid, m.p. 104-105°C.
Concentration of the filtrate to near dryness, addition of
ether and filtration of the semi-solid mass yielded addi-
tional solid. This was washed with ether and air dried,
giving an additional 2.93 g. The total yield was 9.23 g.
(71%).

In another preparation of this compound, a solid, m.p.
95-100°C. was obtained. The N.M.R. indicated that two
isomers were present in the approximate ratio of 2:1.

Infrared (KBr) 3.36w, 6.00s, 6.27m, 6.38m, 6.91m,
        7.06m, 7.15w, 7.56m, 7.65m, 7.78s, 8.38s,
        8.87w, 9.60s, 10.08m, 10.41m, 10.75m,
        12.41m, 13.18m, 13.83s, 14.68s (microns).

N.M.R. (deuterochloroform) singlet, 2.71δ, singlet,
        2.83δ; aromatic multiplet, 7.33-8.18;

singlet, 6.19δ, singlet, 6.26δ.

The total peak areas for the low-field

singlets, aromatic, and upfield singlets are

in the ratio 1:5:3. Each singlet of the

pair is in the ratio of 1:3 with the lower-

field proton of the pair.

Due to the rapid decomposition of this compound, an

analysis was not obtained.

Preparation of 2,3-Diphenyl-2,3-butanediol, V:
Desulfurization and Bimolecular Reduction of ω-
(Methylsulfinyl)-acetophenone with Aluminium Amalgam

A solution of 9.1 g. (50 mmoles) of Ia in 40 ml. of

dry benzene and 40 ml. of absolute ethanol was prepared.

One gram of mercuric chloride was dissolved in 20 ml. of

absolute ethanol and added to the sulfoxide solution. This

solution was added to a 250 ml. two-necked flask equipped

with a reflux condenser and mechanical stirrer and con-

taining 4.9 g. (0.182 mole) of aluminium foil out into 1-2

inch squares. The flask was heated to reflux temperature

and vigorously stirred at that temperature for 9 hours.

All of the aluminium had dissolved. The solution was

poured into 400 ml. of an ice-water slurry containing 50

ml. concentrated hydrochloric acid and the acidic solution

was extracted with five, 50 ml. portions of chloroform.

The chloroform extracts were combined, dried over magnesium

sulfate, filtered and evaporated under reduced pressure. The residue, 5.9 g. (97%) is a very viscous, amber liquid, the infrared spectrum of which is superimposable with an authentic sample of V prepared by reduction of acetophenone with sodium amalgam, m.p. 123-124°C. (literature (118) m.p. 122°C.). However, only a small amount of the crystalline glycol could be obtained from the stereoisomeric mixture. A similar difficulty was experienced in the preparation of this compound from acetophenone (118).

Reduction of the keto sulfoxide, Ia, in absolute ethanol using 20%, 10%, 5% and 2% sodium amalgams gave 12-15% yields of crystalline glycol in addition to acetophenone, alpha-phenyl ethanol and sulfur containing products.

Preparation of β-Hydroxy-β-phenylalkyl Methyl Sulfides: Reduction of β-Keto Sulfoxides with Lithium Aluminium Hydride

β-Hydroxy-β-phenethyl methyl sulfide, VIa

A solution of 4.55 g. (50 mmoles) of ω-(methylsulfinyl)-acetophenone, Ia, in 100 ml. of dry tetrahydrofuran was added slowly to a stirred slurry of 2.85 g. (71.5 mmoles, calculated on the basis of 95% purity) of lithium aluminium hydride in 100 ml. of tetrahydrofuran. The mixture was heated to a rapid reflux for 24 hours. The solution was

hydrolyzed with 15 ml. of water, filtered, and the hydroxides were dissolved with excess dilute hydrochloric acid. The aqueous layer was separated and extracted with three, 50 ml. portions of chloroform. The organic layer was concentrated under reduced pressure. The residue was dissolved in 100 ml. of chloroform and separated from the aqueous layer. The chloroform solutions were combined, dried with magnesium sulfate and concentrated under reduced pressure. The liquid residue, after vacuum distillation through a short-path distillation head, yielded 6.3 g. (75%) of VIa, b.p. 88-91°C./0.3 mm. Hg. The methiodide derivative was prepared by reacting the sulfide with an excess of methyl iodide in acetone solution for three days. The salt was recrystallized from methanol and ether, m.p. 138-139.5°C. (literature (30) sulfide, b.p. 141-142°C./12 mm. Hg; methiodide, m.p. 132.5-133.5°C., corrected).

Infrared (carbon tetrachloride) 2.85w, 3.30w, 3.44w,
6.25w, 6.69w, 6.87m, 7.03w, 7.10w, 7.25w,
7.52w, 8.15w, 8.43m, 9.26w, 9.47s, 9.73w,
9.88w, 10.98w (microns).

N.M.R. (carbon tetrachloride) singlet (area 3) 1.95δ;
multiplet (total area 2) 2.55-2.67δ; singlet
(area 1) 3.22δ; multiplet (total area 1)
4.47-4.70δ; singlet (area 5) 7.2δ.

β-Hydroxy-β-phenylpropyl methyl sulfide, IXa, R' - CH₃

Reduction of 3.92 g. (20 mmoles) of IIIa, R' - CH₃ by the above procedure, but refluxing for 30 hours gave 3.71 g. of a yellow liquid. The infrared spectrum showed a very weak carbonyl and a very strong hydroxyl absorption. The product was purified by distillation through a short-path distillation head, b.p. 98-101°C./2 mm. Hg (literature (30) b.p. 85-87°C./0.3 mm. Hg).

Infrared (carbon tetrachloride) 2.87w, 3.30w, 3.37m, 3.43m, 3.50m, 6.25w, 6.69w, 6.88s, 7.23m, 7.52m, 7.60m, 8.25m, 8.43s, 8.52m, 8.98w, 9.23m, 9.38m, 9.63m, 9.98w, 10.27w, 10.50w, 10.96w (microns).

Preparation of β-Methoxy-β-phenethyl Methyl
Sulfide, XXIV: Reaction of β-Hydroxy-β-phenethyl
Methyl Sulfide, VIa, with Sodium Hydride and Methyl Iodide

A solution of 20.2 g. (0.11 mole) of β-hydroxy-β-phenethyl methyl sulfide, VIa, in 120 ml. of tetrahydrofuran was slowly added to a suspension of 0.13 mole of sodium hydride in 120 ml. of tetrahydrofuran. The mixture was stirred at room temperature until hydrogen evolution ceased. Methyl iodide, 18.5 g. (0.13 mole), was added and the mixture was stirred at 55°C. for 12 hours. After cooling, concentrating under reduced pressure, and filtering, the salts were washed with two, 50 ml. portions of carbon tetrachloride. The

organic portions were combined, washed with 25 ml. of dilute
sodium thiosulfate solution, dried over magnesium sulfate and
filtered. Removal of the solvent and distillation of the
residue through a short-path distillation head yielded
17.7 g. (81%) of XXIVa as a pale yellow liquid, b.p. 94-
96°C./2 mm. Hg.

> Infrared (carbon tetrachloride) 3.35m, 3.43m, 3.55m,
> 6.26m, 6.70s, 6.88s, 6.96s, 7.03m, 7.40m,
> 7.60wb, 8.26s, 8.70m, 9.05s, 9.15s, 9.35m,
> 9.65w, 9.75m, 10.45m, 10.60w, 10.76m,
> 10.98w, 11.80w (microns).

> N.M.R. (carbon tetrachloride) singlet (area 3) 1.95δ;
> multiplet (total area 2) 2.58-2.97δ; singlet
> (area 3) 3.15δ; multiplet (total area 1)
> 4.12-4.32δ; singlet (area 5) 7.26-

The sulfide was identified by conversion to the sulfox-
ide, as described in the next experiment, and comparison of
its infrared with the sulfoxide prepared by Mr. E. T.
Sabourin in these laboratories by O-methylation of the
dimsylsodium-benzaldehyde adduct (57).

Preparation of β-Methoxy-β-phenethyl Methyl Sulfoxide,
XXV: Oxidation of β-Methoxy-β-phenethyl Methyl Sulfide,
XXIV, with Sodium Metaperiodate

The sulfide, XXIV, 5.46 g. (30 mmoles), was added to a
solution of 6.76 g. (31.4 mmoles) of sodium metaperiodate

in 300 ml. of water and 50 ml. of tetrahydrofuran. The mixture was stirred rapidly for 4.5 hours at 0°C. and for 7 hours at room temperature. The aqueous solution was extracted with four, 100 ml. portions of methylene chloride. The methylene chloride was dried over magnesium sulfate and filtered. Evaporation of the solvent yielded 6.13 g. (103%) of a colorless liquid. The liquid was stirred and heated at 35-40°C. for one hour under vacuum. Additional solvent was removed during this period. The product, 5.36 g. (90%) had an infrared spectrum superimposable with the product obtained from the O-methylation of the β-hydroxy sulfoxide (48).

Analysis Calc. for $C_{10}H_{14}O_2S$: C, 60.61; H, 7.07; S, 16.16

Found: C, 60.38; H, 7.13; S, 16.07

Infrared (carbon tetrachloride) 3.28m, 3.34m, 3.41s, 3.53m, 6.25w, 6.68m, 6.88s, 7.02m, 7.12m, 7.37m, 7.70m, 8.25s, 9.10sb, 9.5sb, 10.18m, 10.77m, (microns).

N.M.R. (carbon tetrachloride) pair of singlets (total area 3) 2.46, 2.52δ; multiplet (total area 2) 2.75-3.05δ; pair of singlets (total area 3) 3.19, 3.22δ; multiplet (total area 1) 4.50-4.70δ; aromatic (area 5) 7.3δ.

Preparation of Aryl Alkyl Ketones, VII, VIII:
Reduction of β-Keto Sulfoxides, I, III, with Zinc
and Acetic Acid

Acetophenone, VIIa

A solution of 9.1 g. (50 mmoles) of ω-(methylsulfinyl)-
acetophenone, Ia, in 23 ml. of absolute alcohol and 15 ml.
of glacial acetic acid was added over a 40 minute period to
a rapidly stirred mixture of 16.3 g. (0.25 mole) of zinc
dust in 23 ml. of absolute alcohol and 15 ml. of glacial
acetic acid. The reaction flask was cooled with a cold
water bath and the temperature of the reaction mixture was
kept below 30°C. The mixture was stirred for 45 minutes
after the addition was completed. The suspended solids
were removed by suction filtration and washed three times
by slurrying in 50 ml. portions of benzene and filtering.
Four hundred milliliters of saturated sodium bicarbonate
solution was carefully added in small portions and the
organic layer was separated from the aqueous layer. The
aqueous solution was extracted with two, 100 ml. portions
of benzene. The benzene extracts were combined with the
organic layer, extracted with 50 ml. of saturated aqueous
sodium bicarbonate and 100 ml. of 5% aqueous mercuric
chloride solution, dried over magnesium sulfate and fil-
tered. The solvent was removed under reduced pressure.
Vacuum distillation of the residue yielded 5.28 g. (88%)

of a colorless liquid, b.p. 105-110 C./pressure variable, water aspirator.

Recrystallization of the solid distillation residue yielded 2-3% of the bimolecular reduction product, $(PhC(OH)(CH_3))_2$, m.p. 123-125°C.

The infrared spectrum of the product was superimposable with that of a authentic sample of acetophenone (Matheson Coleman and Bell). Vapor phase chromatographic analysis on an SE-30 column, column temperature 200°C, failed to reveal any products other than acetophenone.

The procedure described above is generally applicable to the reduction of a variety of β-keto sulfoxides, and, if efficient cooling of the reaction vessel can be attained, the reaction can be carried out on a fairly large scale (0.1-0.2 mole). In general, 1 mmole of the keto sulfoxide was dissolved in 7.5 ml. of a solution which was composed of 40% glacial acetic acid and 60% absolute ethanol (% by volume). This was added to a slurry of 5 mmoles of zinc dust in 7.5 ml. of the same solvent mixture at such a rate that the temperature was kept below 30°C. A total reaction time of 1.5-2 hours was found to be sufficient. The product isolation described above is generally applicable. On the larger scale preparations the extraction with the mercuric chloride solution was omitted. Further examples of the reduction are given below.

p-Methylacetophenone, VIIb

Using the procedure described above, 11.7 g. (59 mmoles) of ω-(methylsulfinyl)-p-methylacetophenone, Ib, was converted to p-methylacetophenone in 83% yield (distilled product). The ketone was obtained as a colorless liquid the infrared spectrum of which is superimposable with that of an authentic sample (Eastman Kodak).

p-Methoxyacetophenone, VIIc

Using the procedure described above, 21.2 g. (0.1 mole) of ω-(methylsulfinyl)-p-methoxyacetophenone, Ic, was converted to p-methoxyacetophenone, VIIc, in 87% yield (distilled product). The ketone, a pale yellow solid, m.p. 34-35°C., had an infrared spectrum which was superimposable with that of an authentic sample (Eastman Kodak). The mixed melting point was not depressed.

β-Acetonaphthone, VIIf

A solution of 4.64 g. (20 mmoles) of ω-(methylsulfinyl)-β-acetonaphthone, If, in 25 ml. of glacial acetic acid and 10 ml. of ethyl acetate was stirred with 10.4 g. (160 mmoles) of acid washed, 30 mesh, granular zinc. The mixture was stirred at room temperature for 15 hours and then filtered to remove the suspended solids. The filtrate was diluted with 100 ml. of chloroform and carefully extracted with 50 ml. portions of 1M aqueous sodium bicarbonate solu-

tion and two 50 ml. portions of water. Removal of the solvent by distillation at atmospheric pressure yielded 2.34 g. (71.5%) of an orange liquid residue which solidifies after standing at room temperature for one day. The solid melted at 50-55°C. and left traces of a solid which melted over a wide range, 68-75°C. The ketone can be purified by sublimation to give colorless plates, m.p. 54-55°C. (literature (119) m.p. 56°C.).

This change in the procedure was necessitated by the insolubility of the keto sulfoxide, If, in the ethanol-acetic acid solvent mixture.

Propiophenone, VIIIa, (R' = CH$_3$)

Reduction of 3.82 g. (21.4 mmoles) of α-(methyl-sulfinyl)-propiophenone, IIIa, R' = methyl, according to the procedure described for the preparation of acetophenone, yielded propiophenone. Vacuum distillation through a short path distillation head gave a 96% yield of the ketone as a colorless liquid. The infrared spectrum was superimposable with that of an authentic sample (Matheson Coleman and Bell).

1,3-Diphenyl-1-propanone, VIIIa, (R' = CH$_2$Ph)

Reduction of 2.8 g. (10.6 mmoles) of 1,3-diphenyl-2-(methylsulfinyl)-1-propanone, IIIa, R' = benzyl, according

to the procedure described for the preparation of aceto-
phenone, yielded the ketone VIIIa, R' = benzyl, in 81%
yield, m.p. 69-71°C. (literature (117) m.p. 70°C.).

Preparation of α-Hydroxyacetophenone, Xa:
Reduction of the Methyl Hemimercaptal of Phenylglyoxal,
IIa with Zinc/Acetic Acid or
Sodium Formaldehydesulfoxylate

α-Hydroxyacetophenone, Xa: zinc/acetic acid reduction

A solution of 9.1 g. (50 mmoles) of the hemimercaptal,
IIa, in 100 ml. of glacial acetic acid was cooled to 15-
20°C. and stirred rapidly while 32.7 g. (0.5 mole) of zinc
dust was added. The temperature was maintained at 23-25°C.
by cooling the reaction flask with a cold water bath for
two hours. The solids were removed by filtration and
washed with 100 ml. of benzene. A saturated aqueous solu-
tion of sodium bicarbonate (about one liter) was carefully
added in small portions until vigorous gas evolution
ceased. The aqueous solution was extracted six times with
80 ml. portions of chloroform. The benzene and chloroform
solutions were combined, extracted carefully with 20 ml. of
sodium bicarbonate solution, dried over sodium sulfate and
concentrated by distillation of the solvent at atmospheric
pressure. The residue was vacuum distilled through a
short-path distillation head. A white to pale yellow
solid, 4.23 g. (62.2%), m.p. 82-83°C. The infrared spec-

trum showed traces of acetophenone to be present. Re-crystallization from ethyl acetate gave white crystals, m.p. 87-88°C. (literature (119) m.p. 86°C.).

Further distillation of the reaction mixture yielded 0.2 g. (3.4%) of acetophenone.

α-Hydroxyacetophenone, Xa: sodium formaldehydesulfoxylate reduction

A solution of 9.1 g. (50 mmoles) of the hemimercaptal, IIa, was prepared by heating with 75 ml. of ethanol. The ethanol solution was cooled and treated with an excess (35-40 mmoles, 25 mmoles required) of cupric acetate powder. The mixture was stirred for 1 hour and then filtered. A solution of 7.7 g. (50 mmoles) of sodium formaldehyde-sulfoxylate dihydrate in 35 ml. of water and 5 ml. of 5N sodium hydroxide solution was added. The reaction was allowed to proceed at room temperature for 36 hours with slow stirring. The small amount of brown-black precipitate which formed was removed by filtration, the filtrate was concentrated under reduced pressure, and the solid residue was dissolved by shaking with ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with 25 ml. of ethyl acetate. The organic solu-tions were combined, dried over sodium sulfate and evapo-rated under reduced pressure. A pale yellow solid, 5.4 g. (80%), m.p. 80-82°C. (after recrystallization from ethyl

acetate) was obtained. The infrared spectrum was superimposable with that of an authentic sample.

Reduction of the hemimercaptal by essentially the same procedure except that the precipitation of the mercaptide with copper was omitted resulted in lower yields (40%) of the ketol.

<div align="center">

Preparation of Arylethylene Glycols, XI:
Reduction of Methyl Hemimercaptals of Arylglyoxals,
II, with Lithium Aluminium Hydride

</div>

Styrene glycol, XIa

A solution of 5 g. (27.5 mmoles) of the hemimercaptal, IIa, in 15 ml. of dry tetrahydrofuran was added slowly to a stirred slurry of 1.65 g. (41.3 mmoles, on the basis of 95% purity) of lithium aluminium hydride in 25 ml. of dry ethyl ether. The mixture was refluxed for 28 hours and then hydrolyzed with 10 ml. of water and 25 ml. of 6N hydrochloric acid. The aqueous layer was separated and extracted with two 25 ml. portions of chloroform. The organic portions were combined, washed with 20 ml. portions of water and dilute sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Three grams (79%) of a pale yellow oil were obtained. The oil solidified on cooling. Recrystallization from Skelly-B gave colorless plates, m.p. 61-62°C.; from Skelly-B and

benzene, plates, m.p. 60-61°C.; from carbon tetrachloride, plates, m.p. 63-64°C. (literature (120) m.p. 67-68°C.).

p-Methylstyrene glycol, XIb

A solution of 5 g. (25.5 mmoles) of the methyl hemimercaptal of p-methylphenylglyoxal, IIa, in 15 ml. of tetrahydrofuran was added to 1.65 g. (41.3 mmoles) of lithium aluminium hydride in 25 ml. of ethyl ether and refluxed for 28 hours. After work-up according to the procedure described above, 3.4 g. (95%) of a pale yellow solid were obtained. Recrystallization by repeated extraction with hot Skelly-B gave a 93% yield of colorless plates, m.p. 75-76°C. (literature (121) m.p. 76-77°C.).

α-Naphthylethylene glycol, XIe

A solution of 2.75 g. (97 mmoles) of the methyl hemimercaptal of α-naphthlyglyoxal, IIe, in 25 ml. of ethyl ether was added to excess lithium aluminium hydride in 15 ml. ethyl ether and refluxed for 2.5 hours. Product isolation by the method described in the preparation of XIa yielded 1.33 g. of a white solid, m.p. 149-150°C. (literature (122) m.p. 114.5-115°C.).

<u>Analysis</u> Calc. for $C_{12}H_{12}O_2$: C, 76.52; H, 6.42

Found: C, 77.04; H, 6.72

<u>Infrared</u> (KBr) 3.08s, 3.40m, 6.25m, 6.62m, 6.85w,

7.27m, 7.35m, 7.51m, 8.13m, 8.58m, 9.04s,

9.26s, 9.40s, 9.72s, 9.77m, 10.00m, 10.55w,

10.89m, 11.14m, 11.54m, 12.55s, 12.85s,

13.00s, 13.57m (microns).

N.M.R. (dimethyl sulfoxide) a portion of a multiplet

(blocked by solvent) 3.37, 3.60δ; triplet

(area 1) 4.83δ; multiplet (total area 2)

5.22-5.44δ; multiplet (total area 7) 7.32-

8.25δ.

(dimethyl sulfoxide, deuterium oxide) singlet

3.55δ; multiplet (total area 1) 5.22-5.44δ;

multiplet (total area 7) 7.32-8.25δ.

On the basis of the N.M.R. and some experiments to be
described later it was concluded that the compound isolated
was actually the desired glycol.

