CLEAVAGE OF THE CARBON–SULFUR BOND IN DIVALENT SULFUR COMPOUNDS

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I. Introduction

In order to compare the behavior of carbon–sulfur and carbon–oxygen bonds, and to correlate the effect of changes in structure with the ease of cleavage of carbon–sulfur bonds, a literature survey was made of reactions in which a carbon–sulfur bond is broken. The information is scattered and incomplete, and clearly indicates the need for further fundamental work on sulfur chemistry.

The general field of organic sulfur compounds has been reviewed by Connor (101a) and the tetracovalent compounds of sulfur have been comprehensively treated by Suter (402a).

The present review covers only compounds containing divalent sulfur, and does not attempt to list each case in the literature in which carbon–sulfur bonds have been broken. Only those examples which seem of significance from the theoretical or practical side will be discussed; it is hoped that, in spite of the difficulty in surveying a topic of this type, not too many significant observations have been missed. The interesting topic of biological methylation and transmethylation of sulfur compounds will not be considered (93). Since the highly useful procedure of Raney nickel desulfuration has been well reviewed recently (9), it will not be covered in detail in the present article. No attempt has been made to discuss exhaustively the cleavage of the carbon–sulfur bond in all types of heterocyclic compounds, but it will be found that most of the types of structure which would be present in the heterocyclic systems have been covered.

Some of the general properties of oxygen and sulfur are of importance in contrasting the behavior of carbon–oxygen and carbon–sulfur bonds. Oxygen is more electronegative than sulfur, the values given by Pauling (299) being O = 3.5 and S = 2.5. This is probably the reason that, in contrast to hydroxy compounds, thiophenols and mercaptans show no tendency to associate with themselves by hydrogen bond formation, and the $R—\overset{H}{\underset{|}{S}} \rightarrow HSR$ grouping appears to be very unstable (177). The —SH compounds show only a slight tendency, compared to —OH compounds, to form hydrogen bonds with other types of donor molecules (8, 104, 177). The sulfur atom in sulfides appears to have little, if any, ability to act as a donor in hydrogen bond formation. This lack of intermolecular association in the sulfur compounds is probably one reason why the thiophenols are about 10^4 times as acidic as the oxygen phenols (373), and that the mercaptans are more acidic than alcohols (177).

The sulfur atom in sulfides acts as a donor reagent in numerous reactions to

$$R_2S + RCH_2X \rightarrow \left[R—\overset{R}{\underset{CH_2R}{S}}: \right]^+ X^-$$

form stable ionic compounds (sulfonium salts), and also to form coördination compounds with heavy metal salts such as $(R_2S)_2PtCl_2$.

The oxygen ethers do not undergo the above addition reaction with organic halides; they do form oxonium salts with cations in certain reactions wherein a very stable anion is simultaneously formed (278), such as the following:

$$(CH_3)_2O + CH_3F + BF_3 \rightarrow [(CH_3)_3O]^+(BF_4)^-$$

Ethers do form coördination compounds, such as those involved in Grignard reagents, but these are readily dissociated. However, the boron trifluoride etherates, $R_2\overset{+}{O}\overset{-}{B}F_3$, are more stable than those from alkyl sulfides. These differences between oxygen and sulfur are probably related to the lower electronegativity and larger atomic size of sulfur.

The great nucleophilic activity of sulfur compared to oxygen is illustrated by the observation (190) that the thiophenoxide ion reacts with sodium bromoacetate a thousand times more rapidly than the hydroxyl ion does, although of course hydroxyl ion is a stronger base (to a proton) than is thiophenoxide ion.

In contrast to oxygen, sulfur can exist in several oxidation states, and can form fairly stable chains of two or more atoms, connecting organic groups. The reversible reaction,

$$2RSH \underset{[H]}{\overset{[O]}{\rightleftharpoons}} RSSR$$

which is of great importance in sulfhydryl chemistry, has no exact counterpart in the analogous oxygen compounds, since dialkyl peroxides and alcohols are not directly and readily interconvertible in a similar oxidation–reduction system.

It has been suggested that sulfur compounds can have contributions from resonance forms in which the sulfur has expanded its valence shell to ten electrons. Various isomerization reactions of sulfur compounds (268, 325), the acidity of some sulfur derivatives (130), and studies on the absorption spectra of various sulfur compounds (20, 142) have been interpreted on this basis.

However, in view of the fact that certain properly substituted sulfonium salts, sulfoxides, and sulfinic esters have been obtained as optically active enantiomorphs, it is evident that this concept must await further clarification.

The status of certain sulfur bonds and possible resonance structures have been discussed by Phillips, Hunter, and Sutton (301a) and by Wells (429a).

II. Sulfhydryl Compounds

A. Saturated Aliphatic Mercaptans

Information about the behavior of aliphatic mercaptans on heating without a catalyst is scanty; it is reported (327) that aliphatic mercaptans undergo reactions II-1 and II-2 when heated with cadmium sulfide. However, cyclohexyl

$$2RSH \xrightarrow[300°C.]{CdS} R_2S + H_2S \qquad \text{(II-1)}$$

$$C_nH_{2n+1}SH \xrightarrow[400°C.]{CdS} C_nH_{2n} + H_2S \qquad \text{(II-2)}$$

mercaptan gives only 12–15 per cent of dicyclohexyl sulfide at 300°C., the remainder of the product being cyclohexene. At higher temperatures, reaction II-2 is the sole process; cyclohexyl mercaptan shows a much greater preference for formation of the unsaturated product than do the open-chain mercaptans. It is suggested that the above reactions go through the intermediate formation of the cadmium mercaptide (327). Cyclohexanol is dehydrated more readily than aliphatic secondary alcohols, a fact which parallels this behavior of the mercaptans.

A more extended study (47) of the action of aqueous alkali on aliphatic mercaptans showed that at 260°C. reactions II-1 and II-2 take place and, in addition, a hydrolysis reaction to the alcohol (II-3). The rate of decomposition of the

TABLE 1

Mercaptans and 3 N sodium hydroxide, 2 hr. at 260°C.

MERCAPTAN	DECOMPOSED	R_2S	MERCAPTAN	DECOMPOSED	R_2S
	per cent	*per cent*		*per cent*	*per cent*
Ethyl	55.4	20	*sec*-Butyl	59.1	4
n-Butyl	49.6	16	*n*-Amyl	42.9	9.9
Isobutyl	36.2	16	*sec*-Amyl	56.0	6.3
Isopropyl	65.4	8			

mercaptan is somewhat greater with secondary mercaptans than with primary ones, but the proportion of sulfide (II-1) is less; unfortunately, there are no

$$C_nH_{2n+1}SH + 2NaOH \rightarrow C_nH_{2n+1}OH + Na_2S + H_2O \qquad \text{(II-3)}$$

data for tertiary mercaptans, which would be expected to give still less of the sulfide and more of the olefin. An increase in the concentration of the alkali decreases the proportion of organic sulfide formed, and favors reactions II-2 and II-3. Table 1 gives an idea of the data obtained.