Preparation of Arlyethylene Glycols, XI: Reduction of Methyl Hemimercaptals of Arylglyoxals, II, with Sodium Borohydride

Styrene glycol, XIa

A solution of 5.1 g. (28 mmoles) of the hemimercaptal,
IIa, in 80 ml. of absolute ethanol was slowly added to a
solution of 0.88 g. (28 mmoles) of sodium borohydride in 9
ml. of water and 2 ml. of 2N sodium hydroxide solution.
The mixture was refluxed for 3.5 hours. The reaction mix-

ture was cooled, acidified to pH 3 with dilute hydrochloric acid and concentrated under reduced pressure, heating with a steam bath. The solid which formed was filtered from the aqueous phase and dissolved in chloroform. The filtrate was extracted with chloroform, combined with the first chloroform solution, dried over magnesium sulfate, and filtered. Evaporation of the solvent under reduced pressure gave 3.7 g. (95.6%) of a tan solid. Recrystallization from carbon tetrachloride gave colorless plates, m.p. 63-64°C. (literature (120) m.p. 67-68°C.).

p-Methylstyrene glycol, XIb

Reduction of 4.44 g. (22.7 mmoles) of the hemimercaptal, IIb, according to the procedure described above, gave 3.44 g. (99.5%) of a very pale yellow solid, m.p. 63-67°C. Recrystallization from carbon tetrachloride or hot Skelly-B gave 2.8 g. (81.3%) of small colorless plates, m.p. 76-77°C. (literature (121) m.p. 76-77°C.).

p-Methoxystyrene glycol, XIc

Reduction of 4.5 g. (21.2 mmoles) of the hemimercaptal, IIc, according to the procedure described above for the preparation of XIa gave 3.06 g. (86%) of a pale yellow solid, m.p. 72-75°C. Recrystallization from carbon tetrachloride gave 2.8 g. (78.8%) the glycol as colorless

plates, m.p. 79-81°C. (literature (123) m.p. 82°C.).

α-Naphthylethylene glycol, XIe

The methyl hemimercaptal of α-naphthylglyoxal, IIe, 3.45 g. (15 mmoles) was dissolved in 75 ml. of absolute ethanol. The reduction was carried out as described above. Isolation of the product and recrystallization from 95% ethanol gave 2.65 g. (94%) of white crystals, XIe, m.p. 146-147°C. (literature (122) m.p. 114.5-115°C.).

β-Naphthylethylene glycol, XIf

The methyl hemimercaptal of β-naphthylglyoxal, IIf, 1.68 g. (7.25 mmoles) was dissolved by refluxing in 40 ml. of absolute ethanol. After reduction and work-up in the manner described above, 1.46 g. of a brown semi-solid mass remains. This was slurried with ether and filtered to yield a tan solid, m.p. 123-130°C. Recrystallization from 95% ethanol gave a 40% yield of the desired glycol, m.p. 134-135.5°C.

Analysis Calc. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43

Found: C, 75.97; H, 6.34

Infrared (KBr) 3.09sb, 3.41w, 3.49w, 6.25w, 6.65w,
6.82m, 7.35w, 7.51w, 7.88w, 8.19w, 8.52w,
8.66w, 8.93s, 9.19s, 9.58s, 9.67s, 10.36w,
10.55w, 11.1s, 11.21s, 12.23s, 12.9m,

13.49m (microns).

<u>N.M.R.</u> (dimethyl sulfoxide) multiplet (total area 2.2)

3.5-3.9δ; broad singlet (area 1) 4.2-4.65δ;

rough triplet (area 1.93) 4.65-5.24δ; mul-

tiplet (total area 7.2) 7.2-8.0δ.

(deuterium oxide, acid added) multiplet

(total area 2) 3.62-3.85δ; rough triplet

(area 1) 4.65-5.1δ; multiplet (total area

7.1) 7.2-8.0δ.

Preparation of α-Naphthylethylene Glycol Dibenzoate XIg: Reaction of α-Naphthylethylene Glycol with Benzoyl Chloride

A solution of 0.68 g. (3.62 mmoles) of the glycol,

XIe, in 3.3 ml. of pyridine was cooled to 0°C. Benzoyl

chloride, 1 ml. (83 mmole), was added slowly and the solu-

tion was refluxed for one hour. The pyridine solution was

poured into a solution of 10 ml. of concentrated sulfuric

acid and 100 ml. of water. The aqueous solution was ex-

tracted with two 50 ml. portions of chloroform. The chlo-

roform solution was extracted with 10 ml. of saturated

sodium bicarbonate, and dried over magnesium sulfate.

After evaporation of the solvent, the residual solid was

pulverized, washed with hot Skelly-B and filtered. The

melting point of the product, 107-109°C., did not change

on recrystallization from hot Skelly-B. Evaporation of the

mother liquor and the initial filtrate, and recrystalliza-
tion of the residue yielded additional material. The total
yield of XIg was 1.2 g. (83%), (literature (122) m.p.
107°C.).

Preparation of α-Naphthylethylene Glycol Dibenzoate XIg: Reaction of α-Naphthylethylene with Iodine and Silver Benzoate

A mixture of α-naphthylethylene, 5 g. (32.5 mmoles),
8.25 g. (32.5 mmoles) of iodine, and 14.9 g. (65 mmoles) of
silver benzoate was refluxed in 175 ml. of benzene for 28
hours. The mixture was cooled and the silver iodide (98%)
was removed by filtration. The filtrate was evaporated
under reduced pressure. Treatment of the residual red-
orange oil with ether produced a semi-solid mass which was
filtered. The solid was washed with ether. Evaporation of
the filtrate and repetition of the procedure three times
gave additional solid material. The residual oil from the
final treatment was dissolved in chloroform and extracted
with sodium bicarbonate solution. Evaporation of the sol-
vent and treatment with ether yielded additional crystal-
line material. The solids, 3.48 g. (27%) were recrystal-
lized from hot Skelly-B and yielded material of melting
point 107-108°C. (literature (122) m.p. 107°C.).

The infrared spectra of the dibenzoate, XIg, prepared
by the two different methods, are superimposable.

A solution of 1.65 g. (4.16 mmoles) of the dibenzoate, XIg in 40 ml. of 95% ethanol and 2 ml. of 2.5M sodium hydroxide was refluxed for six hours. The solution was concentrated under reduced pressure and the residue was dissolved by shaking with a chloroform-water mixture. The chloroform layer was separated, washed once with water and then evaporated. The solid residue was recrystallized from 95% ethanol to yield 0.73 g. (83%) of white crystals, m.p. 147-148°C.

Similar treatment of the dibenzoate prepared from the glycol of m.p. 146-147°C. gave a hydrolysis product with the same melting point. The infrared spectra of the product of the hydrolysis of each of the dibenzoates are superimposable with each other and with the glycol obtained from the reduction of the methyl hemimercaptal of α-naphthylglyoxal, IIf. Mixture melting points of the hydrolysis products showed no depression.

Preparation of 1,4-Diphenyl-2,3-
dihydroxybutane-1,4-dione, XIIa: Reduction
of the Methyl Hemimercaptal of Phenylglyoxal,
IIa, with Cupric Acetate/Sodium
Formaldehydesulfoxylate

A solution of 4.55 g. (25 mmoles) of IIa in 50 ml. of 95% ethanol was prepared. Finely powdered cupric acetate monohydrate, 6 g. (30 mmoles) was added. The mixture was stirred vigorously and a solution of 7.2 g. (50 mmoles) of

sodium formaldehydesulfoxylate dihydrate in 50 ml. of water, and 5 ml. of aqueous, 5N sodium hydroxide was added. After one-half hour a yellow precipitate had formed; this slowly changes to a brick-red color over a five hour period. The mixture was stirred at 30-35°C. for sixty-five hours. The precipitate was removed by filtration and the alcohol was evaporated under reduced pressure. The aqueous solution was extracted with four 50 ml. portions of chloroform. The chloroform solution was extracted with 15 ml. of dilute aqueous sodium bicarbonate and dried over magnesium sulfate. Removal of the solvent under reduced pressure left a yellow liquid which formed a semi-solid mass after four hours at room temperature. The solid was removed by filtration and washed with cold carbon tetrachloride. White crystals, 0.57 g. (8.4%) of XIIa m.p. 119-122°C. were obtained, (literature (124, 125) m.p. 119-121°C., 127-128°C.). Concentration of the filtrate and repetition of the isolation procedure gave 0.83 g. of a white solid, m.p. 66-67°C., whose infrared spectrum is superimposable with α-hydroxyacetophenone, (literature (119) m.p. 85-86°C.). In the preparation of α-hydroxyacetophenone described previously it was noted that this compound is very difficult to purify by recrystallization. This could account for the low melting point of the substance isolated. The compo-

sition of the residue (1.2 g., 24.2% by weight) was not determined. No other crystalline material could be obtained from it.

It was found that if crude phenylglyoxal, XVIa, or the hemihydrate, XVIIa, was subjected to the reaction conditions XIIa could be obtained in significantly greater yields. The necessary modification of the above procedure would simply be to react the hemimercaptal with the cupric acetate in the absence of the sodium formaldehydesulfoxylate, filter the precipitated cupric methylmercaptide after one hour, add the sodium formaldehydesulfoxylate solution and adjust the solution to pH 8. The procedure utilizing phenylglyoxal hemihydrate, XVIIa, is described below.

A solution of 5.64 g. (19.7 mmoles) of the hemihydrate, XVIIa, in 60 ml. of 95% ethanol was prepared. A solution of 6.12 g. (40 mmoles) of sodium formaldehydesulfoxylate monohydrate and 0.24 g. (1 mmole) of cupric nitrate trihydrate in 40 ml. of water was added. The solution was adjusted to pH 8 by the addition of 2N sodium hydroxide solution. The reaction was stirred at room temperature for 60 hours; a brick-red precipitate forms during this time. The solid was removed by filtration and the alcohol was removed under reduced pressure. The aqueous-organic mixture was extracted with two, 50 ml. portions of ethyl acetate, acidified to pH 1 with dilute hydrochloric acid

and quickly extracted with a third portion of ethyl acetate. The combined extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The pale yellow solid which remains was pulverized, slurried in ether, filtered, and washed with a small portion of ether. A white solid, 3.16 g. (59.4%), m.p. 105-119°C., was obtained. Some of the crystals which were not in the melt melted at 117-119°C.

The mixture of diastereomers of XIIa can be fractionally recrystallized. Treatment of the solid by partial dissolution in 15 ml. of hot benzene, refluxing the mixture gently for a few minutes, decanting the solution. The solid was partially dissolved by refluxing in 15 ml. of benzene. The liquid was decanted and the solid residue was dissolved by slow refluxing in a minimum amount of benzene. This solution was allowed to cool slowly to room temperature; after several hours colorless prismatic crystals, m.p. 128-129°C., precipitated.

Recrystallization of a portion of the diastereomeric mixture from ethanol gave colorless prisms, m.p. 118-121°C., with some softening around 115°C.

The d,l isomer of this compound, m.p. 119-120°C., was prepared in these laboratories by Dr. E. R. Talaty, by oxidation of trans-1,4-diphenyl-2-butene-1,4-dione with

potassium permanganate. The N.M.R. data for these compounds are given in Table 1.

Infrared (KBr) d,l isomer 2.87s, 3.26w, 3.44w, 5.93s,
6.26s, 6.33m, 6.69w, 6.89m, 7.15m, 7.65m,
7.73m, 8.05s, 8.22m, 8.53m, 9.02s, 9.30m,
9.92m, 10.05m, 10.32s, 10.73m, 11.75w,
11.88w, 12.50m, 13.43s, 14.45s, 14.70m
(microns).

(KBr) meso isomer 2.96s, 3.27w, 5.97s,
6.27m, 6.34w, 6.92m, 7.18w, 7.57m, 7.65m,
8.10m, 8.36m, 9.32m, 9.59m, 9.73m, 9.86m,
10.00w, 10.18w, 10.78w, 12.35w, 12.93w,
13.51m, 13.77w, 14.33s, 14.65s (microns).

Preparation of 1,4-Ditolyl-2,3-dihydroxybutane-1,4-dione, XIIb: Reduction of the Methyl Hemimercaptal of p-Methylphenylglyoxal, IIb, with Raney Nickel

A slurry of approximately 2 g. of Raney nickel (126) in 20 ml. of ethyl ether was refluxed for one hour. A solution of 0.67 g. (3.42 mmoles) of the hemimercaptal, IIb, in 15 ml. of ethyl ether was added. The mixture was stirred under slow reflux for eight hours. The mixture was filtered and the residue was washed with three, 5 ml. portions of ether. Evaporation of the ether gave a semi-solid residue. This, upon treatment with ether, gave 0.27 g. (53%) of a light brown solid. Recrystallization from

gave white crystals, m.p. 128-129°C.; 131-132°C.

<u>Analysis</u> Calc. for $C_{18}H_{18}O_4$: C, 72.24; H, 6.04

Found: C, 72.19; H, 6.08

<u>Infrared</u> (KBr) m.p. 131-132°C.: 2.90m, 3.45w, 5.97s,

6.23s, 6.38m, 6.95w, 7.19m, 7.65s, 7.80s,

8.10s, 8.27m, 8.49s, 9.08s, 9.25s, 9.60m,

10.18m, 10.35s, 11.72m, 11.91m, 12.05m,

12.64m, 13.03m, 14.03w, 14.21m (microns).

A diastereomeric mixture of compounds, from which two isomers of XIIb were isolated, was obtained from another preparation.

A solution of 4.5 g. (23 mmoles) of the hemimercaptal in 100 ml. of ether was added to a slurry of approximately 10 g. of Raney nickel in 25 ml. of ether. The mixture was stirred under reflux for 19.5 hours. The mixture was filtered and the nickel residue was washed with ether. Evaporation of the ether produced a solid. The melting point of this solid indicated it was largely starting material. When the solid was dissolved in 50 ml. of ether, a small amount of white solid was noted. This was removed by filtration and recrystallized from 95% ethanol. Pale yellow needles, m.p. 165-166.5°C., 0.13 g. (3.8%) were obtained. The ether solution was stirred and refluxed with another 10 g. portion of Raney nickel for 9 hours. Fil-

tration and evaporation of the filtrate yielded a solid
mass which, after washing with ether gave 0.82 g. (24%) of
white crystals, m.p. 125-130°C. and 150-155°C. Attempted
separation of the isomers by fractional recrystallization
was unsuccessful.

The analysis for the high melting isomer was not satis-
factory, but the N.M.R. and infrared are consistent with the
diol-dione structure, XIIb.

Analysis Calc. for $C_{18}H_{18}O_4$: C, 72.24; H, 6.04

Found: C, 71.60; H, 5.81

Infrared (KBr) m.p. 165-166: 2.87s, 3.40w, 6.04s,
6.23s, 6.38w, 6.93w, 7.06m, 7.14m, 7.27w,
7.61m, 7.75s, 8.10w, 8.48s, 9.26s, 9.56w,
10.05m, 10.25m, 11.78m, 11.93m, 12.20w,
12.87m, 13.20w, 13.72m, 14.46w (microns).

The reductive, coupling reaction was not observed in
the reduction of the hemimercaptal IIa with Raney nickel.
Only a small amount of unidentified organic material was
obtained from the reaction.[a]

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[a]Dr. E. R. Talaty, Dept. of Chemistry, Iowa State
University, Ames, Iowa. Reduction with Raney nickel.
Private communication, August, 1965.

Table 1[a]. N.M.R. data for the compounds $(ArCOCH_A(OH_X)-)_2$

Ar	m.p., $^\circ$C.	Solvent	$\delta_{H_{Ar}}$ (area)	δ_{H_A} (area)	δ_{H_X} (area)	J_{AX}
Ph	119 (d,l)	$CDCl_3$	M, 7.3-8.1(5)	D[b], 5.34(1)	D[b], 3.89(1)	7.5 c.p.s.
		$CDCl_3/D_2O$	M, 7.3-8.1(5)	S, 5.34(1)	--	--
Ph	128 (meso)	$CDCl_3$	M, 7.2-7.9(5)	S, 5.38(1)	S, 3.84(1)	--
		$CDCl_3/D_2O$	M, 7.2-7.9(5)	S, 5.38(1)	--	--
p-CH$_3$Ph[c]	131	$CDCl_3$	Q, 7.74(4)	D, 5.35(1)	D, 3.93(1)	7.46 c.p.s.
		$CDCl_3/D_2O$	Q, 7.74(4)	S, 5.35(1)	--	--
p-CH$_3$Ph[c]	165	$CDCl_3$	Q, 7.46(4)	D[b], 5.35(1)	D[b], 3.99(1)	6.98 c.p.s.
		$CDCl_3/D_2O$	Q, 7.46(4)	S, 5.35(1)	--	--

[a]M = multiplet, S = singlet, D = doublet, Q = quartet; symmetrical multiplets are given as the position of the center of the multiplet.

[b]Slight further splitting is observed; all splitting is eliminated by minute amounts of acid.

[c]The p-CH$_3$ resonance is at 2.42δ (area 3).

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Attempted Preparation of Phenylacetic Acid,
XIVa (R" = H): Reaction of ω-(Methylsulfinyl)-
acetophenone, Ia, or ω-(Methylsulfonyl)-
acetophenone, XIIIa, with Concentrated
Potassium Hydroxide Solution

Alpha elimination of the methylsulfinyl group from the

anion of Ia or XIIIa would form a carbene intermediate

which could undergo rearrangement to a ketene intermediate.

This could then react with water-hydroxide ion (or t-butyl

alcohol-t-butoxide ion) to form phenylacetic acid or the

t-butyl ester. The following experiments were directed

toward that end.

Reaction of ω-(methylsulfinyl)-acetophenone, Ia

A solution of 5 g. (27.2 mmoles) of the keto sulfoxide,

Ia, in 25 ml. of 50% aqueous potassium hydroxide was pre-

pared. A precipitate formed almost immediately. The mix-

ture was refluxed for 1.5 hours, and then dissolved in 75

ml. of ice water and neutralized with 6.5 ml. of concen-

trated sulfuric acid. The aqueous solution was extracted

with chloroform. Evaporation of the chloroform under

reduced pressure yielded 2.75 g. (84%) of a pale yellow

solid. Recrystallization from hot water gave white plates,

m.p. 120-121°C. Mixed melting point determination and the

infrared spectrum confirmed the substance as being benzoic

acid. The odor of phenylacetic acid could not be detected.

Reaction of ω-(methylsulfonyl)-acetophenone, XIIIa

Repetition of the above procedure with the sulfone, XIIIa, heating for 0.75 hours and standing at room temperature for 6 hours before acidification gave an 80% crude yield of benzoic acid, m.p. 113-115°C. Recrystallization from water gave white plates, m.p. 120-121°C.

Attempted Preparation of t-Butyl
Phenylacetate, XIVa (R" = t-Bu):
Reaction of ω-(Methylsulfinyl)-acetophenone,
Ia, or ω-(Methylsulfonyl)-acetophenone,
XIIIa, with Potassium t-Butoxide

Reaction of ω-(methylsulfinyl)-acetophenone, Ia

A solution of 1 g. (25.6 mmoles) of potassium in 25 ml. of t-butyl alcohol was prepared. A solution of 2 g. (11 mmoles) of the keto sulfoxide, Ia, in 20 ml. of t-butyl alcohol was added. The alcohol was removed by heating under vacuum (2 mm. Hg) until a white solid remained. The solid was heated at 110°C. under vacuum for one hour. The contents of the flask were dissolved in 30 ml. of water. The solution was acidified to pH 1 and extracted with 25 ml. of chloroform. Evaporation of the chloroform yielded 1.6 g. (80%) of starting material, m.p. 81-82°C. Recrystallization from chloroform and ether raised the melting point to 84-85°C. No other organic product was obtained from the reaction.

Reaction of ω-(methylsulfonyl)-acetophenone, XIIIa

A solution of 1.4 g. (36 mmoles) of potassium in 30 ml. of t-butyl alcohol was evaporated to dryness under vacuum. A solution of 2.38 g. (12 mmoles) of the sulfone, XIIIa, in 15 ml. of dimethyl sulfoxide was added. The remainder of the alcohol was distilled by heating strongly under vacuum for a few minutes. The solution was heated at 100-115°C. for 4 hours. After cooling, it was poured into ice water, acidified to pH 1 with concentrated sulfuric acid and extracted with four, 15 ml. portions of chloroform. The chloroform solution was dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Starting material, 2.34 g. (98%), m.p. 103-104°C., was obtained.

The sharp melting point indicates that there are no products due to displacement of the methylsulfonyl carbanion by the methylsulfinyl carbanion or the t-butoxide ion.

Preparation of Arylglyoxal Hemihydrates, XVII: Hydrolysis of the Methyl Hemimercaptals of Arylglyoxals, II in Aqueous Ethanol

Phenylglyoxal hemihydrate, XVIIa

The methyl hemimercaptal of phenylglyoxal, IIa, (5 g., 27.6 mmoles) was dissolved in 20 ml. of 95% ethanol, 50 ml.

of water and 5 ml. of concentrated hydrochloric acid by
heating under reflux. A very slow stream of air was used
to sweep the methyl mercaptan from the flask. After 2.5
hours, 5 ml. of concentrated hydrochloric acid was added
and refluxing was continued for an additional 4.5 hours.
Thirty milliliters of liquid (mainly ethanol) were removed
by distillation. The aqueous solution was cooled in an
ice bath and the pale yellow crystals which formed were
removed by filtration and air dried. The aqueous filtrate
was allowed to evaporate at room temperature over a period
of 36 hours. The pale yellow solid which remained was
identical to that obtained in the initial precipitation.
The total yield of product, the hemihydrate of phenyl-
glyoxal, XVIIa, m.p. 75-77°C., was 3.5 g. (83%). The
literature melting points vary; a compound reported to be
the hydrate of phenylglyoxal, XVIIIa, has a melting point
of 91°C. (127).

    Infrared (KBr) 2.96s, 3.25w, 3.40w, 5.95s, 6.25s,
            6.33m, 6.69w, 6.89s, 7.64s, 8.15s, 8.51w,
            8.76s, 9.03s, 9.33m, 9.94s, 10.01s, 10.33s,
            11.26w, 11.75w, 13.02m, 14.02s, 14.43s,
            14.63s (microns).