It will be seen that the data, as far as they go, show the same features as the ordinary nucleophilic substitutions (primary compounds being slower than secondary, and olefin formation being greater with secondary compounds), such as the action of alkali on alkyl halides (215). The reasons that the mercaptans require such drastic treatment with alkali, compared to alkyl halides, are probably (*1*) the hydrogen sulfide liberated is a very much weaker acid than a halogen acid, and (*2*) the mercaptan exists in strong alkali as $RS^{\ominus}$, and hence the attack on this ion by a second negative ion (OH^-) is necessarily very slow.

Aluminum chloride is reported (442) to liberate hydrogen sulfide from isoamyl mercaptan in naphtha at about 200°C., the products not being identified.

A more interesting reaction involving aluminum chloride is the alkylation of aromatic compounds by *tert*-butyl mercaptan and acid catalysts (276).

$$(CH_3)_3CSH + C_6H_6 \xrightarrow[HCl]{AlCl_3} (CH_3)_3CC_6H_5 + H_2S \qquad \text{(II-4)}$$

(88 per cent yield)

tert-Butylbenzene in turn can be alkylated to yield *p*-di-*tert*-butylbenzene (74 per cent yield); other catalysts (such as boron fluoride) and other aromatic compounds can be used. Benzyl mercaptan likewise alkylates benzene in the presence of aluminum chloride, yielding diphenylmethane (256). It is noteworthy that primary and secondary mercaptans do not react under these conditions (256, 276). Since the reaction is undoubtedly to be interpreted as an electrophilic attack of the complex $(CH_3)_3CSH \cdot AlCl_3$ or of the carbonium ion $(CH_3)_3C^+$ on the aromatic nucleus, and since similar alkylation reactions *can* be carried out with primary and secondary alcohols in the presence of aluminum chloride (307), it can be concluded that the carbon–sulfur bond in primary and secondary mercaptans is not as readily cleaved in an alkylation process as the carbon–oxygen bond in alcohols.

The action of nitrosyl chloride on tertiary mercaptans leads to thionitrites

$$(CH_3)_3CSH + NOCl \rightarrow (CH_3)_3CSNO + HCl \qquad \text{(II-5)}$$

(318), which appear to break down fairly readily to form a sulfur-free product.

The action of heavy metal salts on mercaptans leads to mercaptides, $(RS)_2M$, which on heating may form R_2S and MS (236, 294); some mercaptides decompose to yield the metal and the disulfide $(RS)_2$ (294). The behavior of mercury *tert*-butyl mercaptide (equation II-6) illustrates the tendency of the bond between a tertiary carbon and sulfur to break, with the formation of an olefin (319).

$$((CH_3)_3CS)_2Hg \xrightarrow{190°C.} (CH_3)_3CSH + HgS + CH_2{=}C(CH_3)_2 \qquad \text{(II-6)}$$

The same mercaptide gives with benzyl chloride at 160°C., dibenzyl sulfide and not benzyl *tert*-butyl sulfide. Treatment of $C_6H_5CH(CH_3)SH$ with mercuric chloride yields a mixture of products, including the corresponding alcohol, the ether, the sulfide, the chloride, and styrene; apparently all are formed from the mercaptide (207).

Recent infrared studies (378) show that the carbon–sulfur bond-stretching frequency for R—SH is lower when R is *tert*-butyl, allyl, or benzyl than it is when R is a saturated alkyl group. The carbon–chlorine frequency in R—Cl shows a similar trend, and the observations are interpreted as meaning that the force constant for the carbon–sulfur bond is smaller for the tertiary, allyl, and benzyl compounds than for the saturated compounds. This means that the bond is "weaker" (more easily stretched), and it correlates well with the increased reactivity of the compounds described here, as well as with the ultraviolet spectroscopic data (241).

As might be expected from the similarity between benzyl and *tert*-butyl mercaptans in alkylating benzene (*cf.* page 4), the substitution of α-hydrogens by aryl groups in a mercaptan increases the ease of cleavage of the carbon–sulfur bond, just as with the corresponding carbinols. The ease of replacement of the —SH group thus runs parallel with the stability of the corresponding carbonium

ion. Trityl mercaptan is very readily converted to triphenylcarbinol or to trityl chloride by a variety of reagents (425), such as mineral acid, acetic anhydride,

$$(C_6H_5)_3CSH \longrightarrow (C_6H_5)_3CX \qquad \text{(II-7)}$$

Trityl mercaptan

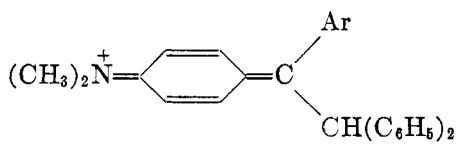
X = OH or Cl.

acetic acid, alcoholic silver nitrate, mercuric salts, or chlorine; reduction with sodium and alcohol yields triphenylmethane (425).

Another example which illustrates the same point is the loss of hydrogen sulfide from benzhydryldiarylmethyl mercaptans (43); in this case, the driving force

$$Ar_2\underset{\displaystyle SH}{\underset{|}{C}}CH(C_6H_5)_2 \longrightarrow Ar_2C{=}C(C_6H_5)_2 + H_2S \qquad \text{(II-8)}$$

for the reaction is the increase in resonance stabilization due to the conjugation in the product. The effect of changes in the aryl groups on the rate of the reaction agrees with the idea that the reaction is favored by increasing stabilization of the carbonium ion: thus for Ar = C_6H_5, refluxing with acetyl chloride is necessary to eliminate hydrogen sulfide. For Ar = p-$CH_3OC_6H_4$, heating on the water bath is sufficient, and for Ar = p-$(CH_3)_2NC_6H_4$, the thiol cannot be isolated. The carbonium ion is obviously stabilized by resonance forms such as:



B. UNSATURATED ALIPHATIC MERCAPTANS

The ease of cleavage of the carbon–sulfur bond in mercaptans, as well as in other types of sulfur compounds, is profoundly affected by the presence and position of unsaturation in the molecule. An unsaturated group Y on the γ-carbon to a carbon–sulfur bond does not seem to have much effect on the ease of cleavage; however, one of the most useful and widely applicable generalizations in the whole field of sulfur chemistry concerns the very rapid rate of cleavage of a carbon–sulfur bond when an unsaturated group is attached to the β-carbon. If B^- is a base, RS is HS, RS, or either of these with sulfur in a higher oxidation state, and Y is an unsaturated group (carbonyl, carboxyl, nitrile, etc.), the process may be represented as follows:

$$RS\underset{\displaystyle H}{\underset{|}{\overset{|}{C}}}-\underset{|}{\overset{|}{C}}-Y + B^- \rightleftharpoons RS-\underset{|}{\overset{|}{C}}-\underset{\displaystyle H\ B^-}{\underset{|}{\overset{|}{C}}}\rightarrow Y \rightleftharpoons RS^- + \underset{|}{\overset{|}{C}}{=}\underset{|}{\overset{|}{C}}-Y + BH \qquad \text{(II-9)}$$

This scheme is, of course, a specific example of the E-2 (bimolecular elimination) mechanism of Hughes and Ingold (216). The process represented by equation

II-9 is evidently dependent on a number of factors: the acidity of the proton on the carbon next to Y, the anionic stability of RS^-, the resonance stabilization of the structure $-\overset{|}{C}=\overset{|}{C}-Y$ due to the conjugation with Y, and the strength of the base B^-, among others. The structures $-\overset{|}{C}=\overset{|}{C}-Y$ and $R-S^-$ may undergo further irreversible reactions.