    N.M.R. (saturated solution in deuterochloroform)
            Pair of doublets (total area 4) 5.04δ,

6.36δ, J_{AB} = 11 c.p.s.; complex multiplet

(total area 10) 7.27-8.34δ.

When the reaction was repeated using 59.5 g. (0.33

mole) of IIa in 400 ml. of 95% ethanol, and 50 ml. of con-

centrated hydrochloric acid, approximately 25 g. of a

yellow orange oil was formed. Workup of the decanted

aqueous solution as described above yielded 18.2 g. (36.4%)

of phenylglyoxal hemihydrate, XVIIa. The oil was dissolved

in 100 ml. of 50% aqueous, acidic ethanol and refluxed for

six hours. The solution was cooled, decanted from the oil

and evaporated to dryness at room temperature. Repetition

of this procedure four times gave an additional 22% (total)

of phenylglyoxal hemihydrate.

p-Methylphenylglyoxal hemihydrate, XVIIb

A solution of the methyl hemimercaptal of p-

methylphenylglyoxal, IIb, 7.1 g. (36.2 mmoles) in 25 ml.

of 95% ethanol and 25 ml. of water was heated to reflux and

then acidified with 6 ml. of concentrated hydrochloric

acid. After one hour, 25 ml. of water and 5 ml. of con-

centrated hydrochloric acid were added. The solution was

refluxed for an additional nine hours. After distillation

of 20-25 ml. of liquid, the solution was cooled and the

aqueous layer was decanted from the yellow oil. The solid

which formed on cooling in an ice bath was removed by suc-

tion filtration and air dried yielding 4 g. (66.7%) of a pale yellow solid, m.p. 95-97°C. (literature (128) softens 95°C., m.p. 101-102°C., reported as the hydrate, XVIIIb).

Infrared (KBr) 2.95s, 3.43w, 6.22m, 6.36w, 6.97wb,
7.11w, 7.25w, 7.7w, 8.15m, 8.27m, 8.42m,
9.03s, 10.37m, 10.51m, 11.62m, 12.4w,
12.69m, 13.57m, 14.42w (microns).

N.M.R. (dimethyl sulfoxide) broad singlet, 5.7δ;
doublet centered at 6.69δ, $J_{AB} = 7-9$ c.p.s.;
quartet centered at 7.68δ; ratio of areas,
roughly -:2:4.

Treatment of the oily residue in the manner described above yielded an additional 6.7% of XVIIb.

p-Methoxyphenylglyoxal hemihydrate, XVIIc

A solution of 6.67 g. (31.4 mmoles) of the methyl hemimercaptal of p-methoxyphenylglyoxal, IIc, in 60 ml. of warm 95% ethanol was added to a solution of 100 ml. of boiling water and 5 ml. of concentrated hydrochloric acid. The remainder of the reaction was carried out as described above. The product obtained was the hemihydrate XVIIc, 2.16 g. (37.8%), m.p. 107-109°C. (literature (129) m.p. 107-109°C.). Treatment of the oily residue in the manner described above and evaporation of the aqueous filtrates obtained in this procedure yielded an additional 2.3 g.

(40%) of XVIIc.

Infrared (KBr) 2.93s, 3.45w, 3.52w, 5.96s, 6.26s, 6.35m, 6.66m, 7.02m, 7.83m, 7.95s, 8.13s, 8.52s, 9.03s, 9.61m, 9.76s, 9.90m, 10.38m, 10.60m, 11.64m, 12.29m, 12.64m, 13.7w, 14.45m (microns).

p-Bromophenylglyoxal hemihydrate, XVIId

Six grams (23 mmoles) of the methyl hemimercaptal of p-bromophenylglyoxal, IId, were dissolved in 25 ml. of 95% ethanol, 25 ml. of water, and 5 ml. of concentrated hydrochloric acid. By the procedure described above, 3 g. (56.5%) of p-bromophenylglyoxal hemihydrate, XVIId, m.p. 107-110°C. were obtained (literature (130) m.p. 127.5-130°C., recrystallized from benzene-water as the hemihydrate, XVIId).

Infrared (KBr) 2.96s, 3.43w, 5.92s, 6.31s, 6.73w, 6.93w, 7.17m, 7.82m, 8.17s, 8.88s, 9.33s, 9.76s, 9.89s, 10.31s, 10.51s, 11.61s, 12.37s, 13.6m, 14.18w, 14.96m (microns).

N.M.R. (acetone) broad singlet, 2.92δ, partially blocked by solvent; broad singlet, 5.88δ; quartet centered at 7.92δ. After 5 minutes, in addition to the above resonances, broad absorption, 6.38δ; singlet, 9.54δ.

Preparation of Phenylglyoxal, XVIa:
Hydrolysis of the Methyl Hemimercaptal
of Phenylglyoxal, IIa, in Aqueous Acetic Acid

An aqueous acetic acid solution (15% by volume acetic
acid) was heated to reflux and the methyl hemimercaptal of
phenylglyoxal, IIa, (one mmole per 2 ml. of solvent) was
added. The solution was vigorously stirred and heated
under reflux at 120-130°C. for 25-30 hours. After cooling
to room temperature, the aqueous phase was decanted from
the small amount of oily residue and neutralized with one-
half molar equivalent of powdered sodium carbonate. The
aqueous solution was extracted with small portions of chlo-
roform until the organic layer was colorless or very pale
yellow (about fifteen extractions). The chloroform was
removed under reduced pressure and the yellow viscous
residue was heated under reduced pressure until the water
was removed, and yellow vapors began to come over. Vacuum
distillation of the crude anhydrous product yielded a clear
yellow liquid, b.p. 65-67°C./3 mm. Hg, 53-55°C./0.3 mm. Hg
(literature (127) b.p. 96-97°C./25 mm. Hg). The anhydrous
glyoxal can be detected by means of the intense absorptions
at 3.56, 5.81, and 6.02 microns in the infrared spectrum.

The yield of phenylglyoxal obtained from this prep-
aration varied with the amount of material prepared: moles
IIa (percent yield of phenylglyoxal), 0.1 mole (81%), 0.23

mole (70%), 0.47 mole (64%).

Preparation of Phenylglyoxal, XVI:
Aqueous Phosphoric Acid Hydrolysis
of ω-(Methylsulfinyl)-acetophenone, Ia

A solution of 4.55 g. (50 mmoles) of ω-(methylsul-finyl)-acetophenone, Ia, in 50 ml. of water and 10 ml. of 85% phosphoric acid was heated to reflux temperature. A precipitate which formed after 15 minutes redissolved when reflux temperature was attained. The solution was stirred vigorously and heated at reflux for 35 hours, and was then cooled and extracted with five 50 ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate. Evaporation of the solvent under reduced pressure and vacuum distillation of the residue gave 4.6 g. (68.6%) of phenylglyoxal as a yellow liquid, b.p. 60-63°C./1 mm. Hg.

Repetition of the above procedure using 75.5 g. (0.42 mole) of Ia in 620 ml. of water and 62 ml. of 85% phosphoric acid gave 33.3 g. (60%) of phenylglyoxal.

Preparation of Arylglyoxals, XVI:
Reaction of the Methyl Hemimercaptals,
II, with Mercuric Oxide or Cupric Acetate

Phenylglyoxal, XVIa: mercuric oxide

A solution of 9.1 g. (50 mmoles) of the methyl hemi-mercaptal of phenylglyoxal, IIa, was prepared by heating the solid in 50 ml. of 95% ethanol. The solution was stirred rapidly and 10.9 g. (50.2 mmoles) of red mercuric oxide powder and 0.27 g. (1 mmole) of mercuric chloride were, added. (If the solution is near reflux temperature when the mercuric oxide is added, a vigorous reaction sets in within a few minutes, causing some decomposition of the organic matter.) Stirring was continued and the mixture was heated at 55-60°C. for six hours. The mixture was cooled and the grey precipitate was removed by suction filtration and washed with 100 ml. of carbon tetrachloride. Evaporation of the filtrate gave a yellow viscous residue which was heated under reduced pressure (water aspirator) at 95-100°C. until all the solvent and traces of water had been removed. Vacuum distillation through a short-path distillation head yielded 4.7 g. (70%) of a yellow liquid, b.p. 67-69°C./0.3 mm. Hg.

The fact that the boiling point is higher than would be expected at the pressure indicated (see previous prep-arations) can be attributed to the close proximity of the

thermometer to the hot distillation flask. The infrared
spectrum in dry carbon tetrachloride was superimposable
with that of an authentic sample of phenylglyoxal.

Phenylglyoxal, XVIa: cupric acetate

A solution of 9.1 g. (50 mmoles) of the methyl hemi-
mercaptal of phenylglyoxal, IIa, in 50 ml. of chloroform
was mixed with 10 g. (50 mmoles) of finely powdered cupric
acetate monohydrate. The mixture was stirred rapidly at
room temperature for one hour and then filtered. The solid
was washed with 50 ml. of chloroform and the chloroform
filtrate was extracted with 20 ml. of water. The aqueous
layer was separated and extracted with two 15 ml. portions
of chloroform. The combined chloroform solutions were
extracted with two 20 ml. portions of saturated aqueous
sodium bicarbonate and dried over magnesium sulfate. Evap-
oration of the solvent yielded a yellow residue which was
vacuum distilled through a short-path distillation head.
Phenylglyoxal, XVIa, 5.93 g. (88.5%) was obtained as a
yellow liquid, b.p. 61-63°C./0.6 mm. Hg.

p-Methylphenylglyoxal, XVIb: cupric acetate

Repetition of the above procedure using 9.8 g. (50
mmoles) of the methyl hemimercaptal of p-methylphenyl-
glyoxal, IIb, gave the anhydrous glyoxal as a yellow

liquid, b.p. 77-80°C./0.35 mm. Hg in 86% yield. The liquid polymerized to a glass-like substance on standing; the monomer can be regenerated by distillation.

p-Methoxyphenylglyoxal, XVIc: cupric acetate

By the above procedure, 10.6 g. (50 mmoles) of the methyl hemimercaptal of p-methoxyphenylglyoxal, IIc, was converted to the anhydrous glyoxal, XVIc, in 75% yield. The product is a yellow liquid, b.p. 92-95°C./0.35 mm. Hg (literature (131) b.p. 125-127°C./6 mm. Hg) which solidifies to a yellow solid on cooling.

Preparation of 1-Phenyl-1,2-propanedione,
XIXa: Reaction of 1-Phenyl-2-(methylsulfinyl)-
1-propanone, IIIa, R' = CH₃,
with Aqueous Phosphoric Acid

A mixture of 6.47 g. (33 mmoles) of the keto sulfoxide in 15 ml. of water and 3 ml. of 85% phosphoric acid was heated to reflux and maintained at that temperature for 94 hours, stirring rapidly. The mixture was cooled and 25 ml. of chloroform was added. The chloroform layer was separated from the aqueous layer and the latter was extracted with two, 20 ml. portion of chloroform. The chloroform solutions were combined and dried over magnesium sulfate, and concentrated under reduced pressure. Vacuum distillation of the residue yielded 2.45 g. (50%) of XIXa as a

clear yellow liquid, b.p. 55-57°C./0.7 mm. Hg (literature
(132) b.p. 55-56°C./0.5 mm. Hg).

The infrared spectrum is superimposable with that of
an authentic sample (Eastman Kodak).

N.M.R. (65% by volume in carbon tetrachloride) singlet
(area 3) 2.38δ; multiplet (total area 5)
7.15-8.0δ.

In the preparation of the arylglyoxals it was noted
that the presence of acids causes extensive decomposition
of the glyoxal during distillation. In this experiment, the
chloroform extract was not washed with sodium bicarbonate
solution.

Preparation of Phenylglyoxalic Acid
Derivatives, XX, XXI, XXII: Decomposition of
ω-Bromo-ω-(methylsulfinyl)-acetophenone, IVa

Preparation of phenylglyoxalic acid, XX

The bromo ketone was prepared by the addition of
bromine in benzene to a solution of 1.82 g. (10 mmoles)
the keto sulfoxide, Ia, in benzene and triethylamine.
This gave a non-crystalline product which was dissolved in
100 ml. of dimethyl sulfoxide, 1 ml. of water and 2 ml. of
concentrated hydrochloric acid. This solution was allowed
to stand at room temperature for twenty-five days. Work-up
of the reaction mixture by dilution with water and extrac-

tion with chloroform yielded a semi-solid residue. This mixture of acids was converted to the esters by treatment with excess diazomethane. The yield of methyl phenylglyoxalate was approximately 41% with trace (less than 3%) of methyl benzoate. Methyl phenylglyoxalate was identified by comparison of the infrared spectrum of the product of this reaction with that of an authentic sample prepared by treatment of the acid (Aldrich Chemical Co.) with diazomethane in ether solution. No attempt was made to optimize the yield from this reaction.

Preparation of methyl phenylglyoxalate, XXII

Preparation of the bromo ketone, IVa, in methanol and triethylamine solution also gave a partially decomposed, non-crystalline product. This was dissolved in methanol and allowed to stand at room temperature for 14.5 days. Removal of the solvent and vacuum distillation of the residue gave 5 g. (60%, calculated on the basis of pure XXII) of a liquid, b.p. 83-90°C./1 mm. Hg. The liquid was identified as methyl phenylglyoxalate by comparison of its infrared spectrum with that of an authentic sample. The infrared also showed the presence of an ether (3.53, 9.03 microns) which has not been identified but is believed to be a solvolysis product of the bromo ketone. The product mixture contained halogen.

Preparation of methyl thiolphenylglyoxalate, XXI

The bromo ketone, IVa, 19.3 g. (74 mmoles) was dissolved in 75 ml. of dimethyl sulfoxide, 25 ml. of water, and 5 ml. of concentrated sulfuric acid and allowed to stand at 30-35°C. for 11.5 days. The solution was poured into 300 ml. of water and extracted thoroughly with four, 50 ml. portions of chloroform. The chloroform solution was washed with two, 15 ml. portions of saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate and evaporated. The residue, 9.22 g., on vacuum distillation yielded 6.59 g. (approximately 49%) of a yellow liquid which contained no halogen. After standing at room temperature for several weeks, the liquid solidified the glass vial was scratched with a steel rod. The solid was recrystallized from 95% ethanol to yield yellow plates, m.p. 39.5-41°C.

Analysis Calc. for $C_9H_8O_2S$: C, 60.00; H, 4.48; S, 17.77

Found: C, 59.88; H, 4.44; S, 17.81

Infrared (carbon tetrachloride) 3.01w, 3.26m, 3.43m, doublet 5.95, 6.02s, 6.27s, 6.91s, 7.05m, 7.22w, 7.48w, 7.63s, 7.90s, 8.26m, 8.48s, 8.65w, 9.35sb, 9.77w, 10.02m, 10.41m, 10.74w, 12.05s (microns).

<u>N.M.R.</u> (carbon tetrachloride) singlet (area 3) 2.37δ;
multiplet (total area 5) 7.72-8.20δ.

The 9.35 micron peak in the infrared spectrum did not
move to a longer wavelength in chloroform solution. This
would indicate that this absorption is not due to a
sulfoxide group in the molecule. (Dimethyl sulfoxide in
carbon tetrachloride shows an intense peak at 9.37
microns.) The liquid obtained initially was contaminated
with a small amount (10-11% by integration of the N.M.R.)
of methyl methanethiolsulfonate, identified by its strong
infrared absorptions at 7.47, 8.78, and 10.51 microns,
identical to those in the spectrum of the thiol ester
prepared by oxidation of dimethyl disulfide (133) and by
weak absorptions in the N.M.R. at 2.60 and 3.25δ (total
area 0.8).

Some of the liquid was dissolved in methanol with a
small amount of sulfuric acid and refluxed for 24 hours.
The solvent was evaporated and the residue was dissolved in
chloroform, extracted with sodium bicarbonate solution,
dried over magnesium sulfate and filtered. Evaporation of
the solvent left a yellow residue, identified as a mixture
of methyl methanethiolsulfonate and methyl phenylglyoxalate,
XXII, by comparison of the infrared spectra with authentic
samples.

Preparation of d,l Mandelic Acid, XXIII:
Benzilic Acid Rearrangement of the Methyl
Hemimercaptal of Phenylglyoxal, IIa

A solution of 8.25 g. of potassium hydroxide pellets
in 15 ml. of methanol was prepared by refluxing gently
until solution had been effected. The solution was cooled
and added to a solution of 5 ml. of formalin and 9.1 g.
(50 mmoles) of IIa in 75 ml. of methanol. The solution was
stirred at 35-40°C. for three hours and then heated at
65°C. for 5 hours. The solution was poured into water and
extracted three times with benzene. The aqueous portion of
the solution was saved. After washing with 100 ml. of
water, the benzene was dried and evaporated under reduced
pressure. The residual solid, recrystallized from carbon
tetrachloride, yielded 0.55 g. (7.25%) of white crystals,
m.p. 117.5-118°C. identified as mandelic acid by compari-
son of its infrared spectrum and melting point with an
authentic sample, (Aldrich Chemical Co.) m.p. 117-118°C.
(literature (119) m.p. 118°C.).

The aqueous solution was acidified to pH 1 with con-
centrated hydrochloric acid and extracted with three, 100
ml. portions of chloroform. Evaporation of the chloroform
yielded a small amount of brown residue which was not
further purified. It was not realized at the time that the
extreme solubility of mandelic acid in aqueous solution

made it difficult to extract. It is felt that a much higher yield of the acid could have been obtained had the solution been more thoroughly extracted.

A more convenient method of preparing the acid is to first precipitate the mercaptan with cupric acetate. A solution of 9.1 g. (50 mmoles) of IIa in 80 ml. of warm absolute ethanol was vigorously stirred for 1 hour with 7.5 g. (37 mmoles) of powdered cupric acetate monohydrate. The precipitate was removed by filtration and the filtrate was mixed with a solution of 8 g. (0.2 mole) sodium hydroxide in 20 ml. of water, and heated at 65-70°C. for 7 hours. A solid mass which formed after 2 hours was broken up by vigorous shaking and the reaction appeared to have been completed after 4 hours.

The slurry was poured into 200 ml. of water, acidified to pH 1 with concentrated hydrochloric acid and filtered to remove the fine suspended solid. The solution was thoroughly extracted with 500 ml. of chloroform in 75 ml. portions. Evaporation of the chloroform left a light brown solid m.p. 104-109°C. The acetic acid formed in the precipitation of the mercaptan was allowed to evaporate over a period of four days to yield 5.3 g. (70%) of the acid m.p. 110-112°C. Evaporation of the aqueous solution yielded an additional 1.4 g. (18%) of the acid. The acid

can be recrystallized very efficiently from carbon tetra-
chloride to remove the last traces of acetic acid and other
impurities and give colorless crystals, m.p. 116-118°C.

Obviously, use of cupric chloride or cupric sulfate
would eliminate contamination of the mandelic acid with
another organic acid.

Preparation of p-Carbomethoxybenzyl p-Tolyl Ketone, XXVI: Self-condensation of Methyl p-Toluate

The apparatus described in the preparation of the
beta-keto sulfoxides, I, was used in this preparation.

A solution of 13.5 g. (0.35 mole) of potassium in 250
ml. of t-butyl alcohol was distilled under reduced pressure
until a white semi-solid mass had formed. This was dis-
solved by the addition of 60 ml. of dimethyl sulfoxide and
distillation was continued until the base mixture was
almost solid. The reaction vessel was cooled and 52 ml.
(0.35 mole) of methyl p-toluate was added. The mixture was
stirred at room temperature for 4.5 hours and then concen-
trated to a syrupy liquid by vacuum distillation of the
solvent. This residue was poured into 700 ml. of ice water
and extracted with four 200 ml. portions of ether. Evap-
oration of the ether yielded 28 g. (68%) of a pale yellow
solid, m.p. 119-122°C. Recrystallization from 95% ethanol
gave white crystals, m.p. 126-127°C. The analysis and

N.M.R. data, which have been published previously (10), support the structure XXVI.

Acidification of the aqueous solution to pH 6, extraction with four 100 ml. portions of chloroform, and evaporation of the chloroform yielded 17 g. (25%) of Ib, m.p. 105-106°C.

DISCUSSION OF RESULTS

The β-keto sulfoxides, very readily obtained by condensation of aromatic esters with dimsylpotassium (10) or dimsylsodium (17, 18), have proven to be very versatile synthetic intermediates. Subsequent reactions generally result in elimination of sulfur from the molecule with the production of compounds with one carbon (or more) added to the side-chain of the original substrate. The reactions will be discussed individually below, but the reader may wish to make frequent reference to the summary of reactions presented in Figure 7 in order to relate the particular reaction under discussion to the over-all reaction scheme. Compounds are referred to by the Roman numeral indicating the type of compound and a lower case letter to designate the nature of the aryl group.