This process is considered at this time because it serves to correlate fairly satisfactorily the observations on the loss of hydrogen sulfide from cysteine and its derivatives, which have been extensively studied because of the biochemical importance of cysteine (e.g., 97, 161). The reaction with cysteine probably takes the following course:

$$\underset{\text{Cysteine}}{HSCH_2CH(NH_2)COOH} \xrightarrow{-H_2S} \left[CH_2{=}C(NH_2)COOH\right] \xrightarrow{H_2O} \underset{\text{Pyruvic acid}}{CH_3COCOOH} \qquad \text{(II-10)}$$

The formation of pyruvic acid as the end product is proved by its isolation as the *p*-carboxyphenylhydrazone (97). In the elimination of hydrogen sulfide from cysteine by alkaline plumbite solution, it is found (161) that acylation of the amino group accelerates the process; this may well be due to the resulting increase in acidity of the α-hydrogen atom which is attacked by the base. The *N*-sulfonyl derivative $HSCH_2CH(NHSO_2R)COOH$, however, loses hydrogen sulfide much more slowly; this must be due to the fact that the base forms the ion $HSCH_2CH(\bar{N}SO_2R)COO^-$, which, since it has negative charges, is not as readily attacked by a second molecule of base with the removal of the α-hydrogen. Hence the reaction goes slowly. This view is supported by the fact that the *N*-methyl-*N*-sulfonyl derivative, which has no acidic hydrogen on nitrogen, loses hydrogen sulfide very readily (161). The observation that hydrogen sulfide is more easily removed from cysteine peptides such as glutathione (212) than from cysteine itself is easy to understand, because in the peptides, the carboxyl group is covered up and cannot form a negative ion with base; hence the attack of the base on the α-hydrogen is not impeded. Observations on other cystine–cysteine derivatives are discussed later (*cf.* page 11).

In view of the mechanism discussed (equation II-9) it is not surprising that homocysteine shows almost no loss of hydrogen sulfide under the same conditions (161).

Penicillamine, which has a thiol group on a tertiary carbon as well as a carboxyl group on the α-carbon, apparently loses hydrogen sulfide on attempted acylation (102, 107).

$$\underset{\text{Penicillamine}}{(CH_3)_2C(SH)CH(NH_2)COOH} \longrightarrow (CH_3)_2C{=}C(NHCOR)COOH + H_2S \qquad \text{(II-11)}$$

There seems to be little information about the behavior of thiol compounds with an unsaturated group attached to the carbon carrying the sulfur. One would expect that allyl mercaptan would resemble *tert*-butyl mercaptan in its reactions, but experiments to support this idea are lacking. It appears that some thiols with an α-carbonyl group lose hydrogen sulfide rather easily (180, 220); thus, thiolbenzoin on standing in concentrated sulfuric acid overnight yields desoxybenzoin (220).

C. ARYL THIOLS

Aryl thiols seem in general to show little tendency for carbon–sulfur cleavage. Leuckart (258) reports that 1-thionaphthol on distillation at 285°C. yields dinaphthyl sulfide and hydrogen sulfide. A similar reaction has been observed with thiophenols in the presence of aluminum chloride (118).

$$C_6H_5SH \xrightarrow[\text{ligroin}]{AlCl_3} (C_6H_5)_2S + H_2S + \text{Thianthrene} \qquad \text{(II-12)}$$

Thiophenol

Thianthrene is a by-product in this reaction, but the mechanism of its formation is obscure.

o- and *p*-Thiocresols react according to equation II-12 to form the corresponding sulfides, but *m*-thiocresol does not react. Neither of these compounds gives a methylated thianthrene (119).

4-Mercaptobiphenyl is rapidly converted by aluminum bromide in chlorobenzene solution at room temperature to biphenyl and hydrogen sulfide; several other thiophenols readily lose hydrogen sulfide under these conditions, but thiophenol itself is not attacked (407).

III. Disulfides

A. ALKYL AND ARALKYL DISULFIDES

The most important reaction of the disulfides is reduction to the corresponding thiol, but some of their reactions involve carbon–sulfur bond cleavages. Dialkyl disulfides (RSSR) are decomposed at 496°C. to yield hydrogen sulfide, the mercaptan (RSH), some of the sulfide (R_2S), and, in some cases, thiophene derivatives (138).

Diaryl disulfides are reported (178, 191) to react on heating at 280°C. as follows, although the evidence for the trisulfide formation is not complete. Alumi-

$$2(ArS)_2 \rightarrow Ar_2S + Ar_2S_3 \qquad \text{(III-1)}$$

num chloride reacts with diphenyl disulfide to form (presumably) diphenyl sulfide and hydrogen sulfide (51).

$$(C_6H_5S)_2 \xrightarrow[C_6H_6]{AlCl_3} (C_6H_5)_2S + H_2S \qquad \text{(III-2)}$$

The following reaction with diphenyl sulfone occurs at 300°C. (246).

$$(C_6H_5S)_2 + (C_6H_5)_2SO_2 \xrightarrow{300°C.} 2(C_6H_5)_2S + SO_2 \qquad \text{(III-3)}$$

More interesting, however, are the reactions of dibenzyl disulfide and its derivatives. A careful investigation (158) of the decomposition at 270°C. showed that the primary process is as follows,

$$(C_6H_5CH_2S)_2 \xrightarrow{270°C.} C_6H_5CH{=}CHC_6H_5 + H_2S + S \qquad \text{(III-4)}$$

and that the other products formed (toluene, 1,2,3,4-tetraphenylbutane, and tetraphenylthiophene ("thionessal")) could be explained by subsequent reactions. It would probably be correct to say that the process is a very complex radical chain reaction. Di(α-phenethyl) disulfide, $(C_6H_5CH(CH_3)S)_2$, decomposes similarly to yield styrene, sulfur, hydrogen sulfide, and two diphenylthiophenes (35). Treatment of the optically active disulfide with bromine gives optically active $C_6H_5CH(CH_3)Br$, an observation that suggests several possible mechanisms for the reaction.

A different type of decomposition is given by dibenzhydryl disulfide (446),

$$[(C_6H_5)_2CHS]_2 \xrightarrow{\text{distill}} (C_6H_5)_2CS + (C_6H_5)_2CH_2 + S + H_2S + (C_6H_5)_2C{=}C(C_6H_5)_2 \qquad \text{(III-5)}$$

the thioketone apparently being identified only by its blue color.

As might be expected, di(triphenylmethyl) disulfide decomposes extremely easily: it is reported to lose sulfur on recrystallization and to be cleaved by a variety of reagents (425). Blicke (48) showed that the solutions in benzene immediately turn deep yellow, the color of triphenylmethyl, and yield triphenylmethyl peroxide when air is bubbled through. This suggests the following free-radical dissociation; from the yield of peroxide it appears that the disulfide free

$$(C_6H_5)_3CSSC(C_6H_5)_3 \rightarrow (C_6H_5)_3C\cdot + \cdot SSC(C_6H_5)_3 \qquad \text{(III-6)}$$

radical does not furnish a triphenylmethyl radical. Sulfite is also found, indicating that some of the sulfur forms sulfur dioxide. It is interesting to note that triphenylmethyl peroxide does not split thermally to give triphenylmethyl radicals, analogous to reaction III-6, but instead splits between the oxygens (435). In these two reactions (III-6 and III-7) it is proper to correlate the ease of

$$(C_6H_5)_3COOC(C_6H_5)_3 \xrightarrow[\text{xylene}]{\text{boiling}} (C_6H_5)_2C(OC_6H_5)-C(C_6H_5)_2(OC_6H_5) \qquad \text{(III-7)}$$

Triphenylmethyl peroxide

cleavage of the carbon–sulfur and carbon–oxygen bonds with the bond strengths, since the cleavage presumably forms radicals rather than ions. The following

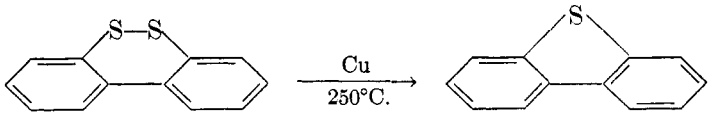
are the appropriate bond strengths, taken from Pauling (299):

BOND	BOND STRENGTH	BOND	BOND STRENGTH
	kcal.		*kcal.*
C—S	54.5	O—O	34.9
C—O	70.0	S—S	63.8

The carbon–sulfur bond cleavage is favored by the amount of resonance energy in the triphenylmethyl radical, whereas the sulfur–sulfur bond is stronger and furthermore would not get the benefit of the resonance energy. The carbon–oxygen bond requires more energy than the carbon–sulfur one; hence before the temperature has been raised sufficiently to cleave it, the weak oxygen–oxygen bond breaks, even although it gets little benefit from the triphenylmethyl resonance energy.

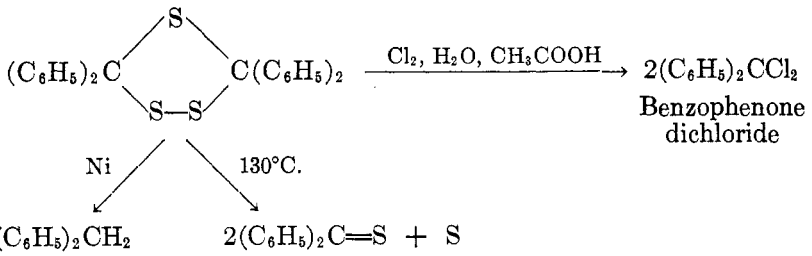
Further studies on reaction III-6, in which it is followed by magnetic susceptibility measurements, might be of much interest.

The cyclic disulfide undergoes the following reaction (26):



(III-8)

The cyclic trisulfide below is obtained by passing dry air through thiobenzophenone. Its structure is proved by chlorination to benzophenone dichloride, and by Raney nickel desulfuration to diphenylmethane (89). Heating regenerates thiobenzophenone (390).



(III-9)

The sulfur–sulfur bond in disulfides is cleaved most readily by reduction to give the sulfhydryl compound, but it is also split hydrolytically to yield a molecule of mercaptan and perhaps of sulfenic acid, both of which may under suitable conditions undergo loss of hydrogen sulfide. The hydrolytic step is represented by the following reaction (157, 334), the sulfenic acid undergoing

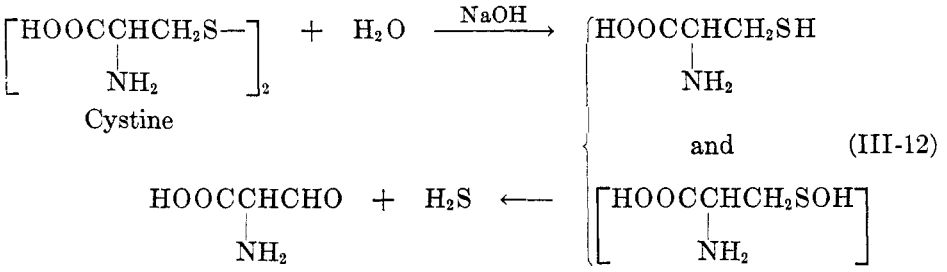
$$(C_6H_5S)_2 + KOH \xrightarrow{\text{alcohol}} C_6H_5SK + C_6H_5SOH \quad \text{(III-10)}$$

$$2C_6H_5SOH \longrightarrow C_6H_5SO_2H + C_6H_5SH \quad \text{(III-11)}$$

disproportionation (for a good review of the sulfenic acids, see reference 233). The reactions above do not involve a carbon–sulfur bond cleavage, but where there are α- or β-hydrogens, such reactions may occur subsequently.

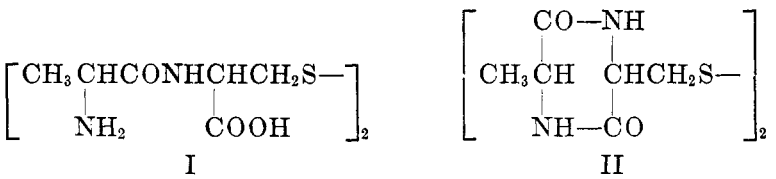
B. DISULFIDES WITH UNSATURATED GROUPS

The process just considered has been studied in detail with cystine and its derivatives, because of the importance of the disulfide linkage in proteins and polypeptides. The reaction with cystine has been formulated as follows (345):

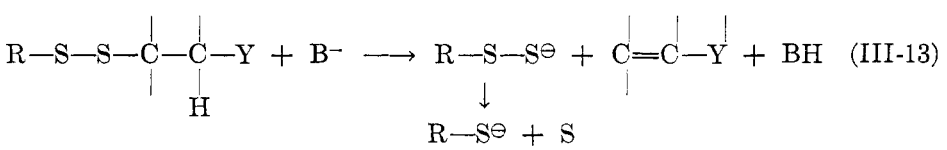


(III-12)

the aldehyde acid presumably undergoing further reaction. In some cases, elementary sulfur is produced in addition to hydrogen sulfide. The cysteine, or derivative of cysteine, formed may undergo loss of hydrogen sulfide, as previously discussed (*cf.* page 7). The process resembles the cleavage of hydrogen sulfide from cysteine derivatives in that the masking of the carboxyl group greatly increases the rate of elimination of hydrogen sulfide. Thus, it is found (45) that dialanylcystine (I) is much more stable to alkali than the corresponding diketopiperazine (II); thus, 1 *N* sodium hydroxide–lead acetate gives 14.3 per cent of the theoretical hydrogen sulfide after 24 hr. at 24°C. from I, while II yields 71 per cent after 30 min. at 18°C.



Numerous other examples have been given (e.g., 7, 63, 344). Furthermore, cystine is very much more rapidly attacked by alkali than is cysteine (344). These facts suggest that the cleavage of disulfides of the cystine type, which have an unsaturated group attached to the carbon β to the sulfur, may be considered to occur by the same mechanism discussed above (equation II-9). The essential step would be the attack of a base on the α-hydrogen, followed by cleavage of the R—S—S$^{\ominus}$ group, which can further decompose to yield sulfur and RS^{-}.