Condensations with Dimethyl Sulfoxide: β-Keto Sulfoxide Formation

Condensation of dimsylpotassium with esters occurs as depicted in the following equations:

$$CH_3SOCH_3 + \underline{t}\text{-BuOK} \rightleftharpoons KCH_2SOCH_3 + \underline{t}\text{-BuOH} \qquad (23a)$$

$$ArCO_2R + KCH_2SOCH_3 \rightleftharpoons Ar\overset{\overset{OK}{|}}{\underset{\underset{OR}{|}}{C}}\text{-}CH_2SOCH_3 \longrightarrow$$

$$\qquad\qquad\qquad (23b)$$

$$ArCOCH_2SOCH_3 + ROK$$
$$(I)$$
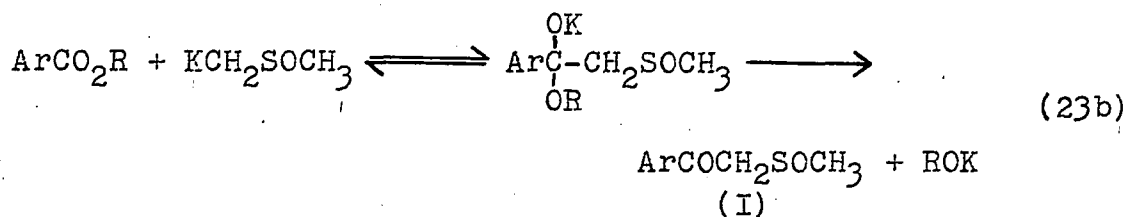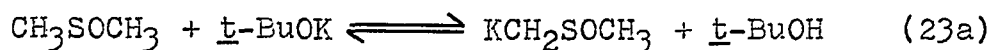
Figure 7. Reactions of β-keto sulfoxides and methyl hemimercaptals of aryl-glyoxals (Ar = a, C_6H_5; b, p-$CH_3C_6H_4$; c, p-$CH_3OC_6H_4$; d, p-BrC_6H_4; e, α-$C_{10}H_7$; f, β-$C_{10}H_7$)

$$ArCO_2CH_3 + CH_3SOCH_3$$

$$\downarrow$$

$$ArCOCH_2SOCH_3 \quad I$$

ArCOCH$_2$SO$_2$CH$_3$
XIII

ArCH$_2$CO$_2$R"
XIV

$$\begin{array}{cc} OH & OH \\ ArC(CH_3)C(CH_3)Ar \end{array}$$
V

ArCH(OH)CH$_2$SCH$_3$
VI

ArCOCH$_3$
VII

$$ArCOCH(R')SOCH_3 \quad III$$

ArCOCH$_2$R'
VIII

ArCH(OH)CH(R')SCH$_3$
IX

$$\downarrow$$

ArCOCOR'
XIX

[ArCOCH(OH)SOCH$_3$]
XV

ArCOCHO
XVI

$$ArCOCH(OH)SCH_3 \quad II$$

ArCOCH$_2$OH
X

ArCH(OH)CH$_2$OH
XI

[ArCOCH(OH)]$_2$
XII

ArCOCHO
XVI

ArCOCO$_2$H
XX

ArCOCOSCH$_3$
XXI

ArCOCOOCH$_3$

ArCH(OH)CO$_2$H
XXIII

ArCOCH$_2$SOCH$_3$
I

ArCOCH(Br)SOCH$_3$
IV

$$ArCOCHO \longrightarrow [ArCOCH(OH)]_2O \longrightarrow 2ArCOCH(OH)_2$$
XVI · XVII · XVIII

$$ArCH(OH)CH_2SCH_3 \longrightarrow ArCH(OCH_3)CH_2SCH_3 \longrightarrow ArCH(OCH_3)CH_2SOCH_3$$
VI · XXIV · XXV

$$2CH_3C_6H_4CO_2CH_3 \longrightarrow CH_3C_6H_4COCH_2C_6H_4CO_2CH_3$$
XXVI

$$\text{ArCOCH}_2\text{SOCH}_3 + \text{ROK} \; \rightleftharpoons \; \overset{\overset{\displaystyle OK}{|}}{\text{ArC}}=\text{CHSOCH}_3 + \text{ROH} \qquad (23c)$$

Acidification of the reaction mixture and extraction with chloroform yields the β-keto sulfoxide, I, generally as a crystalline, ether insoluble solid, in high yield.

Under the conditions normally used to effect the condensation, the equilibrium nature of this reaction is not evident. Distillation of the solvent after the reaction has been allowed to proceed for 2-5 hours forces the equilibria shown in Equations 23a and 23c to the right. However, under equilibrium conditions the amount of β-keto sulfoxide, Ia, formed in the reaction was found to be roughly proportional to the base concentration for a given period of reaction, and proportional to the reaction time for a given base concentration. This latter observation suggests that the equilibrium is not rapidly established at room temperature under these conditions. The reaction of esters with dimsylsodium is complete within one hour (17, 18) since the enolate anion is formed by an irreversible acid-base reaction (reaction with the methylsulfinyl-carbanion) eliminating the need for distillation to shift the equilibrium. These effects are summarized in Table 2.

Dimsylpotassium gave yields of the β-keto sulfoxides which were comparable to, and in some cases better than, those which could be attained using dimsylsodium. However,

Table 2. The effect of base concentration and reaction time at 25°C. on the yield of ω-(methylsulfinyl)-acetophenone, Ia

Ratio, base/ester[a]	Approximate molarity of base	Time (hours)	Ia
1	0.6	4	88%[b]
2	2.5	3	78%[c]
1	0.6	7	<10%
1	0.8	12	17-23%
1	1.0	12	20-25%
1	1.0	24	45-50%

[a]Potassium t-butoxide/ethyl benzoate.

[b]Solvent removed by distillation after 4 hours.

[c]Reaction with dimsylsodium by procedure in reference 18, but no tetrahydrofuran added.

dimsylsodium is the preferred base for the reaction with methyl p-toluate. The data in Table 3 shows that in the reaction of dimsylsodium with methyl p-toluate the condensation product, ω-(methylsulfinyl)-p-methylacetophenone, IIb, is formed in high yield with no apparent formation of the self-condensation product, p-carbomethoxybenzyl p-tolyl ketone, XXVI. The ratio of IIb to XXVI shows an apparent

Table 3.   The effect of base and ester concentration in the
          self-condensation of methyl p-toluate (at 25°C.)

Base/ester	Approximate molarity of base	XXVI	Ib
2[a]	2	--	87%
2[b]	2	6.7%	68%
2[b]	5	5-7%	79%
1[b]	6	19%	50%
1[b]	7	60%	30%

[a]Prepared using dimsylsodium according to the proce-
dure in reference 18, but no tetrahydrofuran used.

[b]Potassium t-butoxide-t-butyl alcohol-dimethyl
sulfoxide system.

dependence on both the base concentration and the base to

ester ratio.

Two points must be emphasized. First, because of the

method and apparatus used (Experimental, pp. 41, 103. Base

concentration was adjusted by removing varying amounts of

alcohol by distillation.) the base concentration could only

be estimated. This is especially true of the data dis-

played in Table 3. Consequently this data must be con-

sidered as illustrative rather than difinitive. Second,

the reaction using dimsylpotassium involves concentration

of the reaction mixture at the end of the reaction, whereas

the reaction using dimsylsodium does not. Thus, the two

systems are not strictly comparable, and the effect of the

initial base concentration in the dimsylpotassium system

may be obscured.

The observed results may be attributed to several fac-

tors. The reactions which can occur in this reaction medium

are shown in Equations 24a-e.

$$CH_3SOCH_3 + \underline{t}\text{-BuOK} \rightleftharpoons KCH_2SOCH_3 + \underline{t}\text{-BuOH} \qquad (24a)$$

$$CH_3ArCO_2CH_3 + \underline{t}\text{-BuOK} \rightleftharpoons KCH_2ArCO_2CH_3 + \underline{t}\text{-BuOH} \qquad (24b)$$

$$CH_3ArCO_2CH_3 + KCH_2SOCH_3 \rightleftharpoons KCH_2ArCO_2CH_3 +$$
$$CH_3SOCH_3 \qquad (24c)$$

$$CH_3ArCO_2CH_3 + KCH_2SOCH_3 \rightleftharpoons CH_3ArCOCH_2SOCH_3 +$$
$$KOCH_3 \qquad (24d)$$

$$CH_3ArCO_2CH_3 + KCH_2ArCO_2CH_3 \rightleftharpoons CH_3ArCOCH_2ArCO_2CH_3$$
$$+ KOCH_3 \qquad (24e)$$
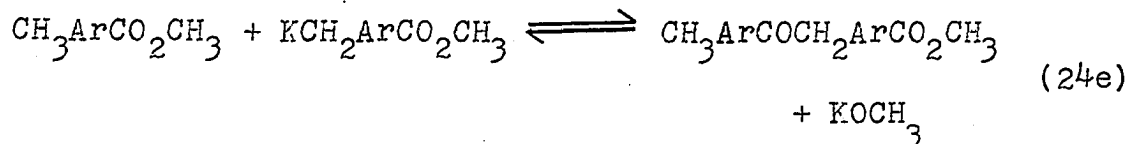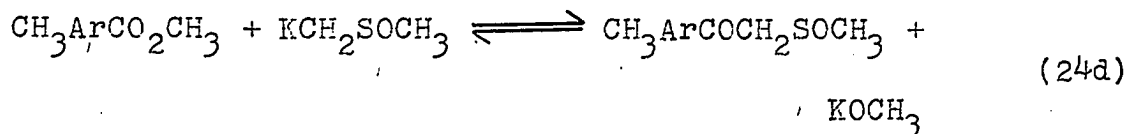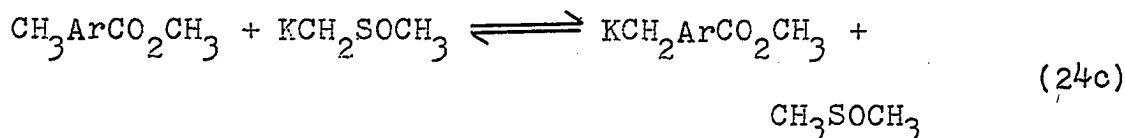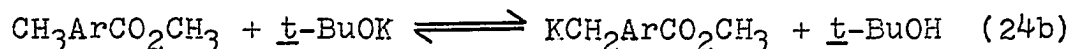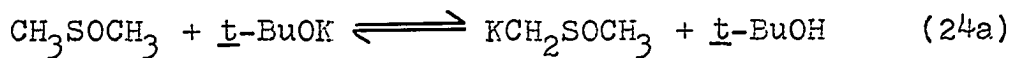
$$(Ar = C_6H_4,\ p\text{-substituted})$$

Dimethyl sulfoxide and methyl p-toluate would be expected

to have approximately equal acidities. Assuming that the

rate determining step in the reaction sequence is carbanion

formation from methyl p-toluate or dimethyl sulfoxide and

that the addition of either carbanion to the carbonyl group

is rapid, an increase in ester concentration should favor
formation of XXVI. Such an effect was observed (Table 3).
Since the base concentration could be considered to be
essentially constant, within the limitations of the method,
the over-all effect of the decrease in the base to ester
ratio was to increase the ester concentration.

Reference has been made to the increase in the basic-
ity of a dimethyl sulfoxide-methanol-sodium methoxide sys-
tem as the alcohol content of the medium was decreased
(15, 16). In the present work, the base concentration of
the medium was increased by distilling varying amounts of
alcohol from the solvent-base mixture. By this technique,
not only was the base concentration increased, but the
basicity of the medium was also increased. While ioniza-
tion of the methyl groups of methyl p-toluate and dimethyl
sulfoxide should be favored by these effects, the change
in the solvent to a more highly solvating medium could
affect the rate of ionization of either methyl p-toluate or
dimethyl sulfoxide. If such an effect is operative, it
appears to favor ionization of methyl p-toluate.

Of obvious importance to the reaction are the rates
of ionization of the protons of the p-methyl group with
potassium t-butoxide and with dimsylpotassium. Conditions
under which the methylsulfinylcarbanion concentration is
low relative to the potassium t-butoxide concentration

would favor the formation of XXVI if the rates of ionization by the two species were approximately equal. This is due to the fact that the formation of XXVI is, within this system, a general-base catalyzed reaction whereas formation of Ib specifically requires the methylsulfinylcarbanion.

The difference in the products of the reaction of dimsylsodium as opposed to those with dimsylpotassium might also be attributed to differences in their rates of reaction in the ionization (Equation 24c). Or, it might be another manifestation of the difference in the nature of the reaction medium. Dimsylsodium has been shown to be an effective nucleophile toward bromide and saturated carbon atoms, (19, 21). In the reaction with methyl p-toluate there is an apparent preference for nucleophilic addition to the carbonyl carbon rather than ionization of a proton from the activated p-methyl group. On the other hand, in reactions involving dimsylpotassium, there are two basic species in solution, the alkoxide base and the carbanion base. The alkoxide base can ionize the p-methyl group and this carbanion then would react as shown in Equation 24e. This reaction has been shown to occur to an appreciable extent when methyl p-toluate and potassium t-butoxide are reacted in N,N-dimethylformamide (10). Thus, even if the two carbanionic species, dimsylpotassium or dimsylsodium,

have about the same degree of nucleophilicity, the competitive reaction, ionization of the active hydrogens in this extremely good ionizing medium, changes the course of the reaction. This would also account for the failure during the present work to effect condensations with aliphatic esters, e.g., diethyl succinate, with dimsylpotassium, whereas dimsylsodium reacts readily with diethyl adipate (17, 18).

The β-keto sulfoxides prepared (isolated and characterized) by condensation of aromatic esters with dimsylpotassium and by subsequent α-substitution reactions are shown in Table 4.

The condensation of ethyl α-naphthoate with dimsylsodium has been reported (18) to give a quantitative yield "of the β-keto sulfoxide as a pale yellow oil which crystallized upon standing overnight in a cold room." The solid is reported to have a melting point of 111-113°C. The N.M.R. spectrum reported agrees well with that obtained earlier in these laboratories during the course of this work. The β-keto sulfoxide, Ie, has never been obtained as a solid. However, when subjected to the conditions of the Pummerer rearrangement a pale yellow solid, m.p. 110-112°C. was obtained. The N.M.R. spectrum, the infrared spectrum, and the analysis support the methyl hemimercaptal structure,

Table 4. Yields of β-keto sulfoxides (I) and methyl hemimercaptals of aryl-
glyoxals (II)

Ar	Compound	Yield[a]	m.p.($^\circ$C.)	Compound	Yield[b]	m.p.($^\circ$C.)
C_6H_5	Ia	88%	85–86	IIa	95%	105–106
p-$CH_3C_6H_4$	Ib	87%	106–107	IIb	96%	90–91
p-$CH_3OC_6H_4$	Ic	95%	101–102	IIc	87%	92–94
p-BrC_6H_4	Id	79%	128–130	IId	77%[c]	86–88
α-$C_{10}H_7$	Ie	>95%	--	IIe	63%	110–112
β-$C_{10}H_7$	If	91%	93–94	IIf	63%[c]	94–97
C_6H_5, R' = CH_3	IIIa	86%[d]	75–76			
C_6H_5	IVa	66%[e]	104–105			

[a]Condensation on a 50 mmole scale.

[b]Yield from β-keto sulfoxide.

[c]Yield of product before recrystallization.

[d]Over-all yield from ethyl benzoate; yield on methylation is 98%.

[e]Over-all yield from ethyl benzoate; yield on bromination is 75%.

IIe (see p. 50, Experimental). It is possible that the reported N.M.R. spectrum was obtained on the liquid and that traces of acid present from the workup caused the re-arrangement.

The use of other types of organic molecules as substrates was generally unsuccessful. Several attempts were made to obtain a product from the reaction of dimsyl-potassium with aromatic nitriles. Dark colored, resinous materials were the only organic substances isolated from the reaction under a variety of conditions. The product, $ArC(=NK)CH_2CH_3$ would be prone to oxidation, hydrolysis, and polymerization. When the reaction was carried out at room temperature or at 0°C. under a nitrogen atmosphere, resin formation occurred. Hydrolysis of the product in acid solution did not produce the β-keto sulfoxide, I, or the rearranged product, II.

Reaction of dimsylpotassium with styrene oxide produced 3-(methylsulfinyl)-1-phenyl-1-propanol as a mixture of diastereomers. The chemistry of this compound was not explored, but on the basis of the known chemistry of sulfoxides it could serve as an intermediate for a series of compounds: $PhCH(OH)CH_2X$ (X = CHO, CO_2H, SCH_3), and $PhCH(OH)CH=CHX$ (X = H, SCH_3).

The asymmetry of the sulfoxide group causes the meth-

ylene protons of the β-keto sulfoxides to be nonequivalent.
In all of the compounds of type I which have been prepared
during the course of this work, the N.M.R. spectrum shows
an AB-quartet centered between 4.3 and 4.5δ, with a geminal
coupling constant of 14-15 c.p.s. This characteristic has
been noted in a variety of sulfoxides of the type $R'SOCH_2R$
(34, 41, 42, 43). Only one exception to this has been
noted in the present series. The N.M.R. spectrum of ω-
(methylsulfinyl)-p-bromoacetophenone, Id, in deuterochloro-
form shows a sharp singlet at 2.73δ (-$SOCH_3$) and a sharp
singlet at 4.35δ (-CH_2SO-) with areas in the ratio of three
to two. The aromatic A_2B_2 quartet was centered at 7.77δ.

The N.M.R. spectrum of Ia in deuterochloroform shows
an AB-quartet centered at 4.42δ for the methylene protons.
However, in dimethyl sulfoxide, the methylene protons of Ia
appear as a singlet at 4.68δ. The methylene protons of
2-thiaindan-2-oxide show increased or decreased splitting
as the temperature is increased or decreased, a phenomenon
attributed to increasing the molecular association as the
temperature was decreased until the molecules became asso-
ciated in such a manner as to place the methylene protons
in an essentially equivalent environment (42), as illus-
trated schematically in Figure 8. Since Ia was present in
low concentration (about 0.6M) in deuterochloroform and in

monomer   association dimer
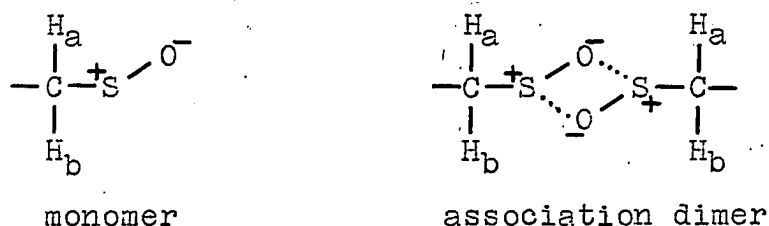
Figure 8. Planar projection of a portion of the 2-
         thiaindan-2-oxide molecule showing the monomeric
         and associated forms

relatively high concentration (1.67M) in dimethyl sulfoxide,
a similar association-dissociation phenomenon could occur
as a result of the concentration change. Alternatively,
dimethyl sulfoxide could form an association complex with
Ia which would distort the tetrahedral configuration of
sulfur to the extent that the methylene protons would be in
an equivalent environment. The formation of dimers and
association polymers of sulfoxides is a well known phenome-
non (134) and has been postulated to occur during the dis-
proportionation of sulfoxides to sulfides and sulfones
(2, 5).

The utility of β-keto sulfoxides, I, as intermediates
in synthetic chemistry can be seen in Figure 7. Their use
as synthetic intermediates can be extended because of the
possibility of readily forming the methyl hemimercaptals
of arylglyoxals (II), and α-alkylated (III) or α-brominated
(IV) derivatives.

Methyl Hemimercaptals of Arylglyoxals:
Pummerer Rearrangement

The Pummerer rearrangement of β-keto sulfoxides yields the methyl hemimercaptals or arylglyoxals, (Equation 25). The rearrangement can be effected under acidic conditions

$$ArCOCH_2SOCH_3 \xrightarrow{H^+} ArCOCH(OH)SCH_3 \qquad (25)$$
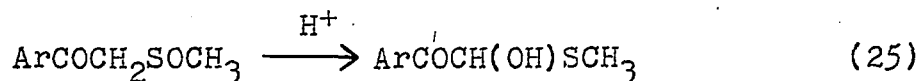
in a variety of solvents such as water, alcohol, acetic acid, dimethyl sulfoxide, and mixtures of these. The method of preparation described in this work was chosen. because the reaction occurred readily at room temperature in the polar medium and the product was almost quantitatively precipitated from the predominantly aqueous solution.

This type of compound has also been prepared by oxidation of phenylacetylene in the presence of mercaptans; methyl mercaptan reacted to give a 70-80% yield of IIa, but the yields were variable, and with other mercaptans, low (34). Obviously, treatment of arylglyoxals with a mercaptan and an acid catalyst will also produce the hemimercaptal (135), but this necessitates the prior preparation of the desired glyoxal, often a laborious procedure. For the purposes of the present work this preparation would be unnecessary since the reactions to be described actually involve the glyoxal formed from the methyl hemimercaptal in solution.

Since the methyl hemimercaptals can be prepared from readily available esters and dimethyl sulfoxide, the tedious preparation of the glyoxal can be eliminated. Thus it becomes practical to consider the synthesis of a variety of compounds, including arylglyoxals, utilizing these polyfunctional compounds as intermediates. Most of the reactions of II to be described later can be visualized as occurring by initial elimination of methyl mercaptan to form the arylglyoxal in solution, Equation 26.

$$ArCOCH(OH)SCH_3 \longrightarrow ArCOCHO + HSCH_3 \qquad (26)$$
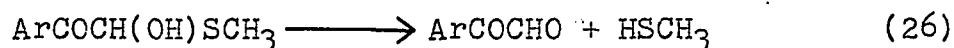
α-Substitution Reactions of β-Keto Sulfoxides

In addition to forming the hemimercaptals, the β-keto sulfoxides can be converted to other useful intermediates by substitution of an alkyl group for a hydrogen of the methylene group.