(III-13)

This idea explains why the reaction is slower when Y is a free carboxyl group, because in that case the carboxyl group would be in the carboxylate ion form, which would be attacked at the α-hydrogen only slowly by the base. The same

reasoning shows why cysteine is attacked more slowly than cystine; the former would exist partly as the mercaptide ion in basic solution. The above mechanism seems to be as useful in correlating the observations as the sulfenic acid mechanism, because these acids are very unstable and their formation can be inferred only from the products. The ion R—S—$S^{\ominus}$ might, of course, hydrolyze to R—SOH and H_2O, and the sulfenic acid (R—SOH) then hydrolyze further. In the analytical use of the reaction, lead salts are frequently used, which probably function by removing hydrogen sulfide irreversibly from the primary products of the reaction. (The extensive literature on this reaction is indicated in references 127, 344, and 345.)

Disulfides containing unsaturated groups attached to the carbon carrying the sulfur undergo easy cleavage, in general. A number of α-dithio acids have been studied, and the following mechanism postulated (342, 343):

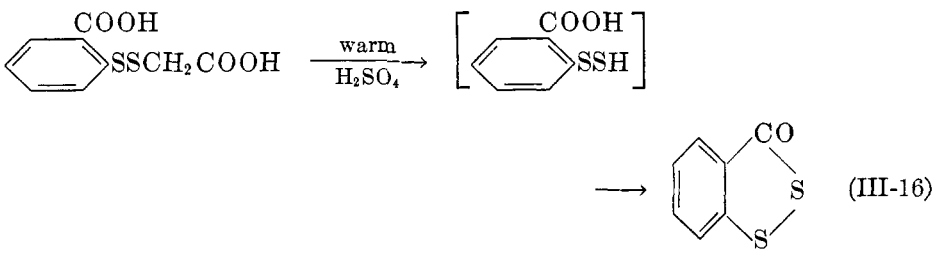
$$\left[\begin{array}{l}\text{RCHS—}\\ \quad\vert\\ \quad\text{COOH}\end{array}\right]_2 + H_2O \xrightarrow{\text{NaOH}} \begin{array}{l}\text{RCHSH}\\ \quad\vert\\ \quad\text{COOH}\end{array} + \begin{array}{l}\text{RCHSOH}\\ \quad\vert\\ \quad\text{COOH}\\ \quad\downarrow\\ \text{RCOCOOH} + H_2S\end{array} \qquad \text{(III-14)}$$

The keto acids can be isolated as the *p*-carboxyphenylhydrazones, but the sulfenic acids cannot be obtained as such. The cleavage of the disulfide linkage will occur slowly according to equation III-14 in neutral solution, but will be greatly accelerated by base; because of the occurrence of the reaction under mild conditions, it is suggested that it may be of importance biochemically (343).

Several other scattered observations on compounds of this type may be mentioned. Diphenacyl disulfide is reported to yield dibenzoylethane (180),

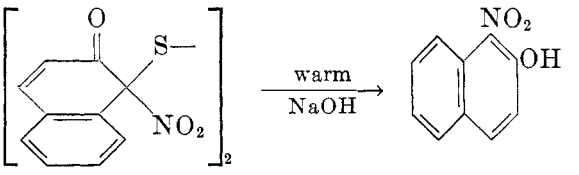
$$\underset{\text{Diphenacyl disulfide}}{(C_6H_5COCH_2S)_2} \xrightarrow{\text{alc. KOH}} \underset{\text{Dibenzoylmethane}}{(C_6H_5COCH_2)_2} \qquad \text{(III-15)}$$

in a reaction whose mechanism can only be guessed. The following reaction (380)



indicates cleavage of a carbon–sulfur bond in a disulfide linkage; the same product is also formed by the reaction of hydrogen sulfide on 2-thiolbenzoic acid.

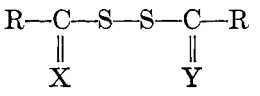
Another example (427) shows the elimination of a disulfide group, in which



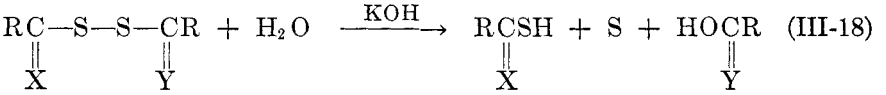
(III-17)

the driving force is the tendency to form an aromatic system.

The behavior of disulfides which have the disulfide group attached directly to unsaturated groups, of the type

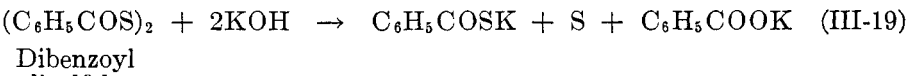


where X and Y are oxygen, sulfur, or nitrogen, has been discussed in detail (156). Many of these compounds, where R is an organic radical, are cleaved according to the following scheme, with formation of elementary sulfur:



(III-18)

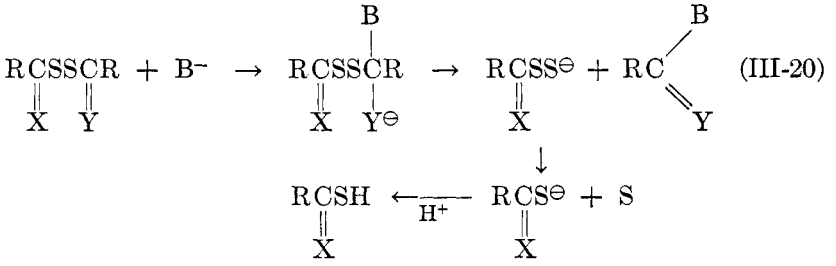
Ammonia and amines behave similarly, with the formation of $H_2NC(=Y)R$ or $R'NHC(=Y)R$. For instance, dibenzoyl disulfide is cleaved as follows (160),



(III-19)

Dibenzoyl disulfide

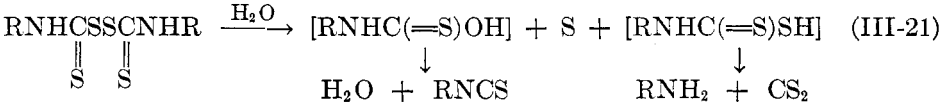
and numerous similar examples are reported (156, 160). It seems reasonable to consider the following mechanism for the reaction, which assumes the same



(III-20)

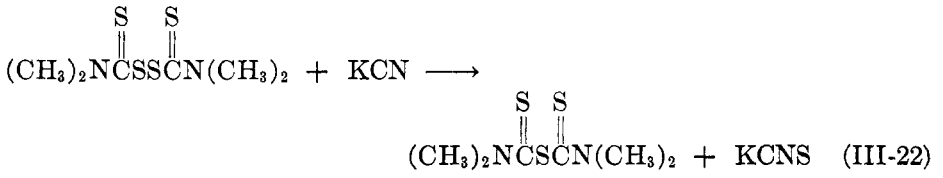
type of intermediate, $R'SS^{\ominus}$, which was suggested above (equation III-13) for other disulfide cleavages.

Thiuram disulfides, $RNHC(=S)SSC(=S)NHR$, decompose on heating to give products which can be explained by equation III-18, with subsequent further reaction (156): the isothiocyanate may react with the primary amine to



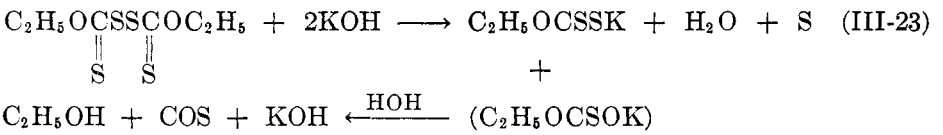
(III-21)

form the thiourea RNHCSNHR, and the carbon disulfide may also react to form this product. The higher thiuram disulfides decompose (65) according to equation III-21 more readily than do the lower homologs; the relative amounts of isothiocyanate and of thiourea derivative formed vary, depending on the compounds. The thiuram disulfides are cleaved by cyanide in aqueous alcohol, to yield the thiuram sulfides in a process which probably goes by a different path from the hydrolytic cleavage (72).



$$(CH_3)_2NCSSCN(CH_3)_2 + KCN \longrightarrow (CH_3)_2NCSCN(CH_3)_2 + KCNS \quad \text{(III-22)}$$

The dixanthate esters also are cleaved by base according to equation III-18 (156), with subsequent decomposition of the thiocarbonate.

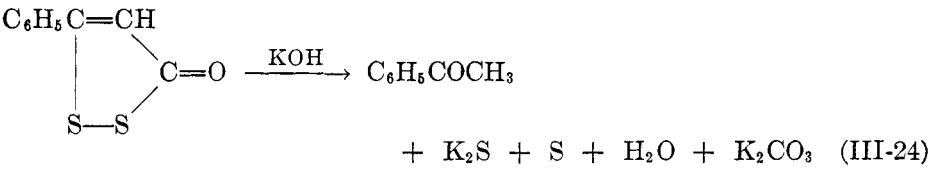


$$C_2H_5OCSSCOC_2H_5 + 2KOH \longrightarrow C_2H_5OCSSK + H_2O + S \quad \text{(III-23)}$$

$$+$$

$$C_2H_5OH + COS + KOH \xleftarrow{HOH} (C_2H_5OCSOK)$$

Fromm's mechanism (equation III-18) thus serves to correlate the transformations of disulfides of various structures. Compounds with the unsaturated groups (C=X and C=Y) as part of a stable ring system may undergo cleavage of the disulfide link, but sulfur is not lost (*cf.* equations III-10 and III-11). Compounds with the disulfide grouping as part of a ring may undergo cleavage with loss of sulfur (156).

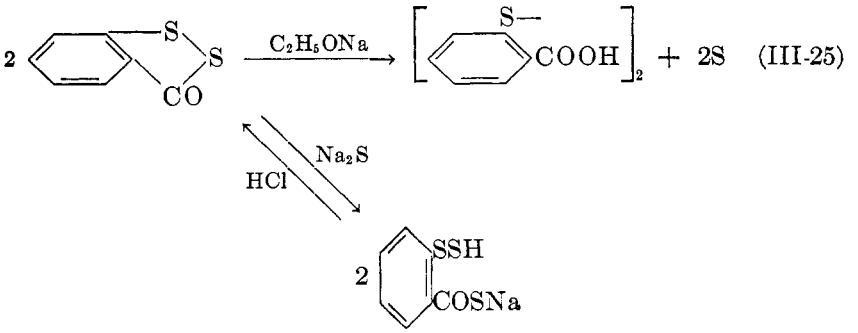


$$C_6H_5C{=}CH \quad C{=}O \xrightarrow{KOH} C_6H_5COCH_3$$

$$S{-}S$$

$$+ K_2S + S + H_2O + K_2CO_3 \quad \text{(III-24)}$$

This probably goes through the formation of $C_6H_5C(=S)CH_2COOH$, which then undergoes hydrolysis and decarboxylation. The interesting compound of Smiles (*cf.* equation III-16) is stable to acids, but is cleaved by sodium ethoxide, with loss of sulfur and subsequent oxidation (380); the ring is also cleaved by



$$2 \quad \xrightarrow{C_2H_5ONa} \left[\quad\right]_2 + 2S \quad \text{(III-25)}$$

$$\xrightarrow[HCl]{Na_2S} \quad 2$$

aqueous sodium sulfide, to form presumably the above compound, which can re-form the starting material without loss of sulfur from the disulfide function. "Trithiones" of the type below have recently been studied (263); one method of preparation involves action of heat on cinnamyl trisulfide.

$$(C_6H_5CH{=}CHCH_2)_2S_3 \longrightarrow C_6H_5C{=}CH + C_6H_5CH_2CH_2CH_3 \quad \text{(III-26)}$$
$$\text{Cinnamyl trisulfide} \qquad\qquad \underset{SSC{=}S}{|\ /}$$

In contrast to the preceding disulfides, the isothiuram disulfides,

$$RN{=}C\underset{SR'}{|}S\underset{SR'}{|}C{=}NR$$

decompose according to the following scheme (67).

$$C_6H_5N{=}C\underset{SR}{|}S\underset{SR}{|}C{=}NC_6H_5 \rightarrow 2C_6H_5NCS + (RS)_2 \quad \text{(III-27)}$$

When R = methyl, a temperature of 100–130°C. is necessary for reaction, but when R = allyl, the compound decomposes on standing at room temperature for a few days. The completely aliphatic analogs are harder to purify, but also split according to equation III-27 (67). The *S*-acylisothiuram disulfides decompose spontaneously to diacyl disulfides, so that the method is recommended as

$$\left[RN{=}C\underset{SH}{|}S{-}\right]_2 + 2R'COCl \rightarrow \left[(RN{=}C\underset{SCOR'}{|}S{-})_2\right] \rightarrow R'C\overset{O}{\overset{\|}{S}}S\overset{O}{\overset{\|}{C}}R' \quad \text{(III-28)}$$

a good synthetic procedure for these substances. This reaction can also be used to make the corresponding derivatives from carbamyl chlorides, $(C_6H_5)_2NCOS{-}SCON(C_6H_5)_2$ (67).

IV. Sulfides

A. Saturated Dialkyl Sulfides

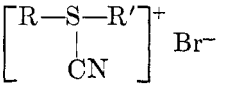
There is little data on the pyrolytic decomposition of dialkyl sulfides, but it is reported (138) that diethyl and diisoamyl sulfides are partially decomposed by passage through a hot tube at 496°C., hydrogen sulfide, mercaptan, and gaseous hydrocarbons being produced.

The cleavage of sulfides by cyanogen bromide has been studied in numerous cases; the cleavage can take two courses with unsymmetrical sulfides and mixtures may be obtained (69, 71).

$$RSR' + BrCN \xrightarrow{60\text{–}70°C.} RSCN + R'Br \quad \text{(IV-1)}$$

Cleavage of sulfides with a secondary carbon attached to sulfur does not give the expected products; hydrogen bromide is formed, probably from the secondary bromide, apparently accompanied by polymerization of the olefin (69). A benzyl or allyl group is cleaved from the sulfur in preference to a saturated alkyl group, forming the corresponding benzyl or allyl bromide; this result would

be expected in view of the cationic stability of the benzyl or allyl group, compared to saturated alkyl groups. It seems quite probable that the cleavage of sulfides by cyanogen bromide, as well as by numerous other reagents, for that matter, may go through the formation of a sulfonium type compound, either as such or as a phase in the transition state. The group which would be split off from a sulfonium salt such as



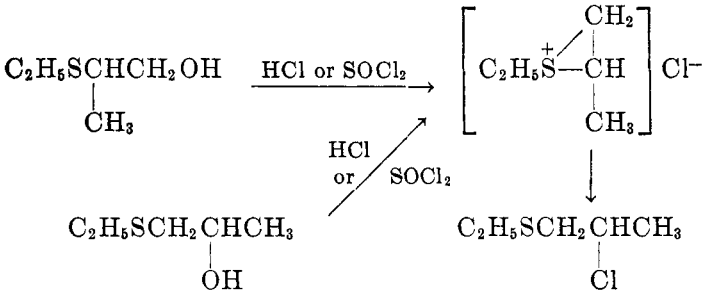
would be the group with the greatest cationic stability, as shown by Ingold and coworkers (174), and would appear as the bromide. von Braun's work with cyanogen bromide has been extended to aralkyl and aryl sulfides (*cf.* pages 35 and 40).