Initially, Ia was alkylated in dimethyl sulfoxide solution in an attempt to prepare the enol ether. It was thought that the highly polar reaction medium could favor O-alkylation (136); only C-alkylated product was obtained (Equation 27b). The same result has been reported for the

$$ArCOCH_2SOCH_3 \underset{R'I}{\overset{t\text{-BuOK}}{\bigg\langle}} \quad \begin{array}{c} \overset{OR'}{|} \\ \longrightarrow ArC{=}CHSOCH_3 \qquad (27a) \\[2em] \overset{R'}{|} \\ \longrightarrow ArCOCHSOCH_3 \qquad (27b) \end{array}$$
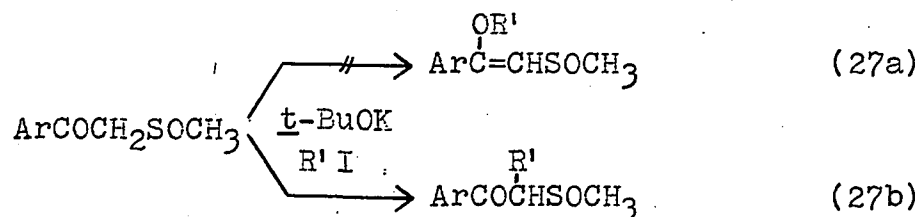
reaction of the sulfone derived from Ia with benzyl chloride. The enol benzoate, however, could be prepared by reacting the sulfone with benzoyl chloride in basic, alcoholic solution (137).

Preparation of the C-alkylated derivatives, IIIa, $R' = CH_3$, C_2H_5, and CH_2Ph, has been accomplished in dimethyl sulfoxide using potassium t-butoxide as the base. While the methylation with methyl iodide occurs readily, the ethylation (ethyl iodide) and benzylation (benzyl chloride) are not as cleanly and readily accomplished, probably due to steric factors and the much slower rates of reaction of these halides (138). Benzylation has also been effected by the method described for the reaction with the sulfone (137).

Methylation of Ia with methyl iodide in tetrahydrofuran using sodium hydride as the base occurs in nearly quantitative yield. However, ethyl iodide and benzyl chloride did not react in this non-polar medium, even under vigorous conditions.

Since a new asymmetric center is introduced into the molecule in the alkylation reaction, four possible isomers exist. While all of the alkylated products are believed to be solids, their preparation as stereoisomeric pairs generally gives liquid products. Only one isomer of IIIa,

R' = CH_3, has been obtained in a crystalline state. The other compounds, R' = C_2H_5, and CH_2Ph, non-crystalline and non-volatile liquids, have been identified only by reduction to the sulfur-free ketones which are known compounds.

Reaction of Grignard reagents with sulfoxides has not been widely studied. The β-keto sulfoxides seemed like especially interesting molecules to react with Grignard reagents for two reasons. Reaction could occur at any of four sites, the carbonyl group, and in analogy with Grignard reactions with other sulfoxides, at the α-carbon atoms (61) and at the sulfoxide group (58, 59). If reactions were to occur at the methyl or methylene group, it would offer a means of introducing aryl groups into the molecule, a reaction which would not be possible by the usual methods used for alkylation.

Refluxing Ia with phenylmagnesium bromide (1 to 2 ratio of Ia to phenylmagnesium bromide) in tetrahydrofuran for twelve hours, followed by work-up under acid conditions, yielded a dark colored liquid. Attempted vacuum distillation of the product resulted in complete decomposition.

Surprisingly, the infrared spectrum of the crude product reveals that the carbonyl group is still present. The products of the reaction have not been isolated. A small amount of trimethylsulfonium iodide was isolated

after treatment of the crude reaction product with methyl
iodide in acetone solution for several days. This might
indicate that dimethyl sulfoxide or dimethyl sulfide was
displaced from the carbonyl by the phenylmagnesium bromide.
However, simple reduction of the sulfoxide by the Grignard
reagent (58, 59) and reaction of the resultant methyl
phenacyl sulfide with methyl iodide and/or hydrogen iodide
could ultimately lead to the same product.

The N.M.R. of the crude reaction mixture shows a sharp
singlet at 2.03δ, the normal position for an -SC$\underline{H}_3$ resonance.
Also present are singlets at 2.31δ, 2.44δ, and 5.23δ. A
stable base-line could not be obtained so the integral is
only of slight value. However, the integral for the 2.31δ
and 2.44δ peaks is well defined and shows the intensities
to be in the ratio of 1 to 1. Their position and intensity
ratio is suggestive of two different methylene groups. The
5.23 singlet is at a position nominal for a carbon bearing
three electronegative substituents (e.g., PhCOC$\underline{H}$(Br)SOCH$_3$,
6.1-6.2 $\underline{vs}$. PhCOC$\underline{H}$(CH$_3$)SOCH$_3$, 4.75δ).

The reaction is believed to take the course shown in
Figure 9, similar to that proposed earlier for the reaction
of arylmagnesium halides with dimethyl sulfoxide. Reaction
at the carbon of the ylid (9a or 9b) with a second molecule
of phenylmagnesium bromide with loss of magnesium oxide

$$PhCOCH_2SOCH_3 + PhMgBr$$
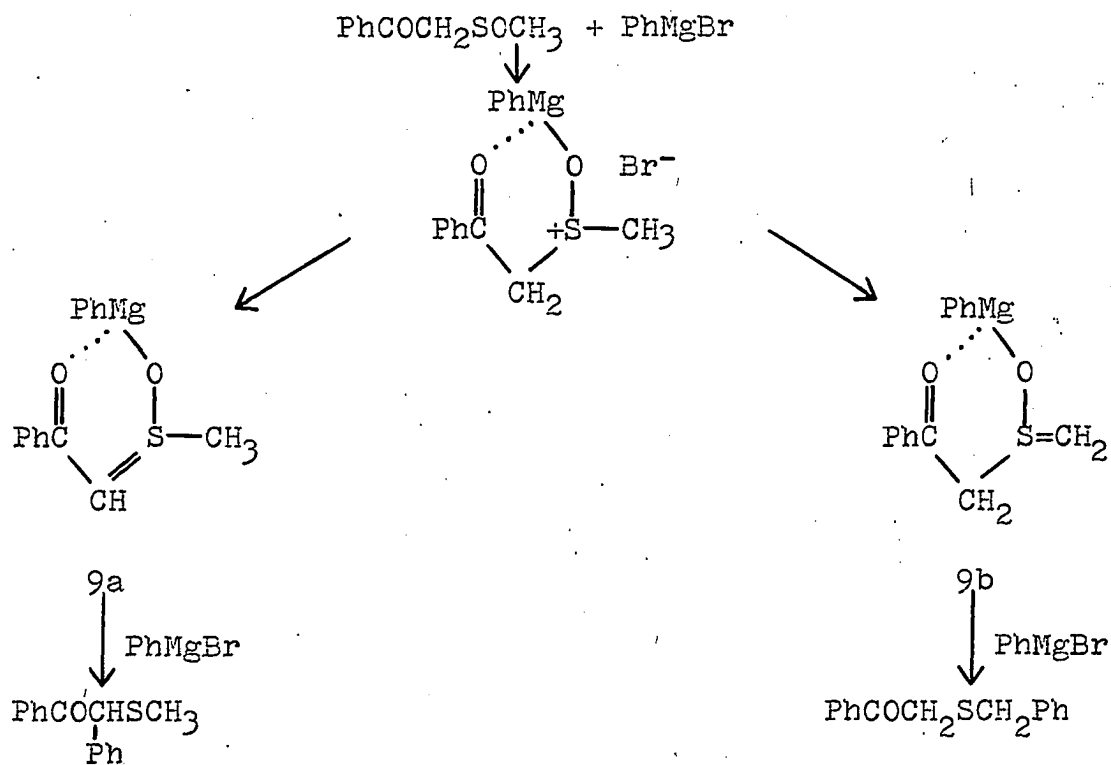
Figure 9. Proposed path for the reaction of phenyl-
magnesium bromide with ω-(methylsulfinyl)-
acetophenone

leads to the observed products. The striking parallel with

the mechanism previously proposed for the Pummerer re-

arrangement (Figure 2, p. 25) is intended. The magnesium

(+II) ion is a Lewis acid; the Pummerer rearrangement gen-

erally results in the incorporation of the acid anion at

the α-position of the sulfoxide.

If the reaction does, in fact, give this mixture of

products, it would not be of much value as a synthetic

method. Because of the ease of ionization of the methylene

proton, the product from 9a should predominate. This methylene group might partake in a keto-enol type of resonance to afford stabilization to the chelate intermediate. This might favor the intermediate 9b and would be consistent with the greater intensity of the resonances attributed to the methylene protons. However, judging from the relative intensities of the methyl and methylene resonances, a product with an SCH_3 group predominates. This could also be methyl phenacyl sulfide.

The alkylation reactions, in principle, extend the utility of the reactions developed for the β-keto sulfoxides, I. A limitation arises by virtue of the fact that the Pummerer rearrangement of the alkylated β-keto sulfoxides does not proceed as cleanly as with I. Since the rearrangement is an important reaction in the synthetic scheme, the utilization of compounds of type III has been somewhat limited. Under conditions where Ia rearranges smoothly, IIIa, $R' = CH_3$, precipitates as a liquid which does not contain either an hydroxyl or a second carbonyl group. The infrared spectrum showed an olefinic band at 6.1 microns. This could arise by dehydration of the keto hemimercaptal (2h, Figure 2, p. 25) or loss of a proton from the methyl group of an intermediate of type 2f, Figure 2, during the rearrangement.

The last product to be derived from the β-keto sulfoxide by a substitution reaction to the α-carbon is the brominated compound, IVa (Equation 28). The reactions of

$$\text{PhCOCH}_2\text{SOCH}_3 \xrightarrow[\text{2. Br}_2]{\text{1. NaH}} \overset{\text{Br}}{\underset{\text{IVa}}{\text{PhCOCHSOCH}_3}} \tag{28}$$
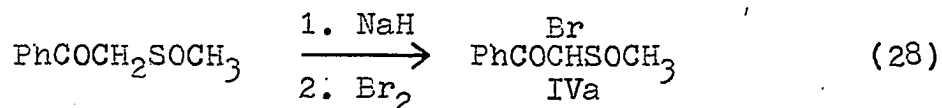
this compound will be discussed later. This compound, though also produced as a diastereomeric mixture of compounds, can be obtained crystalline under the proper conditions. The N.M.R. of one sample of IVa, m.p. 95-100°C. showed two enantiomers to be present in the ratio of 2 to 1 (at 6.26δ, -BrCH-, and 2.84δ, -SOCH$_3$, for one enantiomer and at 6.19δ and 2.71δ for the other). This suggested the possibility of an asymmetric induction by the sulfoxide group. The mother liquor from the recrystallization yielded additional solid, m.p. 103-104°C. after evaporation of the solvent. The N.M.R. of this solid showed only one component with singlets at 6.13δ and 2.86δ. Though the position of the methyl proton resonance corresponds closely to that of the major component of the mixture, the methine resonance is at a higher field than either of the other two. This could be a concentration effect, though this seems unlikely. A more reasonable explanation is that the higher melting compound is the diastereomer which has the same configuration at sulfur as one of the enantiomers of

the mixture. No further work was done to establish whether
the observed results were actually a fortuitous consequence
of the isolation and purification procedure, or do in fact
occur as the normal course of the reaction.

<div align="center">

Glycol, Alcohol and Ketone Formation
from β-Keto Sulfoxides

</div>

Figure 7 shows the types of products which can be
derived from the β-keto sulfoxides I and III by reduction.

The reduction (with aluminium amalgam) of Ia to aceto-
phenone with simultaneous or subsequent bimolecular reduc-
tion of the carbonyl group to the pinacol-type product, Va,

$$PhCOCH_2SOCH_3 \xrightarrow{AlHg} (PhCH(OH)CH_3)_2 \qquad (29)$$
$$Va$$
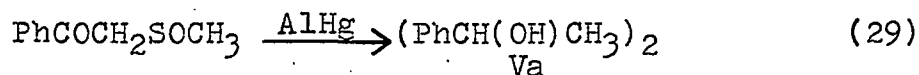
shown in Equation 29, occurs readily and in high yield.
Because of the formation of stereoisomers, the product is
difficult to obtain in a crystalline state. The formation
of Va as the product in this reaction was established by
comparison of the infrared spectrum of the product with
that of an authentic sample. A similar difficulty has been
experienced in the reduction of acetophenone by the same
method of reduction (119).

Sodium amalgam in various concentrations (20, 10, 5,
and 2% by weight sodium) produces 15-30% yields of crystal-
line Va along with acetophenone, α-phenethanol, and sulfur

containing liquids. The yields are variable and show no particular dependence on the amount of sodium in the amalgam.

Reduction of either I or III with lithium aluminium hydride results in the formation of β-hydroxy sulfides, VIa

$$PhCOCH(R')SOCH_3 \xrightarrow{LiAlH_4} PhCH(OH)CH(R')SCH_3$$

$$VIa, R' = H; IXa, R' = CH_3$$

(30)
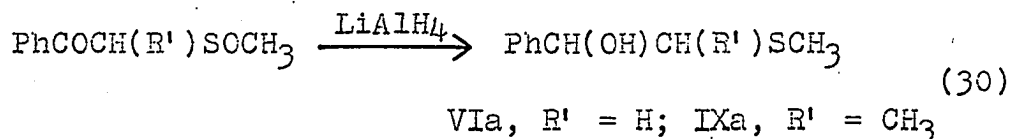
and IXa, as illustrated in Equation 30. Consistent with previous observations (46, 47), the carbon-sulfur bond is not cleaved by this reducing agent. This type of compound had previously been prepared by reaction of an α-halo ketone with a mercaptan and reduction of the resultant keto sulfide with aluminium iso-propoxide (30).

The inability to effect complete reduction of the β-keto sulfoxide with less than a one to one molar ratio of keto sulfoxide to lithium aluminium hydride and the generation of an intense purple color during the reduction suggests the formation of complexed ions (or, less likely, radical-ions) as intermediates. The color fades on cooling under nitrogen, but it can be regenerated again by heating the solution to reflux temperature. The net change in the oxidation state of Ia corresponds to a four-electron gain which could be accounted for by incorporation of two hy-

dride ions into the molecule, by donation of one electron by each of four hydride ions, or a combination of these two modes of reduction. Reduction by two hydride ions would require a third for the ionization of the methylene; the electron transfer or a combination-mechanism would require at least four hydride ions. The sensitivity of the colored intermediate to oxygen and/or moisture, and the necessity of working at 60-70°C. discouraged attempts to transfer the solution to a cell for observation of the substance in the E.S.R.

This reaction was studied as a part of a route to the preparation of enol ethers involving reduction of the keto sulfoxide, O-methylation of VIa and sulfonium salt formation followed by elimination of dimethyl sulfide by base. The hydroxyl group can be alkylated to give the methyl ether, $PhCH(OCH_3)CH_2SCH_3$, XXIVa. While the alcohol (VIa) forms a sulfonium salt readily, the ether does not.

As an alternate method, treatment of XXIVa with potassium $\underline{t}$-butoxide in 80% dimethyl sulfoxide-20% $\underline{t}$-butyl alcohol at 80°C. resulted in the formation of some of the desired enol ether, $Ph(CH_3O)C=CH_2$, among other products. The intermediacy of the sulfoxide derived from XXIVa by oxygen exchange with dimethyl sulfoxide (2, 5) was ruled out by preparing this sulfoxide by sodium metaperiodate

oxidation and subjecting it to the reaction conditions. An olefinic product, different (by infrared) from that obtained from the sulfide, was produced. The olefin was later isolated and identified as β-(methylsulfinyl)-styrene, PhCH=CHSOCH₃ (work by Mr. E. T. Sabourin (57)).

Because of the mixture of products obtained, this method of preparation of enol ethers from the β-keto sulfoxides was developed further. No attempt was made to find conditions which would favor the formation of the enol ether and decrease the by-products.

The β-keto sulfoxides I and III can be readily reduced to the ketones. A reduction using aluminium amalgam (17, 18) has already been reported for the conversion of β-keto sulfoxides of type I to the corresponding aryl alkyl ketones. Reduction with zinc dust in acetic acid-ethanol solution, Equation 31, has also been found to be effective for this reduction and a useful procedure for large scale (0.1-0.2 mole) conversion of I to ketones has been developed during the course of the present work. It is felt that the aluminium amalgam reduction is useful for the preparation of millimole quantities of the ketone or for use on acid-sensitive molecules. However, the need to manipulate the large quantities of solvent and aluminium foil when the reduction is carried out on a larger scale makes the zinc reduction more favorable.

$$ArCOCH(R')SOCH_3 \xrightarrow[\;C_2H_5OH\;]{Zn,CH_3CO_2H} [ArCOCH(R')SCH_3]$$

(31)

$$\longrightarrow ArCOCH_2R' \quad VII, \; R' = H; \; VIII, \; R' = CH_3$$
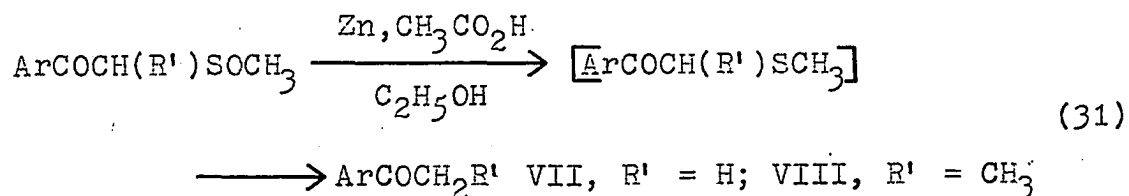
The reduction was carried out under many different conditions but the reaction variables (metal surface area, solvent composition, time, and temperature) were not changed in a manner that would permit observation of trends due to change in a single variable. A few points are worthy of note.

Because of the much greater surface area to weight ratio, reduction with zinc dust (5 to 1 molar ratio to the sulfoxide) is much more rapid and vigorous than that with granular zinc (30 mesh, 8 to 1 ratio); cooling of the reaction mixture is imperative.

Reaction at 75-80°C. with granular zinc in 75% acetic acid-25% water (or ethanol) resulted in the formation of appreciable amounts of Va, and α-phenethyl acetate. A higher yield of the glycol was obtained in an aqueous medium than in an alcoholic solution (21% vs. 4.7%).

Extended reaction times lead to the production of the glycol, Va, α-phenethanol and the corresponding acetate. Zinc dust in 40% acetic acid-60% ethanol with Ia gave an 88% yield of acetophenone after 1.25 hours and only a 46% yield after 13 hours. The amounts of the by-products were

not determined.

The rate of reduction increases with change in solvent in the order: 100% acetic acid < ethanol-acetic acid < water-acetic acid. This parallels the increase in the acidity of the medium.

The intermediate sulfide illustrated in Equation 31 has not been isolated; thus direct reduction of the C-SO bond is a possible reaction path.

As would be anticipated, reduction of Ia with Raney nickel resulted in carbon-sulfur bond scission and formation of acetophenone in 75% yield. It has been pointed out that mild reducing agents, aluminium amalgam/water or zinc dust/acetic acid, do not ordinarily bring about carbon-sulfur bond scission. Since α-substituted ketones are known to be readily reduced to the ketones, the very facile reduction in the case of the β-keto sulfoxides must be attributed to this property rather than to a low reduction potential for the carbon-sulfur bond (or the C-SO bond) or to any intrinsic properties of these two reducing agents.

The activation provided by the ketone group is dramatically illustrated by the results of the attempted reduction, illustrated in Equation 32. After refluxing the α-hydroxy sulfoxide in acetic acid for 24 hours with zinc dust, only starting material (11%; mixed melting point,

$$(Ph)_2CH(OH)CH_2SOCH_3 \xrightarrow[CH_3CO_2H]{Zn} (Ph)_2C=CHSCH_3 \qquad (32)$$
$$XXVII$$
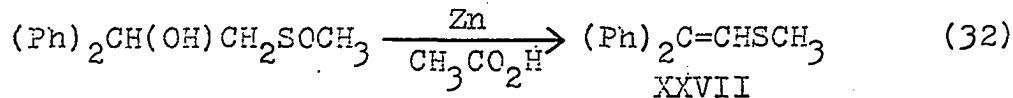
infrared) and 1,1-diphenyl-2-methylmercaptoethylene, XXVII
(60%; m.p. 71-72°C., N.M.R.: singlet (area 3) 2.27δ;
singlet (area 1) 6.42δ; singlet (area 5) 7.14δ; singlet
(area 5) 7.27δ). The β-keto sulfoxide is completely reduced
within two hours at room temperature!

It is interesting to note that refluxing the β-hydroxy
sulfoxide in tetrahydrofuran with lithium aluminium hydride
for 24 hours also produced XXVII. This compound was ini-
tially prepared by the "pyrolysis" of the β-hydroxy sul-
foxide (14, 15).

Reference has been made to the reduction of a sulfoxide
to a sulfide by sodium metabisulfite (44) in aqueous solu-
tion. It was presumed that the reducing agent was bisulfite
ion, formed by hydration of the metabisulfite ion. An
attempt to reduce the β-keto sulfoxide, Ia, to the β-keto
sulfide or acetophenone using sodium bisulfite gave only
starting material (23%) and the water soluble bisulfite
addition product of phenylglyoxal after four days at room
temperature. A small amount of a yellow liquid was ob-
tained during the isolation of Ia; this may have contained
some acetophenone.

Reduction of the methyl hemimercaptals of the aryl-

glyoxals, II provides access to compounds which are some-
times difficult to obtain by other methods. A number of
examples will serve to illustrate this point.