The only other cleavage reaction of dialkyl sulfides which seems potentially of general significance is the acetyl iodide procedure (181).

$$C_2H_5SC_2H_5 + CH_3COI \rightarrow C_2H_5I + CH_3COSC_2H_5 \qquad \text{(IV-2)}$$

The reaction is much slower than that of the corresponding oxygen ethers, and requires many days at room temperature; the ethyl iodide formed reacts with unchanged sulfide to form triethylsulfonium iodide. Acetyl chloride at 100°C. is without effect on diethyl sulfide after 7 days (181).

An interesting type of cleavage of dialkyl sulfides, which results in isomerization and which is also of importance with the corresponding nitrogen compounds, was noted (164, 165) in connection with studies on mustard gas and related compounds. Replacement of the hydroxyl group with halogen in β-hydroxyisopropyl ethyl sulfide leads to isomerization, which is explained by the intermediate



(IV-3)

formation of an ethylenesulfonium compound, with subsequent ring cleavage. In the cases studied, the ring cleavage takes place in one direction only. This is in agreement with the idea of cleavage *via* an intermediate sulfonium compound, i.e., the secondary carbon–sulfur bonds are cleaved in preference to primary carbon–sulfur bonds. Similar ethyleneimmonium intermediates from β-substituted ethylamines have recently been demonstrated by kinetic and preparative methods, in connection with studies on nitrogen mustards (e.g., 27, 176). The

greater ease of cleavage of a tertiary carbon–sulfur bond is shown by the following reaction (219):

$$HOCH_2CH_2SC(CH_3)_3 + SOCl_2 \rightarrow ClCH_2CH_2SC(CH_3)_3 + (CH_3)_3CCl \quad \text{(IV-4)}$$

(30 per cent yield) (25 per cent yield)

The action of halogens upon aliphatic sulfides has been mentioned occasionally, but it is not a practical method of cleavage with these compounds, although it is useful with aryl or aralkyl sulfides (*cf.* pages 37 and 41). Chlorine apparently leads to cleavage and chlorination of the fragments (387), and iodine is reported to form trimethylsulfonium iodide from dimethyl sulfide at 120°C. (91). Diethyl sulfide yields ethyl polysulfides when heated with sulfur in a sealed tube at 180°C. for 1 day, and is extensively decomposed by sulfur halides under the same conditions (58).

TABLE 2

Rates of hydrolysis of α-halogen sulfides

COMPOUND	RELATIVE RATE OF HYDROLYSIS	COMPOUND	RELATIVE RATE OF HYDROLYSIS
$ClCH_2SC_6H_5$	1	ICH_2SCH_3	840
$ClCH_2SCH_2C_6H_5$	17	$BrCH_2SC_2H_5$	240
$ClCH_2SCH_3$	220	$CH_3CH(Cl)SCH_3$	2700
$ClCH_2SC_2H_5$	220	$C_6H_5CH(Cl)SCH_3$	1.6×10^7

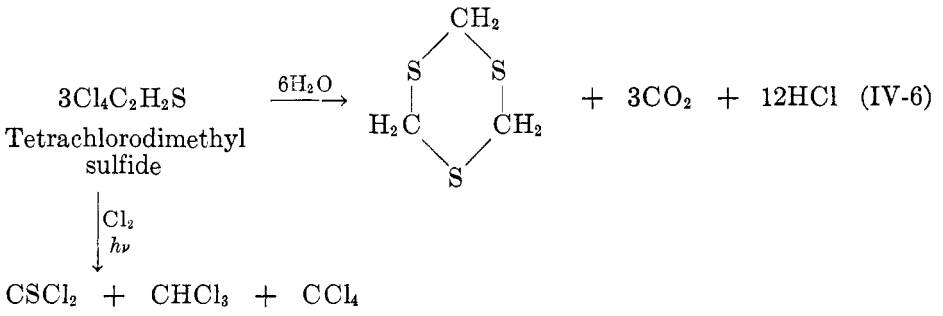
The α-halogen sulfides resemble the α-halogen ethers in the ease of hydrolysis and ease of replacement of the halogen (52). The equation for the hydrolysis reaction apparently is the following (55):

$$2ClCH_2SR + H_2O \rightarrow CH_2(SR)_2 + CH_2O + 2HCl \quad \text{(IV-5)}$$

Ingenious measurements of the rate of hydrolysis in aqueous dioxane, in which the reaction was followed by titration of the acid with a standard solution of tribenzylamine in acetone, using *p*-dimethylaminoazobenzene as indicator, show that the α-halogen ethers hydrolyze much more rapidly than the α-halogen sulfides (54); the reaction is catalyzed by hydrogen chloride. It is interesting to note that the β-halogen sulfides hydrolyze very much more rapidly than the corresponding β-halogen ethers, by a factor of 10^3–10^4 (57).

The relative rates of hydrolysis of a series of α-halogen sulfides under the above conditions are indicated in table 2 (55). The close correspondence in rates for the chlorine, bromine, and iodine derivatives would indicate that the slow step is a first-order ionization process.

Tetrachlorodimethyl sulfide hydrolyzes rapidly to give trithioformaldehyde and also undergoes chlorination in the presence of ultraviolet light to yield several products (143).



The action of metallic sodium on butyl chloromethyl sulfide gives the following products (219):

$$ClCH_2SC_4H_9 \xrightarrow{Na} \underset{\text{(trace)}}{(C_4H_9SCH_2)_2} + (C_4H_9S)_2CH_2 + \text{olefins} \quad \text{(IV-7)}$$

With 2-chloroethyl sulfides ($RSCH_2CH_2Cl$) the main reaction is cleavage, with formation of ethylene (219). The evolution of ethylene is more rapid when R is tertiary butyl than it is when R is a primary or secondary group; zinc is also effective in the reaction (219). Magnesium metal does not react with $ClCH_2CH_2SC_6H_5$ (5, 219), but the bromo compound, $BrCH_2CH_2SC_6H_5$, is rapidly attacked according to the above equation (5). The β-halogen ethers also give ethylene when treated with metals; the reaction may be viewed as follows (5):

$$RYCH_2CH_2Cl + M \rightarrow [RYCH_2CH_2]^{\ominus}M^{+} + MCl \quad \text{(IV-8)}$$
$$\downarrow$$
$$RY^{-} + CH_2{=}CH_2$$

Y = O or S; M = Na, Zn/2, etc.