Desulfurization of the Methyl Hemimercaptals of Arylglyoxals

Conversion of IIa to α-hydroxyacetophenone, Xa, can be
accomplished by reduction with zinc dust in glacial acetic
acid, illustrated in Equation 33. The reaction can reason-
ably be postulated as proceeding by formation of the
glyoxal in solution and subsequent reduction on the metal

$$PhCOCH(OH)SCH_3 \longrightarrow \left[PhCOCHO + HSCH_3\right] \xrightarrow[Zn]{H_2} PhCOCH_2OH$$

$$+ (PhCOCH_2)_2 + Zn(SCH_3)_2 \tag{33}$$
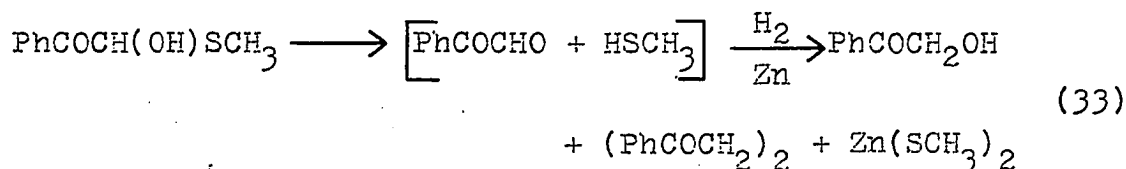
surface. This particular method has some limitations.
Like the ketone preparation, the reaction is heterogeneous
and even more sensitive to solvent and temperature vari-
ations. The product is rapidly reduced to the ketone at
temperatures above $30^{\circ}C$. and in the presence of small
amounts of water. Small amounts (1-3%) of 1,4-
diphenylbutane-1,4-dione have been isolated, suggesting
that the reduction proceeds through radical intermediates,
presumably the radical-anion of the glyoxal which can
dimerize and undergo a second reduction resulting in loss
of the hydroxyl groups and formation of the 1,4-diketone.

There was little apparent variation in yield with temperature, below, 25°C. In the range 25-35°C., the ketol yields were reduced. Because of the need for temperature control, and therefore for efficient heat transfer from the reaction mixture, the yield of Xa was even dependent on the rate of stirring. This factor also prohibited carrying the reaction out efficiently on a larger scale.

In 40% acetic acid-60% ethanol reduction of the ketol appeared to be as fast as its formation since the yield of acetophenone was often equal to or greater than that of Xa. However in glacial acetic acid, using a 10 to 1 mole ratio of zinc dust to IIa, a 57-62% yield of Xa could be obtained after the reaction for 2 hours at 25°C. with rapid stirring, on a 50 mmole scale. With high speed stirring and the use of a cold water bath during the reaction, the temperature could be controlled within the desired range and reproducible yields could be obtained.

Sodium formaldehydesulfoxylate (SFS), $NaOSOCH_2OH$, is a mild reducing agent which converts IIa to α-hydroxyacetophenone in moderate yield. The advantage over the zinc/acetic acid reduction is that the reaction variables need not be as carefully controlled.

The reducing agent in 50% aqueous ethanol has a pH of 10-11. Addition of IIa lowers the basicity to pH 6-7, and

after two days at room temperature, the reaction mixture is slightly acidic (pH 2-3). This suggests the reaction sequence illustrated by Equations 34a and 34b. The reaction is a crossed-Cannizzaro reaction with SFS serving as a source of formaldehyde in the basic solution. The

$$PhCOCH(OH)SCH_3 + HO^- \rightleftharpoons PhCOCHO + H_2O + CH_3S^- \qquad (34a)$$

$$PhCOCHO + H_2O + NaOSOCH_2OH \longrightarrow PhCOCH_2OH + HCO_2H \qquad (34b)$$
$$+ NaOSOH$$
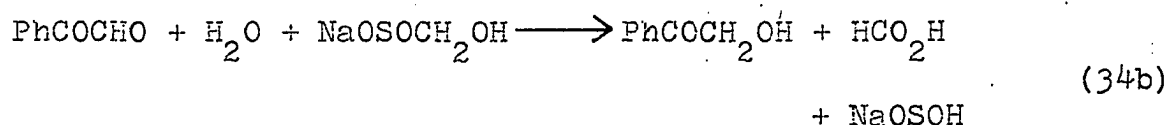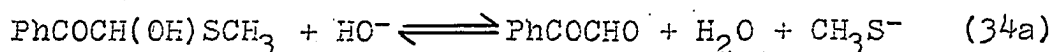
generation of sodium hydrogen sulfoxylate in the reaction is indicated by the rapid formation of colloidal sulfur when the reaction mixture is acidified. Sulfoxylic acid is known to be unstable and to decompose to sulfur and water.

Significantly higher yields of the ketol were attained by reduction of the hemihydrate of phenylglyoxal, XVIIa, which can be simply and quickly prepared by the method described in the Experimental involving precipitation of the mercaptan from a solution of IIa with cupric or mercuric salts. When mercuric salts were used to precipitate the mercaptan, the reduction could be carried out on the crude product by adding the reducing agent and adjusting the solution to pH 8. While cupric salts are less desirable for removal of the mercaptan in this particular reaction, a good yield of the ketol was obtained in the presence of

cupric salts by controlling the pH.

Bimolecular Reduction of Methyl Hemimercaptals of Arylglyoxals

When cupric salts are used for precipitating the mercaptan, some cupric ion goes into solution even in non-aqueous solvents (ethanol, chloroform, acetone). A complication then arises by virtue of the fact that the reaction of IIa or XVIIa with SFS in the presence of cupric ion may take either of two courses, producing either the ketol, Xa or the dimer, XIIa. The results in Table 5 suggest that the reaction is strongly pH dependent, but the optimum conditions for the production of either Xa or XIIa in the presence of cupric ion have not been established.

The bimolecular reduction is believed to proceed according to the sequence shown in Equations 35a-c. An aqueous solution of cupric nitrate and SFS

$$2Cu^{+2} \xrightarrow{\text{SFS}} 2Cu^{+} \tag{35a}$$

$$2PhCOCHO + 2Cu^{+} \rightleftharpoons 2\left[Ph\overset{\bullet}{C}OCHO^{-}\right]Cu^{+2} \xrightarrow{?} 2PhCOCH_2OH \tag{35b}$$
$$Xa$$

$$2\left[Ph\overset{\bullet}{C}OCHO^{-}\right]Cu^{+2} + (+2H^{+}) \longrightarrow PhCOCH(OH)-CH(OH)COPh$$
$$XIIa$$
$$\tag{35c}$$
$$+ 2Cu^{+2}$$
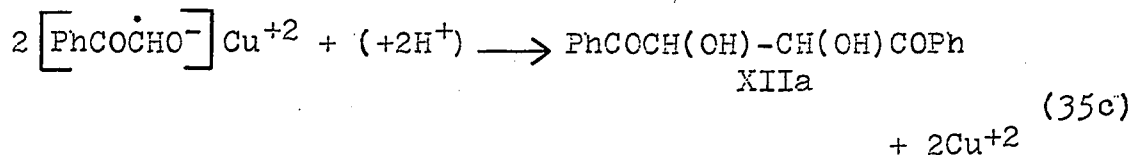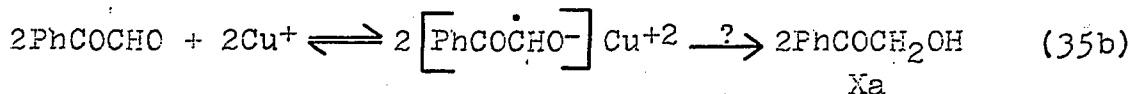
Metallic copper precipitates from an aqueous solution of cupric nitrate and SFS after three days at room temper-

Table 5. Product selectivity in the reduction of phenyl-glyoxal derivatives (at 25°C.)

Reactant[a]	Ratio, reactant/Cu^{+2}	pH	Time (hours)	Xa	XIIa
XVIIa[c]	3.5	_b	24	82.5%	--
XVIIa[c]	5.4	7	72	--	36%
XVIIa[d]	8.3	_b	48	--	56%
XVIIa[d]	16.6	7-8	60	--	59%
XVIIa	_e	8	112	91%	--
IIa	1.66	8	65	24%	8.3%

[a]Compound in 60% ethanol-40% water (1 mmole/5 ml.) with SFS (1 mmole compound/2 mmole SFS).

[b]pH of solution not checked after mixing; in other cases, found pH 6-8 at this point.

[c]Common source of starting material.

[d]Common source of starting material but different from that used in the first two experiments.

[e]No cupric ion present.

ature, demonstrating that SFS is able to effect the initial reduction shown in Equation 35a. The one-electron reduction of the carbonyl group is a well known reaction and has been effected with arylglyoxals using magnesium and iodine in

benzene and ether; the yields were generally poor (125).

The reverse of reaction 35c is known to occur in basic solution and the radical anion of phenylglyoxal has been observed by E.S.R. (139). This cleavage of the central carbon-carbon bond in basic solution may explain, in part, the apparent pH dependence of this reaction and the formation of the dimer when the initial pH was near the neutral point rather than around pH 8 (Table 5). The radical-anion could revert to phenylglyoxal or form the enolate anion of Xa by a one-electron oxidation or reduction (Equation 35b). The ketol if formed by this path, could also be recycled to phenylglyoxal by oxidation by cupric ion (140, 141). The competitive reduction of phenylglyoxal by the Cannizzaro reaction would be eliminated in the neutral or slightly acidic solution, and the bimolecular reduction product should predominate under these conditions.

On the basis of the factors discussed above pertaining to control of the pH-dependent reactions, it is felt that the reaction can be specifically directed to the formation of either Xa or XIIa. A slightly basic solution (about pH 8) would direct the reaction to the formation of Xa, with SFS acting as the reducing agent in a crossed-Cannizzaro reaction with phenylglyoxal. Strongly basic

solutions are to be avoided since mandelic acid is formed
under these conditions. A neutral or slightly acidic solu-
tion (pH 6) would direct the reaction to the formation of
the ketol dimer, XIIa. In this reaction SFS reduces the
cupric ion to the cuprous ion which then reacts in the
electron-transfer step.

The catalytic nature of the reaction can be seen in
the stoichiometry indicated in Table 5. Note the relative-
ly constant yield when the molar ratio of phenylglyoxal to
cupric ion was changed from 16.6 to 1 to 33.2 to 1 (one
mole of the hemihydrate can yield two moles of phenyl-
glyoxal).

Perhaps the most unique feature of this reaction is
the simplicity of the method. The bimolecular reduction
of carbonyl compounds normally occurs only under strictly
anhydrous conditions, the previously cited magnesium-iodine
reduction of arylglyoxals and the aluminium amalgam reduc-
tion of Ia being pertinent examples. However, the bimo-
lecular reduction described here occurs in reasonable yield
in aqueous solution with pH control being the only apparent
critical factor.

An analogous compound, XIIb, derived from the methyl
hemimercaptal of p-tolylglyoxal has been prepared by reduc-
tion with hydrogen deficient Raney nickel. The efficiency
of the reduction was quite variable, as might be expected

with a heterogenous system utilizing a catalyst subject to ageing effects. The reaction sequence shown in Equations 35a-c, with nickel acting as the electron donor, could occur. However, homolytic scission of the carbon-sulfur bond during desulfurization reactions has been observed (54). Radical coupling could then lead to the observed product.

The cuprous ion reduction of IIb has not been attempted, and an attempt by Dr. E. R. Talaty in these laboratories XIIa by Raney nickel reduction of IIa was not successful. Thus, the generality of either reduction has not been established.

Glycol Formation from Methyl Hemimercaptals of Arylglyoxals by Metal Hydride Reductions

An exceptionally straight-forward and efficient preparation of arylethylene glycols, XI, has been developed. This type of compound has normally been prepared by peracid oxidation of the olefin and hydrolysis of the epoxide, or by the Provost reaction, involving reaction of an olefin with silver benzoate and iodine, followed by saponification of the vicinal dibenzoate.

Reduction of the methyl hemimercaptals of arylglyoxals, II, with lithium aluminium hydride or sodium borohydride, illustrated by Equation 36, gives the glycols, XI, in high

$$\text{ArCOCH(OH)SCH}_3 \xrightarrow[\text{2. H}^+]{\text{1. H}^-} \text{ArCH(OH)CH}_2\text{OH} + \text{CH}_3\text{SH} \quad (36)$$
$$\text{XI}$$
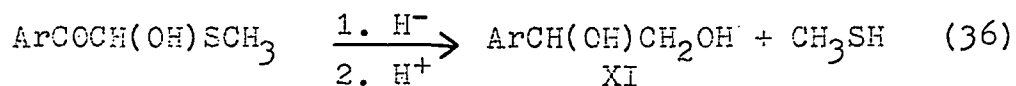
yield. Sodium borohydride reduction is the method of choice since it does not require anhydrous solvents and is generally more efficient than lithium aluminium hydride, though both give good yields of the glycols. For example, ethyl benzoate can be converted to styrene glycol in 75% over-all yield from the ester. Ethyl α-naphthoate was converted to α-naphthylethylene glycol in an over-all yield of 58%; the yield of this glycol from the Provost reaction was 23%, and the starting material is not as readily obtained as the ester. The yields of the glycols obtained by the two methods are given in Table 6.

Table 6. Yields in the preparation of ArCH(OH)CH$_2$(OH) by metal hydride reduction

Ar	Compound	Yield by reduction with:	
		LiAlH$_4$	NaBH$_4$
C$_6$H$_5$	XIa	79%[a]	95%[a]
p-CH$_3$C$_6$H$_4$	XIb	95%[a]	99%[a], 82%[b]
p-CH$_3$OC$_6$H$_4$	XIc	--	86%[a], 80%[b]
α-C$_{10}$H$_7$	XIe	73%[b]	94%[b]
β-C$_{10}$H$_7$	XIf	--	52%[b] (minimum)

[a]Yield of product before recrystallization.

[b]Yield of purified product.

Only one literature reference could be found for the preparation of α-naphthylethylene glycol. The melting point of the product obtained by reduction of IIe did not agree with the literature value (122). The absence of a carbonyl group in the infrared spectrum of XIe and the loss of two protons (by N.M.R.) when the compound was treated with deuterium oxide in dimethyl sulfoxide were observations consistent with a glycol structure. Since a benzoate group could have been lost by a β-elimination during the saponification leading to the formation of XIe, the reactions illustrated in Figure 10 were carried out to check the identity of the products obtained by the two methods.

Melting points and infrared spectra of the glycol and dibenzoate obtained by both reaction schemes confirm the identity of the compounds. Mixed melting points of the glycols and dibenzoates from the two reactions showed no depression.

$$\alpha\text{-NpCOCH(OH)SCH}_3 \xrightarrow{\text{NaBH}_4} \alpha\text{-NpCH(OH)CH}_2\text{OH}$$
$$\text{m.p. } 147^\circ\text{C.}$$

$$\xrightarrow[\text{pyridine}]{\text{BzCl}}$$

$$\alpha\text{-NpCH=CH}_2 \xrightarrow[\text{I}_2]{\text{AgOBz}} \alpha\text{-NpCH(OBz)CH}_2\text{OBz} \xrightarrow[\text{EtOH}]{\text{NaOH}} \alpha\text{-NpCH(OH)CH}_2\text{OH}$$
$$\text{m.p. } 108^\circ\text{C.} \qquad\qquad \text{m.p. } 145^\circ\text{C.}$$
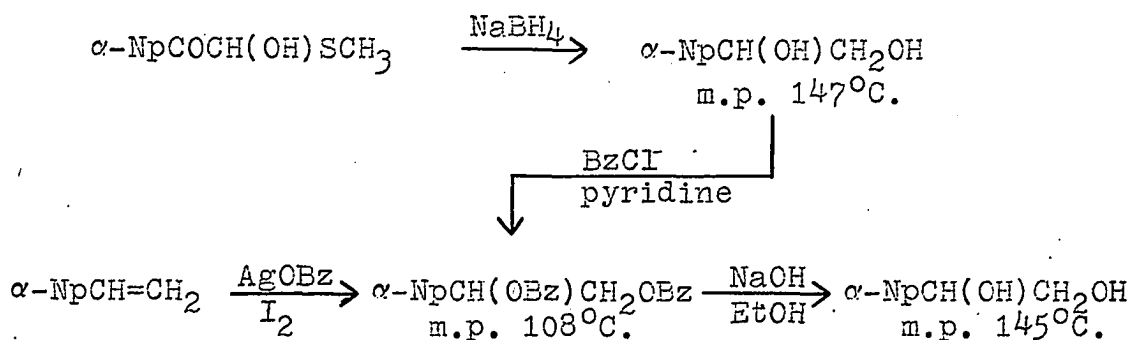
Figure 10. Reactions in the preparation of α-naphthyl-ethylene glycol

A New Method for the Synthesis of α-Dicarbonyl Compounds

Another group of compounds which can readily be prepared from the methyl hemimercaptals of arylglyoxals are the arylglyoxals, XVI. Reference has been made to the preparation of α-hydroxyacetophenone and its α-dimer, XIIa, from phenylglyoxal. A method of synthesis which would require phenylglyoxal or other arylglyoxals as starting material would only be practical if an efficient synthesis for arylglyoxals were available. Several different methods for converting IIa to phenylglyoxal were studied.

A report of the preparation of isocyanates by mercuric or silver ion assisted elimination of mercaptan from S-methyl-N-arylthiolcarbamates (142), as depicted by Equation 37 suggested that such a method might be applicable to the conversion of IIa to XVIa. Initial attempts to produce

$$ArNHCOSCH_3 + Ag^+ + R_3N \longrightarrow ArN=C=O + AgSCH_3 + R_3NH^+ \quad (37)$$

phenylglyoxal, pure and in high yield, were unsuccessful largely due to the isolation and purification procedures used at that time.

Consequently, a number of hydrolytic conversions of IIa to XVIa were attempted. Refluxing IIa in aqueous ethanol in the presence of hydrochloric acid, or in aqueous acetic acid produces phenylglyoxal hemihydrate, XVIIa, from which the anhydrous glyoxal can be obtained by distillation.

Since the hemihydrate is volatile, the mercaptan cannot be swept out of the reaction mixture without simultaneous loss of XVIIa. Thus, the loss of methyl mercaptan must essentially be a diffusion process, and the extended period of reflux necessary for diffusion to occur causes some decomposition of the product and considerable product loss due to side reactions. Two products, formed as illustrated in Equation 38a and 38b, have been isolated and identified from the residue of the aqueous ethanol hydrolysis of IIa. When the reaction was carried out on a 0.4-0.5 mole scale

$$2PhCOCH(OH)SCH_3 \longrightarrow PhCOCH(SCH_3)_2 + PhCOCHO \quad (38a)$$

$$PhCOCH(OH)SCH_3 + H_2O \longrightarrow PhCH(OH)CO_2H + CH_3SH \quad (38b)$$
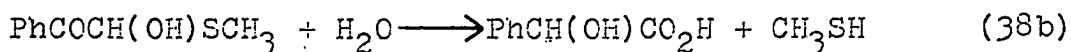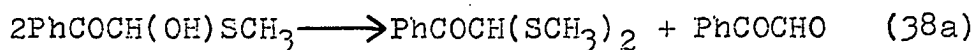
as much as 45% (by weight) of the starting material was lost. Decrease in yield of phenylglyoxal as the scale of the reaction was increased was noted in all the preparations involving hydrolysis. The by-products of the preparation of the other glyoxals have not been identified, but they are presumed to be of the same type as those formed in the preparation of phenylglyoxal.

Isolation of mandelic acid from the phenylglyoxal preparation was unexpected since this product is normally formed from phenylglyoxal in basic solution in a manner analogous to the rearrangement of benzil in basic media (143). Rearrangement of α-keto aldehydes and related com-

pounds has been reported to occur on refluxing the compounds in 6N aqueous hydrochloric acid. Phenylglyoxal has been converted to mandelic acid in this manner (144). The reaction was pictured as proceeding via a 1,2-hydride shift from an aldehyde group. In concentrated acid solution, a second reasonable mechanism would involve acid catalyzed enolization to a hydroxy ketene intermediate, followed by hydration in the usual manner to yield the hydroxy acid.

During the course of studying the cupric ion catalyzed nitrogen dioxide oxidation of the hemimercaptal, IIa, it was noted that the blue color of the cupric ion was discharged immediately upon mixing with a solution of IIa. This was attributed to its oxidation to the cuprous state by the mercaptan. However, when larger amounts of the salt were added, it was noted that the discharge of color was accompanied by precipitate formation. This led to the development of a very simple and efficient method for the synthesis of arylglyoxals, illustrated in Equation 39.

$$2ArCOCH(OH)SCH_3 + Cu(O_2CCH_3)_2 \longrightarrow 2ArCOCHO +$$

$$Cu(SCH_3)_2 + CH_3CO_2H \tag{39}$$
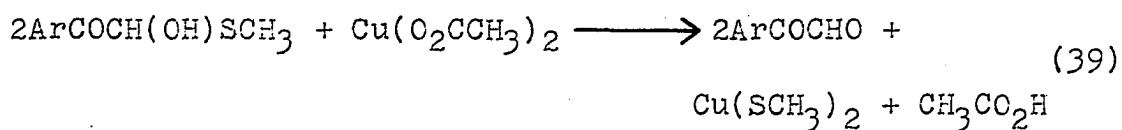
Cupric mercaptide can be removed from the alcohol or chloroform solution by filtration, leaving the glyoxal and acetic acid in solution. After neutralization of the acid and evaporation of the solvent, vacuum distillation yields

the anhydrous glyoxal in good yield. For example, the aryl-glyoxals XVIa, XVIb, and XVIc were prepared on a 50 milli-mole scale in yields of 88, 86, and 74% respectively.

In principle, the method should be applicable to the preparation of α-diketones, XIX, from the alkylated β-keto sulfoxides, III. However, as mentioned previously, the product of the Pummerer rearrangement has not been isolated. Nevertheless, the preparation of 1-phenylpropane-1,2-dione has been effected by acid hydrolysis of the β-keto sul-foxide IIIa, R' = CH$_3$, as illustrated by Equation 40. This

$$PhCOCH(R')SOCH_3 + H_3PO_4 \xrightarrow[C_2H_5OH]{H_2O} PhCOCOR' + CH_3SH$$

$$(40)$$

$$R' = H \ (XVIa), \ CH_3(XIXa)$$
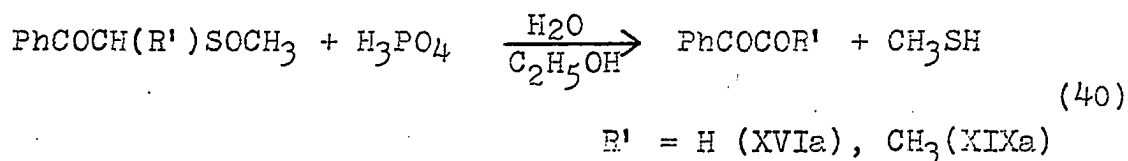
method had been applied originally to the β-keto sulfoxide Ia as a possible method of preparing phenylglyoxal. In both reactions the yield was low (XVIa, 65%; XIXa, 50%) due to decomposition of the product in the acid medium.

The reaction of sulfoxides with thionyl chloride (70) was utilized in an attempt to find a milder method for preparation of the α-diketones. The crude product from the reaction did not contain a sulfoxide function (by infrared analysis) and was presumed to be the α-chlorosulfide, PhCOCH(Cl)(CH$_3$)SCH$_3$. Hydrolysis in aqueous alcohol in the presence of mercuric oxide did not produce the diketone.

The product(s) from this reaction was not identified.

As alternatives to the hydrolytic methods, and prior to the development of the heavy-metal ion assisted elimination of mercaptan, other methods of preparation of glyoxals from II had been unsuccessfully investigated. Two of these are worthy of mention.

Pyrolysis of α-bromo-α-acetoxyacetophenone has been reported to yield phenylglyoxal and acetyl bromide (145). This suggested that α-methylmercapto-α-acetoxyacetophenone, prepared from Ia by reaction with acetic anhydride, might undergo a similar elimination to yield phenylglyoxal and methyl thiolacetate. Heating the α-acetoxysulfide under vacuum did not result in decomposition. This type of decomposition has been observed in other cases under more severe conditions.

Attempted oxidative conversions of the mercaptan to the disulfide were also unsuccessful. Potassium hypochlorite in acidic or basic solution did not effect any change; only starting material was recovered, though not in quantitative yield. The similarity of the infrared spectra of the starting material and the hemihydrate makes identification of the latter compound by this method somewhat difficult; some XVIIa could have been produced and escaped detection.

Thus, essentially five methods of preparing aryl-

glyoxals from β-keto sulfoxides have been developed during the course of this work. They are: (1) the acid hydrolysis of β-keto sulfoxides, I, (2) the hydrolysis of the methyl hemimercaptals of arylglyoxals, II, with aqueous, ethanolic hydrochloric acid, (3) hydrolysis with aqueous acetic acid, (4) removal of the mercaptan from II by oxidizing it to the disulfide and, (5) precipitation of the mercaptan with cupric or mercuric salts.

The hydrolytic methods, starting with either the β-keto sulfoxide or the hemimercaptal, are time consuming and limited to use in small scale preparations. The formation and the nature of the by-products from these methods have been described.

The last procedure is the method of choice. It is fast, efficient, and appears to be applicable, with little variation in yield, to preparations carried out on almost any scale. The use of mercuric oxide with an acid catalyst gave small amounts of the diethyl acetal as a byproduct, but this does not account for the large decrease in yield noted in the 0.25 mole preparation. In this preparation however, the temperature of the reaction mixture was not controlled and a large amount of a gummy residue was formed, rather than the granular solid produced in the other experiments.

The oxidation of the mercaptan to the disulfide with

nitrogen dioxide and a trace of cupric ion has not been
effective. While phenylglyoxal was produced in the re-
action, it was contaminated by the oxidation product of
methyl disulfide. (The reaction will be discussed more
fully below.) The facile oxidation of the disulfide will
impose a limitation on any other method based on this
method: a specific and mild oxidizing agent must be used.

Some typical results illustrating the efficiency of
the hydrolysis and precipitation procedures can be seen in
Table 7.

A reaction of interest is the cupric ion catalyzed
oxidation of IIa with nitrogen dioxide. The reaction does
produce phenylglyoxal, but it is not a useful reaction from
a synthetic point of view. The N.M.R. spectrum of the dis-
tilled product showed an impurity having two equal inten-
sity singlets at 2.54δ and 3.13δ. This, and the infrared
spectrum suggested a substance of the type $CH_3S(O)_nSCH_3$,
n = 1 or 2. Oxidation of methyl disulfide with nitrogen
dioxide gave a substance with a very strong parent ion peak
at mass 126 (n = 2) and a very low intensity peak at mass
110 (n = 1). The N.M.R. of the substance shows singlets of
equal intensity at 2.69δ and 3.27δ, and the strong infrared
absorptions at 7.47, 8.78 and 10.51 microns are close to
the absorptions reported for methyl methanethiolsulfonate,

Table 7. Comparison of the efficiency of various methods for the preparation of arylglyoxals, $ArCOCHO(H_2O)_n$

Method	Ar	Yield for a given scale of reaction (moles)			
		0.02-0.04	0.1	0.25	0.35-0.45
1[a]	C_6H_5	69%	49%[b]	--	60%
2	C_6H_5[c]	83%	--	45%	40%
2	p-$CH_3C_6H_4$[c]	73%	--	--	--
2	p-$CH_3OC_6H_4$[c]	78%	--	--	--
2	p-BrC_6H_4[d]	57%	--	--	--
3[a]	C_6H_5	--	81%	70%	64%
5[a,e]	C_6H_5	89%	87%	82%	88%
5[e]	p-$CH_3C_6H_4$	86%	--	--	--
5[e]	p-$CH_3OC_6H_4$	74%	--	--	--
5[f]	C_6H_4	70%	68%	55%	--

[a]Product isolated as the anhydrous glyoxal, (n = 0) by distillation, when these procedures were used.

[b]The total product mixture (extract and oily residue) was not distilled in this experiment; a slight increase in yield was noted when this was done in the other two experiments.

[c]Product isolated as the hemihydrate (n = $\frac{1}{2}$).

[d]Product isolated as the hydrate (n = 1).

[e]With cupric acetate.

[f]With mercuric oxide and a 1/50 mole ratio of mercuric chloride.

n = 2 (81, 133). These absorptions are also seen on the spectrum of the impure phenylglyoxal. A downfield shift of this substance in phenylglyoxal can be attributed to the magnetic anisotropy of the "solvent". For these reasons, the impurity in the phenylglyoxal is believed to be methyl methanethiolsulfonate.

The proposed thiol ester could arise by initial oxidation of the mercaptan to methyl disulfide and further oxidation by nitrogen dioxide (146) to a transient disulfoxide, $CH_3SOSOCH_3$, which can undergo intramolecular disproportionation to a sulfone and a sulfide group. A second alternative is oxidation of only one of the sulfur atoms to form a thiolsulfinic ester, which can disproportionate to the thiolsulfonic ester and methyl disulfide (2).

An interesting possibility for this reaction is that it proceeds through the unknown α-hydroxy-β-keto sulfoxide, XVa. This intermediate could then lose methanesulfenic acid to produce phenylglyoxal. The methanesulfenic acid could disproportionate to yield the ester and methyl disulfide (Equation 41b).

$$\left[\underset{XVa}{PhCO\overset{\overset{\displaystyle OH}{|}}{C}H-SOCH_3} \right] \longrightarrow \underset{XVIa}{PhCOCHO} + CH_3SOH \qquad (41a)$$

$$4CH_3SOH \longrightarrow CH_3SO_2SCH_3 + CH_3SSCH_3 + 2H_2O \qquad (41b)$$
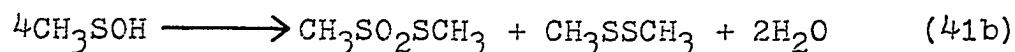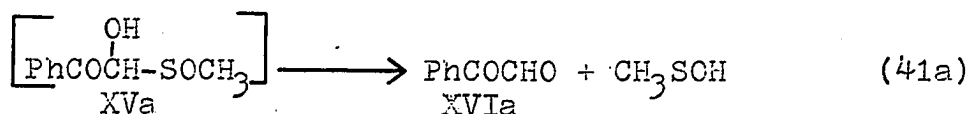
Both methyl methanethiolsulfonate and methyl disulfide

have been found in the reaction mixture. As a result, no choice between the two reaction paths can be made on the basis of the products isolated.

The same product mixture was obtained when the oxidation was carried out using potassium persulfate, ferric chloride and nitrogen dioxide, a molar equivalent of cupric nitrate, and dilute nitric acid. Cupric nitrate forms cupric methyl mercaptide and nitric acid; in alcohol or acetone solution, a very vigorous oxidation commences after a few minutes. Addition of pyridine appears to decrease the amount of thiolsulfonate ester formed by this side reaction, but because of the small difference between the boiling points of the ester and phenylglyoxal the two substances cannot be separated efficiently.

When the reaction was carried out with catalytic amounts of cupric acetate in the presence of suspended, powdered sodium carbonate, there was no apparent reaction. Bubbling oxygen through the solution for 8 hours with cupric acetate as a catalyst resulted in the formation of traces of methyl disulfide, but the hemimercaptal was recovered in almost quantitative yield.

The Structure of Hydrated Arylglyoxals

The arylglyoxals prepared by the hydrolysis methods did not always have melting points which agreed with those

in the literature. The glyoxals can exist in the anhydrous form, ArCOCHO (XVI), or as the hemihydrate, $(ArCOCH(OH)-)_2$ (XVII), or hydrate ArCOCH(OH)$_2$ (XVIII). The anhydrous glyoxals which have been prepared by the various methods described can be distilled. They generally solidify to a glass or a crystalline solid after several days.

The hemihydrates and hydrates usually are readily converted to one another which makes identification of either form difficult. Examination of the infrared and N.M.R. spectra of the compounds is very instructive in this regard.

The correlation of the melting points with the structures of the hydrates of p-methoxyphenylglyoxal has been accomplished (129). The hemihydrate XVIIc, m.p. 107-109°C. was formed by melting the hydrate, XVIIc (melting at about 70°C.; resolidified at 75°C.) or by heating IIc with hydrochloric acid. The N.M.R. spectrum of XVIIc was definitive in that it showed a pair of doublets (representing the H_A-C-OH_X group) centered at 6.32δ (H_A) and 5.12δ (H_X), with J_{AX} = 10.3 c.p.s.

The melting points reported for "phenylglyoxal hydrate" range from 73°C. to 91°C.; the latter melting point has been assigned to the hydrate, XVIIIa. A solid of this melting point could not be obtained from any of the preparations developed in this work. The melting point would

vary depending on the solvent used for the recrystallization and was generally in the 67-75°C. range.

Determination of the structure of some of the glyoxals by studying the N.M.R. spectra was of limited value due to the low solubility of the hydrates of phenylglyoxal and the p-methyl and p-bromo derivatives. A saturated solution of hydrated phenylglyoxal, m.p. 75-77°C., in deuterochloroform, showed a pair of doublets centered at 6.36δ (H_A, area 2) and 5.04δ (H_X, area 2), with $J_{AX} = 11$ c.p.s. This is fully consistent with the hemihydrate structure, XVIIa. Other samples gave less definitive spectra, usually showing only a broad absorption for H_X.

A hydrated p-methylphenylglyoxal in dimethyl sulfoxide solution showed a rough doublet centered at 6.69δ, with $J_{AX} = 7$-9 c.p.s. and a broad absorption at 5.78δ. Because of the broad solvent absorption, a good integral could not be obtained for the entire spectrum, but the ratio of the aromatic protons to the 6.69δ doublet was 4:2. The ratio of the doublet to the singlet was approximately 2:2. This ratio is indicative of the hemihydrate structure. After being warmed in the probe for 10-15 minutes, the doublet collapsed to a broad singlet. The solution turned yellow, indicating that dehydration and formation of the anhydrous glyoxal was occurring. No aldehyde proton could be detected, presumably due to the low concentration of this species.

The N.M.R. spectrum of p-bromophenylglyoxal, m.p. 122-124°C., obtained in acetone solution, was of little value. Due to the broad solvent absorptions, only a broad singlet at 5.88δ and an A_2B_2 quartet, centered at 7.92δ could be clearly distinguished. Again, a good integral could not be obtained. After several minutes in the probe, the sample showed a broad singlet at 6.3δ and a sharp singlet at 9.63δ in addition to the above mentioned resonances. The resonance at 6.3δ is at a position nominal for H_A of the hemihydrate structure; the resonance at 9.54δ increased in intensity with time and was attributed to the aldehyde proton of the free glyoxal.

Recently p-bromophenylglyoxal, m.p. 125-126.5°C. has been reported to have an N.M.R. spectrum (in dimethyl sulfoxide) consisting of a triplet contered at 5.79δ (area 1, J = 6 c.p.s.) and a doublet at 6.87δ (area 2.05, J = 6 c.p.s.). This and the elemental analysis is consistent with the hydrate structure, XVIIId (104).

It has been necessary to use polar solvents in order to attain concentrations of the compounds which are suitable for N.M.R. work. These solvents may promote dehydration of the compounds or set up an equilibrium between the hydrate, hemihydrate, and anhydrous forms. Formation of a small amount of p-bromophenylglyoxal when the hydrate was

dissolved in acetone supports this idea. This tends to decrease the utility of this method of determining the degree of hydration of glyoxals. Use of infrared analysis of the compounds may be more beneficial.

The hemihydrate structure (C-C-C) group was tentatively proposed for the hydrated phenylglyoxal obtained in these laboratories on the basis of the broad infrared absorption of the substance (in chloroform solution) between 9.0 and 9.2 microns. An intense, sharp absorption at 9.03 microns was found when the spectrum was obtained on a sample in a potassium bromide pellet. Examination of the infrared spectrum of p-methoxyphenylglyoxal (in potassium bromide) revealed that this compound also had an intense absorption at 9.03 microns.

The p-methyl derivative (m.p. 95-97°C.), for which the N.M.R. suggests the hemihydrate structure, also has the 9.03 micron absorption. This compound has been reported as the hydrate (128), m.p. 101-102°C. (with softening at 95°C.).

A sample of p-bromophenylglyoxal obtained by hydrolysis for IId had a melting point (107-109°C.) which did not correspond to that reported for the hydrate or the "hemihydrate" (m.p. 125-126.5°C. (104), and 127.5-130°C. (130), respectively). Recrystallization from acetone raised the

melting point to 122-124°C. A lack of an absorption from this sample (in potassium bromide) at 9.03 microns suggests that there is no C-O-C group present, and supports the hydrate structure proposed on the basis of the N.M.R. spectrum (104).

There is a obvious need for a systematic and thorough examination of the hydration phenomena of this class of compounds. The sensitive instrumental methods utilized in these preliminary studies seem to be, ideally suited for this purpose.

Oxidation and Oxidation-reduction Reactions on β-Keto Sulfoxides and Methyl Hemimercaptals of Arylglyoxals

The preparations discussed up to this point have involved the reactions of the β-keto sulfoxides, or the methyl hemimercaptals derived from them, with reducing agents. The arylglyoxal preparation is an exception in that the net result of the Pummerer rearrangement and precipitation of the mercaptan has resulted in oxidation of the methylene group of the β-keto sulfoxide to a carbonyl group, even though no oxidizing agents were used in the reactions.

Attempts to derive compounds from either I or II by reacting them with oxidizing agents have been markedly less fruitful than the reduction reactions. Some obvious oxidation products which could not be prepared are shown in

Figure 7.

Oxidation of the β-keto sulfoxide Ia to the sulfone with hydrogen peroxide in acetic acid could not be accomplished. The difficulty in this case was the ease with which Ia rearranges under acidic conditions. Since the sulfone can be obtained directly from ethyl benzoate by condensation with dimethyl sulfone (33), the reaction is of little synthetic value.

An attempted preparation of the α-hydroxy-β-keto sulfoxide XVa by bubbling oxygen through a solution of Ia in t-butyl alcohol-potassium t-butoxide for 8 hours was unsuccessful. Starting material was recovered in almost quantitative yield. Nitrobenzene failed to catalyze the oxidation. The possible formation of this compound by oxidation of IIa with nitrogen dioxide has already been discussed.

Conversion of Ia to phenylacetic acid or its t-butyl ester might be visualized as proceeding through the reaction sequence shown in path B, Figure 11. A related reaction, the photochemical conversion of the S-alkylated salt of Ia in methanol to methyl phenylacetate has been reported (147). In the reaction in basic solution, the anticipated α-elimination of the methane sulfenate anion to form a carbenoid intermediate, which could rearrange to the ketene intermediate 11b, did not occur. The reaction at 110-115°C.

$$\text{PhCOCH}_2\text{Y} + \text{E}^- \rightleftharpoons \text{PhCO}\overline{\text{C}}\text{HY} + \text{EH} \longrightarrow \text{PhCOCH:} + \text{Y}^-$$

<u>A</u>

<u>B</u>

$$\overset{\text{O}^-}{\underset{\overset{|}{\text{E}}}{\text{Ph-}\overset{|}{\text{C}}\text{-CH}_2\text{Y}}}$$

$$\text{PhCH=C=O}$$

11a

11b

$$\text{Ph-CO-B} + {}^-\text{CH}_2\text{Y}$$

E⁻

H⁺

$$\text{PhCH}_2\text{-CO-B}$$

11c

11d

$$\text{Y} = \text{SOCH}_3, \ \text{SO}_2\text{CH}_3 \qquad \text{E} = \text{HO}^-, \ \underline{\text{t}}\text{-BuO}^-$$
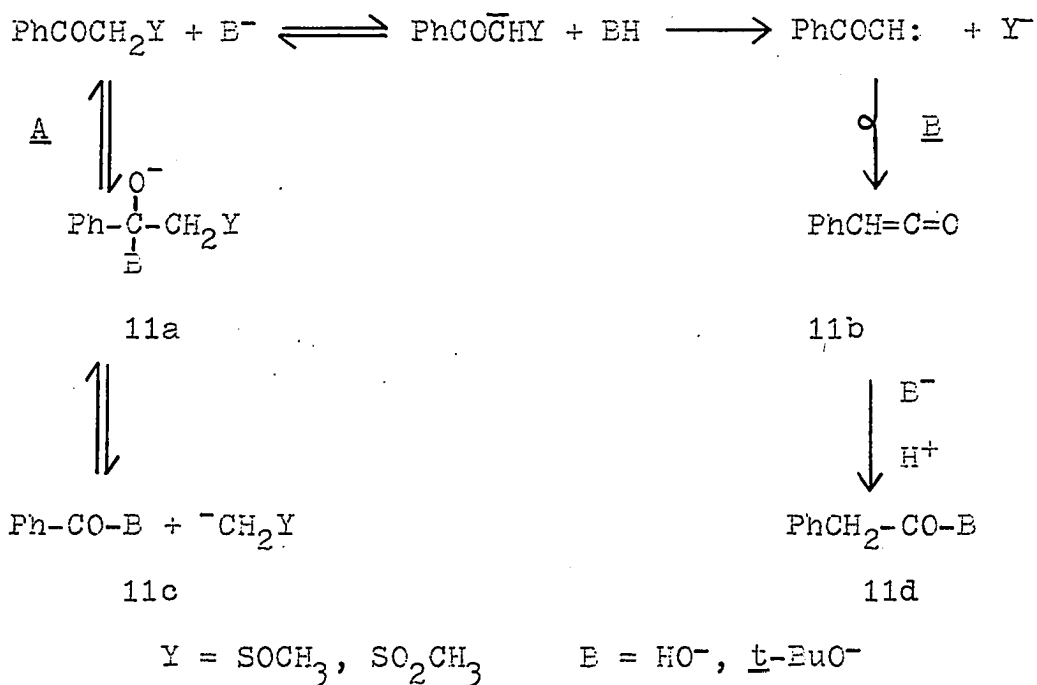
Figure 11. Reaction path for the proposed conversion of
ω-(methylsulfinyl)-acetophenone to phenylacetic
acid derivatives

of the sulfoxide and the sulfone with excess potassium <u>t</u>-
butoxide in <u>t</u>-butyl alcohol and <u>t</u>-butyl alcohol-dimethyl
sulfoxide respectively for one and four hours yielded
starting material as the only isolable organic product (82
and 93% respectively). Use of 50% aqueous potassium hy-
droxide with the sulfoxide and sulfone gave benzoic acid in
84% and 82% yield respectively, after 1.5 and 0.75 hours at
100°C.

Thus, the only reaction with hydroxide ion is by path
A. Potassium <u>t</u>-butoxide probably only ionizes the methyl-

ene group of Ia ($Y = SOCH_3$). If the reaction with potassium
$\underline{t}$-butoxide does occur by path A, the equilibrium would be
expected to lie predominantly on the side of starting
material. The reaction of the sulfone with potassium $\underline{t}$-
butoxide in the presence of dimethyl sulfoxide might be
expected to form some β-keto sulfoxide, since the base could
form dimsylpotassium. If this reacted by addition to the
carbonyl carbon, the intermediate 11a ($Y = SO_2CH_3$, B =
$CH_3SOCH_2^-$) should preferentially eliminate the weaker base,
the methylsulfonylcarbanion. However, 98% recovery of the
sulfone makes reaction by path A very unlikely in this case.
On the basis of these results, it has been concluded that
the intramolecular oxidation-reduction of ω-(methyl-
sulfinyl)-acetophenone does not occur in basic solution.

Intramolecular oxidation-reduction of the methyl hemi-
mercaptal of phenylglyoxal illustrated in Equation 42, has
been accomplished. When IIa was dissolved in aqueous sodium

$$PhCOCH(OH)SCH_3 + NaOH \longrightarrow PhCH(OH)CO_2H + NaSCH_3 \qquad (42)$$
$$\text{IIa} \qquad\qquad\qquad\qquad \text{XXIIIa}$$
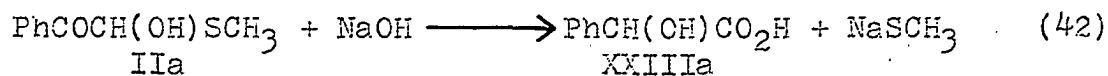
hydroxide and stirred at room temperature for 8 hours, a
small amount of acetophenone was obtained from the reaction
mixture. An acidic product, presumed to be mandelic acid,
was obtained, but the product was not identified. The re-
action was intended simply to cause methyl mercaptan to be
eliminated from IIa to produce phenylglyoxal. Formation of

the acid was not anticipated in the attempted crossed-Cannizzaro reaction of IIa with formaldehyde in basic solution, a reaction intended to produce α-hydroxyacetophenone. A small amount of XXIIa but no ketol was isolated from this reaction. Under the conditions of the reaction (3 hours at 40°C. and 5 hours at 65°C.) considerable tarry material was formed. This Benzilic Acid Rearrangement of phenylglyoxal was later found to result in a higher yield of more pure product if the mercaptan was first removed by precipitation with cupric acetate in absolute ethanol. After filtration, treatment of the alcohol solution with a three-fold excess of 7M aqueous sodium hydroxide at 65°C. for 6 hours yielded 85-90% of mandelic acid. Though the reaction had not been considered during the course of this work, use of sodium methoxide could result in the direct formation of the methyl ester of XXIIIa (143).

As in the case of the reduction of IIa to the ketol (Xa) and in the bimolecular reduction of IIa to XIIa, the desired reaction did occur with the hemimercaptal, but improved yields were attained by the simple expedient of removing the mercaptan from the solution of IIa prior to adding the reagents.

Since II contains a potential aldehyde group, it should undergo facile oxidation to a carboxylic acid group; a reaction which would result in the formation of arylglyoxalic

acids,, XX. The oxidation of IIa with potassium hypochlorite or hydrogen peroxide gave starting material as the only identifiable product, as did sodium metaperiodate at 0°C. in neutral solution. At room temperature, the latter reagent effected oxidation and decarboxylation; benzoic acid was the only product isolated. Tollen's reagent did not yield any identifiable organic material. Potassium permanganate yielded only benzoic acid, although phenylglyoxalic acid can be prepared by permanganate oxidation of acetophenone (148).

Oxidation of the -CH-OH group of II would produce the thiol ester of arylglyoxalic acids, XXI. Reaction of IIa and IIb with manganese dioxide yielded only starting material and some mercaptal (from IIa, a compound later found to be an artifact of the purification of the hemimercaptal).

Though direct oxidations appear to be of no practical value, the phenylglyoxalate moiety can be generated as the acid, thiomethyl ester, or alkyl ester by decomposing the α-bromo-β-keto sulfoxide, IVa, under controlled conditions. The reactions are illustrated in Figure 12.

Decomposition of the solid (IVa) occurs when it stands at room temperature for about two days. If the reaction mixture is worked up after about a day, phenylglyoxalic acid can be obtained in low yield (15-30%). Since hydrogen bromide is evolved in the reaction, the glyoxalic acid is

readily converted to benzoic acid under the strongly acidic conditions. The major product of the decomposition was a brown liquid containing halogen and sulfur. Distillation gave a clear yellow liquid which redecomposed after several days. No attempt was made to identify this substance.

If compound IVa is dissolved in methanol or ethanol with a small amount of acid, rapid decomposition of the bromo ketone yields methyl or ethyl phenylglyoxalate as the major product. A small amount of an ether, presumably the solvolysis product of the bromo ketone, is also obtained. The presence of an alkoxide group at the α-carbon retards the Pummerer rearrangement in the pyrimidothiazine system, discussed previously (74). The ether, if indeed it is formed, could yield the glyoxalate ester by the same type of rearrangement, but the reaction may be quite slow. However, even when the reaction was carried out in refluxing methanol and dimethyl sulfoxide under acidic conditions for 3 days, the ether was not eliminated from the product mixture. Either more vigorous conditions are needed to effect the rearrangement of this compound, or the compound is not the α-methoxy sulfoxide.

Finally, when the decomposition is carried out in acidic, aqueous dimethyl sulfoxide, the thio ester XXIa can be obtained in 50-55% yield as a yellow crystalline solid, m.p. 39-40°C. No identifiable products could be obtained

by treatment of the bromo ketone with dimethyl sulfoxide and sodium carbonate. This oxidation should occur readily, since the reaction is favored by electron withdrawing groups attached to the halogen bearing carbon (95, 88). The mechanism for this oxidation has already been presented (Figure 6, p. 37). By analogy with the reactions leading to α-keto aldehydes and α-diketones, the mechanism for the conversion of IVa to the phenylglyoxalate derivatives is visualized as proceeding by an initial Pummerer rearrangement and spontaneous decomposition of this product, as illustrated in Figure 12.

Numerous other possibilities exist for the conversion of the α-bromo ketone to the thioester: intermolecular oxidation of the carbon atom of one molecule by the sulfoxide group of another, and intramolecular oxidation of the carbon by the adjacent sulfoxide function are interesting possibilities. The apparent acid catalysis and the stability of the α-bromo ketone in dilute chloroform solution argue against the intramolecular oxidation. Similarly, the intermolecular oxidation should not show acid catalysis. In actual fact, a number of paths or combinations of paths could give the observed products. Regardless of the mechanism, the sulfoxide function would be reduced by the action of hydrogen bromide, and thus, the

Figure 12. Formation of α-dicarbonyl compounds using the
          Pummerer Reaction on β-keto sulfoxides

$$
\underset{\underset{Z}{|}}{\overset{\overset{O}{||}\ \overset{H}{|}\ \overset{O}{|}}{Ph\overset{}{C}-\overset{}{C}-\overset{\uparrow}{S}CH_3}} \quad \xrightarrow{H^+} \quad \underset{\underset{Z}{|}}{\overset{\overset{O}{||}\ \ \overset{OH}{|}}{Ph\overset{}{C}-\overset{}{C}-SCH_3}}
$$

$\underline{Z = H:}$
$$
\underset{\underset{H}{|}}{\overset{\overset{O}{||}\ \ \overset{O-H}{|}}{Ph\overset{}{C}-\overset{}{C}-SCH_3}} \quad \longrightarrow \quad \overset{\overset{O}{||}\ \overset{O}{||}}{Ph\overset{}{C}-\overset{}{C}-H} \quad + \quad CH_3SH
$$

$\underline{Z = CH_3:}$
$$
\underset{\underset{CH_3}{|}}{\overset{\overset{O}{||}\ \ \overset{O-H}{|}}{Ph\overset{}{C}-\overset{}{C}-SCH_3}} \quad \longrightarrow \quad \overset{\overset{O}{||}\ \overset{O}{||}}{Ph\overset{}{C}-\overset{}{C}-CH_3} \quad + \quad CH_3SH
$$

$\underline{Z = Br:}$

$$
\overset{\overset{O}{||}\ \overset{O}{||}}{Ph\overset{}{C}-\overset{}{C}-Br} \quad \xleftarrow{\ -CH_3SH\ } \quad \underset{\underset{Br}{|}}{\overset{\overset{O}{||}\ \ \overset{OH}{|}}{Ph\overset{}{C}-\overset{}{C}-SCH_3}} \quad \xrightarrow{\ -HBr\ } \quad \overset{\overset{O}{||}\ \overset{O}{||}}{Ph\overset{}{C}-\overset{}{C}-SCH_3}
$$

$$
\downarrow \qquad\qquad\qquad \searrow \ \ CH_3OH \qquad\qquad CH_3OH \ \swarrow \qquad \uparrow \ -CH_3OH
$$

$$
\overset{\overset{O}{||}\ \overset{O}{||}}{Ph\overset{}{C}-\overset{}{C}-OH} \qquad\qquad \overset{\overset{O}{||}\ \overset{O}{||}}{Ph\overset{}{C}-\overset{}{C}-OCH_3} \qquad H^+
$$

$\underline{or:}$

$$
\underset{\underset{Br}{|}}{\overset{\overset{O}{||}\ \overset{H}{|}\ \overset{O}{|}}{Ph\overset{}{C}-\overset{}{C}-\overset{\uparrow}{S}CH_3}} \quad \longrightarrow \quad \underset{\underset{OCH_3}{|}}{\overset{\overset{O}{||}\ \overset{H}{|}\ \overset{O}{|}}{Ph\overset{}{C}-\overset{}{C}-\overset{\uparrow}{S}CH_3}} \quad \xrightarrow[H^+]{\ -CH_3SH\ } \quad \underset{\underset{OCH_3}{|}}{\overset{\overset{O}{||}\ \ \overset{O-H}{|}}{Ph\overset{}{C}-\overset{}{C}-SCH_3}}
$$
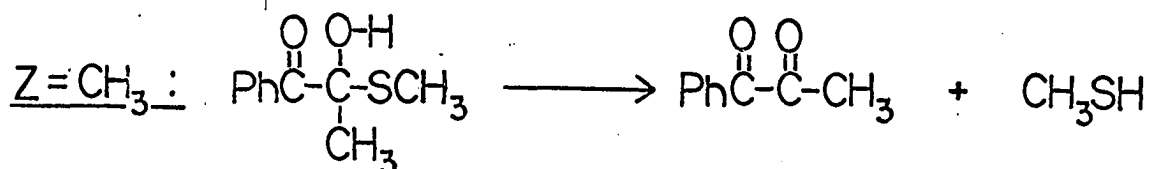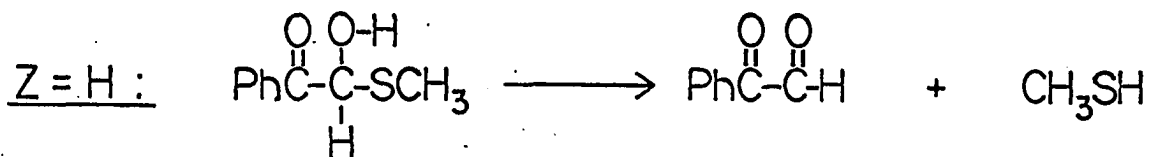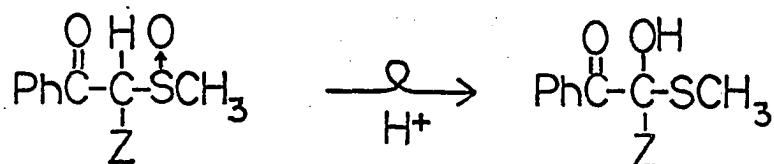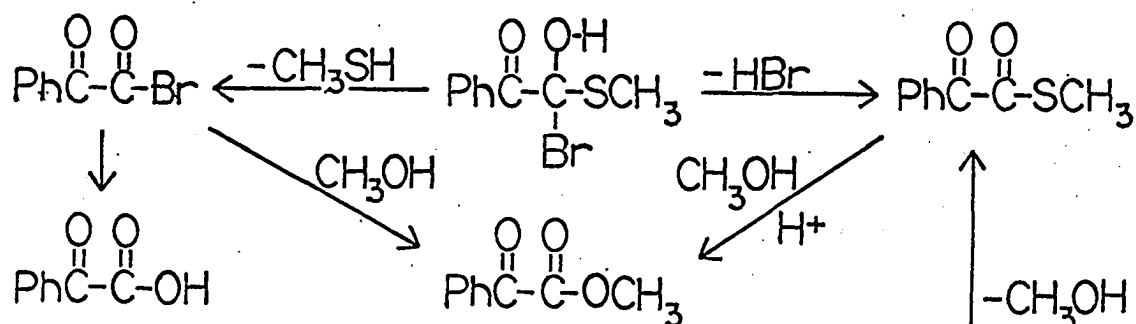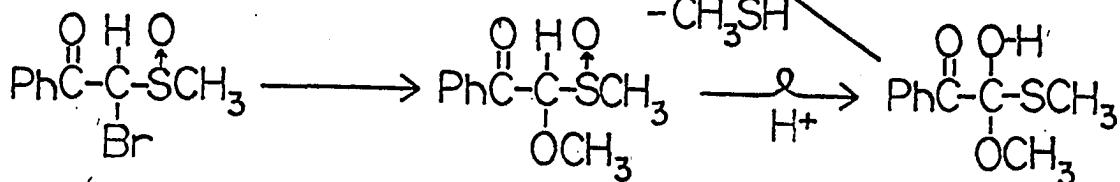
isolation of a sulfide does not implicate the sulfoxide function as the oxidizing agent.

One interesting aspect of this thiol ester was its infrared spectrum. The intense peak at 9.35 microns suggested a sulfoxide group; the slightly broad absorption at 5.95-6.02 microns suggested the presence of only one carbonyl group.

Alkyl benzoates exhibit an infrared absorption near 5.8 microns whereas the corresponding thiol esters absorb around 6.0 microns. Since the carboxyl of methyl phenylglyoxalate absorbs at 5.75 microns, a similar shift in the thiol ester would place this absorption under the ketone carbonyl at 5.96 microns.

On the assumption that a dicarbonyl compound was obtained, it was formulated as containing an -SCH$_3$ rather than an -SOCH$_3$ on the following basis: (1) the "sulfoxide" infrared absorption did not exhibit the usual 0.2-0.3 micron shift to a longer wavelength when the solvent was changed from carbon tetrachloride to chloroform, (2) the -CH$_3$ resonance in the N.M.R. appeared at 2.37δ, a position intermediate between that for an -SCH$_3$ (~2.0δ) and an -SOCH$_3$ (~2.7δ), and consistent with a 0.2-0.4δ downfield shift when an -OCH$_3$ or ⊃NCH$_3$ is bonded to a carbonyl carbon rather than a saturated carbon atom.

After eventual purification, the elemental analysis established the efficacy, if not the validity, of this approach.

SUMMARY

The condensation of aromatic esters with dimethyl sulfoxide has been shown to be a general reaction. Optimum conditions have been established for the conversion of aromatic esters to β-keto sulfoxides of the type $ArCOCH_2SCCH_3$, I, with Ar = (a) C_6H_5, (b) $p-CH_3C_6H_4$, (c) $p-CH_3OC_6H_4$, (d) $p-BrC_6H_4$, (e) $\alpha-C_{10}H_7$, and (f) $\beta-C_{10}H_7$.

The chemistry of these compounds parallels the known reactions of sulfoxides, which have been reviewed. The chemistry of the methyl hemimercaptals derived from the β-keto sulfoxides has been explored with regard to synthetic applicability.

All of the β-keto sulfoxides readily undergo the Pummerer rearrangement in aqueous, acidic dimethyl sulfoxide at room temperature. Under these mild conditions the methyl hemimercaptals of arylglyoxals, $ArCOCH(OH)SCH_3$, II, precipitate and can be isolated in yields in excess of 80%; IIa and IIb were prepared in 94-96% yield.

Numerous reactions have been described illustrating the chemistry and synthetic utility of the β-keto sulfoxides and the hemimercaptals. Reaction of β-(methylsulfinyl)-acetophenone, Ia, with aluminium amalgam produces 2,3-diphenyl-2,3-butanediol. This same β-keto sulfoxide was reduced to the corresponding β-hydroxy sulfide with lithium

aluminium hydride. Reduction of the β-keto sulfoxide with
zinc dust in ethanolic acetic acid has been developed as a
method for preparing aryl methyl ketones. Phenylglyoxal
has been prepared from Ia by hydrolysis in aqueous acid
solution.

An attempt to extend the utility of these last two re-
actions to the preparation of aryl alkyl ketones and α-
diketones has met with only limited success, due largely to
difficulty in alkylating Ia with groups other than a methyl
group. While the reduction of the alkylated derivatives
was efficient, the efficacy of the hydrolysis reaction
leading to the formation of α-diketones was reduced by the
occurrence of acid catalyzed dehydration and condensation
reactions.

Reactions with the methyl hemimercaptals have been
more productive. Reduction of these compounds with sodium
borohydride (or lithium aluminium hydride) produces aryl-
ethylene glycols. The method is presented as being a
marked improvement over existing methods. Hydrolysis of
the hemimercaptals in aqueous acid produces the arylglyoxal
hydrates, but mercaptal formation and acid catalyzed re-
arrangements, resulting in decreased yields of the glyoxal
hydrates, have been shown to occur. However, precipitation
of methyl mercaptan from the methyl hemimercaptals with
cupric or mercuric salts in non-aqueous media does provide

an efficient and convenient method for the preparation of arylglyoxals. In a typical experiment, ethyl benzoate was converted to phenylglyoxal in an over-all yield of 68%.

Desulfurization of IIa with zinc dust in acetic acid produced α-hydroxyacetophenone; the same product was obtained by reaction of IIa with sodium formaldehyde-sulfoxylate (SFS) in aqueous ethanol. The reaction of IIa with SFS in the presence of cupric ion produced a mixture of α-hydroxyacetophenone and its dimer, $(C_6H_5COCH(OH)-)_2$. The p-tolyl derivative of this latter compound was obtained by Raney nickel desulfurization of the corresponding methyl hemimercaptal. Finally, the reaction of IIa with concentrated aqueous base produces mandelic acid.

These reactions can be visualized as proceeding through the intermediate formation of the glyoxal in solution. In fact, improved yields of the ketol, the dimer, and mandelic acid were realized by the simple expedient of precipitating methane thiol from a solution of IIa, removing the cupric mercaptide by filtration, and then adding the other reactants to the crude phenylglyoxal.

Reactions utilizing this procedure appeared to be strongly pH dependent. The effect of the basicity of the medium was accounted for on the basis of its effect on three reactions: (1) on the dimerization of the phenyl-glyoxal radical anion, formed by reduction of Cu(+II) to

Cu(+I) by SFS and subsequent electron transfer by Cu(+I) to

phenylglyoxal, (2) on the crossed-Cannizzaro reaction of

phenylglyoxal with formaldehyde or its equivalent, formed

from SFS in the basic solution and, (3) on the Benzilic

Acid Rearrangement of phenylglyoxal.

A limited number of attempts to oxidize the α-keto

sulfoxides have been unsuccessful. Conversion of Ia to

phenylglyoxal represents an oxidation of the methylene

group of the original molecule, but this was not effected

by a direct oxidation reaction.

Oxidation of Ia with oxygen in $\underline{t}$-butyl alcohol-

potassium $\underline{t}$-butoxide failed to produce the hypothetical

compound, $C_6H_5COCH(OH)\overset{O}{S}CH_3$. The stable enolate anion formed

in basic solution could not be oxidized in the presence of

nitrobenzene. The possible formation of this β-hydroxy

sulfoxide as a transient intermediate in the oxidation of

IIa with nitrogen dioxide could not be ruled out on the

basis of the products isolated.

Oxidations of IIa with common oxidizing agents, in-

tended to effect specific oxidation of the hemimercaptal

to a carboxylic acid or to oxidize the -CH-OH group to a

carbonyl group, have resulted in either oxidative cleavage

to benzoic acid or the recovery of starting material. How-

ever, the hoped-for phenylglyoxalic acid derivatives have

been obtained indirectly. Mono-bromination of the methylene

of Ia yielded phenylglyoxalic acid and benzoic acid (in variable yields) by a spontaneous decomposition after a few days at room temperature. The methane thiol ester, or the alkyl ester of phenylglyoxalic acid were obtained by decomposition of the solid in aqueous acidic dimethyl sulfoxide or alcohol. The formation of these compounds was explained in terms of an initial Pummerer rearrangement though several other possibilities, including oxidation by dimethyl sulfoxide or the sulfoxide function within the molecule, do exist.

SUGGESTIONS FOR FURTHER WORK

Further investigation of the alkylation reaction would appear to be of value since this would enhance the utility of the reactions which have been developed to date. The course of the Pummerer rearrangement on these compounds is somewhat obscure and might profitably be studied.

Since considerable effort was directed toward obtaining optimum conditions for many of the reactions, mechanistic aspects of many of the reactions had to be ignored. Qualitative information regarding mechanisms could often be obtained simply from observations made during the course of the reaction or during work-up. The competition between the formation of α-hydroxyacetophenone and the bimolecular reduction product, with variation in the pH of the medium, seems interesting at this stage of development.

The mechanism, proposed on the basis of rather meager evidence, for the reaction of phenylmagnesium bromide with ω-(methylsulfinyl)-acetophenone is of interest because of the parallel to the Pummerer rearrangement. Thus far, the rearrangement has been reported to occur only in acid solution.

A detailed study of the Pummerer rearrangement within this β-keto sulfoxide system could substantiate some of the more subtle aspects of the mechanism. The facile rearrange-

ment of the phenyl derivative stands in marked contrast to the p-methoxyphenyl compound in that the latter does not rearrange readily under the same conditions as the phenyl substituted compound. The p-methyl derivative appears to occupy an intermediate position.

These effects, if real, would have bearing on a mechanism involving proton removal from the methylene group of the protonated sulfoxide, or enolization and intramolecular proton transfer to the sulfoxide oxygen. A comparison of the rate of exchange of the methylene protons in acid media and the rate of the rearrangement should be instructive in this respect. This could be done with N.M.R. since the disappearance of the methylene or $-SOC\underline{H}_3$ and the appearance of the $-OH$ and $-SCH_3$ could be observed.

The intramolecular proton transfer mechanism could account for the slow decomposition of purified samples of the β-keto sulfoxide.

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