The γ-chloropropyl sulfides yield cyclopropane with sodium, instead of propylene (219).

$$ClCH_2CH_2CH_2SR \xrightarrow[\text{toluene}]{Na} \underset{\diagdown\,\diagup}{CH_2{-}CH_2}\ \underset{}{CH_2} + RSNa + NaCl + RSCH_2CH_2CH_2SR \quad \text{(IV-9)}$$

The δ-chlorobutyl compounds yield *n*-butane, ethylene, 1-butene, and

$$RS(CH_2)_4SR$$

as well as some cyclic sulfonium compound (219).

It is reported that diethyl sulfide dissolves in anhydrous hydrogen fluoride, apparently forming $(C_2H_5)_2\overset{+}{S}HF^{-}$, but the sulfide can be recovered unchanged. Diethyl ether behaves similarly (237).

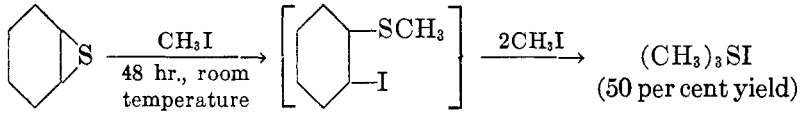
B. POLYMETHYLENE SULFIDES

1. Ethylene sulfides

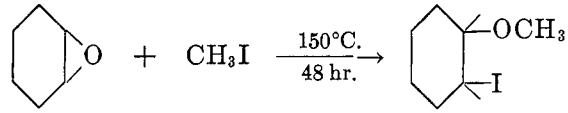
The ethylene sulfides are the most interesting of the saturated ring compounds containing sulfur in the ring, and have been studied fairly extensively of late.

Ethylene sulfide, $CH_2—CH_2$ (S bridging), polymerizes very readily, even on standing for some time in the dark; the process is catalyzed by a variety of reagents, including mineral acids, acetic acid, concentrated aqueous alkali, aqueous ammonia, pyridine, and heavy metal salts (114, 115), and is inhibited by small amounts of mercaptans, hydrogen sulfide, or alkyl sulfides (101, 383). There seems to be little known about the nature of the polymers formed or the mechanism of the polymerization process; the polymers obtained from cyclohexene sulfide vary in properties from viscous liquids to hard nonvolatile solids (108). It is possible that the acid-catalyzed reaction proceeds through the ethylenesulfonium ion, by a mechanism similar to that proposed for the polymerization of ethyleneimine (227). If this is the case, the mercaptan may prevent polymerization by reacting with the ethylenesulfonium ion faster than ethylene sulfide does. Propylene sulfide and the higher homologs seem to polymerize less readily than ethylene sulfide itself (115a, 382a).

It is apparently not possible to convert the sulfur atom in the ethylene sulfide ring to the tri- or tetracovalent state without rupturing the ring (108); the only exceptions are unstable sulfones from arylethylene sulfides (391, 424), which were not prepared by oxidation of the corresponding sulfides. Apparently the bond angles of the tri- or tetracovalent sulfur atom cannot be distorted enough to form a stable three-membered ring. The action of methyl iodide on ethylene sulfides leads to trimethylsulfonium iodide, probably through an intermediate methyl sulfide (108). The cleavage of an analogous epoxide requires very much more drastic conditions (108).

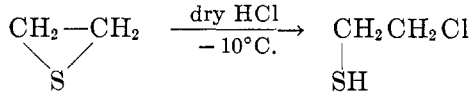


(IV-10)



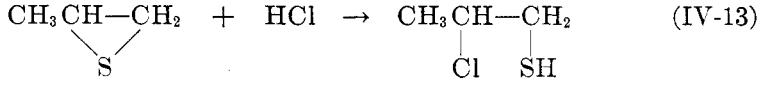
(IV-11)

The ethylene sulfide ring is cleaved by dry hydrogen chloride to form the chloromercaptan in good yield (275a), but in some cases either ring-opening or



(IV-12)

polymerization may occur with hydrogen chloride, depending on the conditions (108). With propylene sulfide, aqueous hydrochloric acid gives the secondary chloride, whose structure appears definitely established (112).



(IV-13)

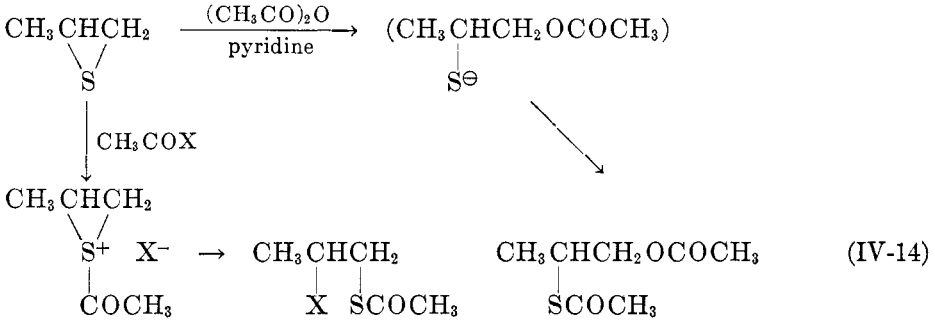
This mode of ring-opening (cleavage of the secondary carbon–sulfur bond) is the reverse of that shown by propylene oxide under these conditions, which yields the secondary alcohol (the so-called normal product) (112).

Acyl chlorides react with ethylene sulfide to form the thiol esters,

$$RCOSCH_2CH_2Cl$$

(2, 108, 275a). With propylene sulfide, the ring opening can occur either way, depending on the conditions (112, 399).

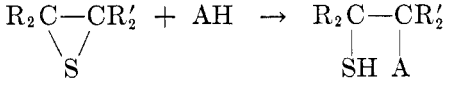
The normal cleavage of the propylene sulfide by acetic anhydride–pyridine may be attributed to the attack of acetate ion on the primary carbon, which has a lower electron density than the secondary carbon. The reversed mode of cleavage by acetyl halides may be due to formation of a sulfonium compound, followed by cleavage of this to form the secondary carbonium ion (for the occurrence of sulfonium-ion intermediates and their cleavage to give secondary or tertiary halides, see pages 16, 16, and 22).



(IV-14)

The different mode of ring opening, with acetyl halides, of the propylene sulfide compared to the epoxide can be attributed to the greater tendency of the sulfide to form onium-type intermediates (112).

Alcohols, amines, and mercaptans, including hydrogen sulfide, can cleave the ring in some cases, to yield β-amino-, alkoxy-, or thio-substituted mercaptans



(IV-15)

A = RO, R_2N, RS, HS.

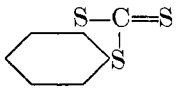
(108, 383). The reaction with amines occurs at 100°C. and in general gives good yields; with isobutylene sulfide the addition takes place to form mainly, if not exclusively, the tertiary mercaptan (383), indicating that in this case the primary carbon–sulfur bond is more readily broken than the tertiary one.

The addition of mercaptans to ethylene sulfides requires boron fluoride or sodium ethoxide as catalyst, and with isobutylene sulfide a mixture of primary and tertiary mercaptans is obtained, resulting from cleavage of both carbon–sulfur bonds; the primary mercaptans usually predominate, and the proportion of primary mercaptans is greater when sodium ethoxide is used than it is with

boron fluoride (384). These relationships are opposite to those observed in the alcoholysis of propylene oxide under acidic and alkaline conditions (95). The reaction of cyclohexene sulfide with ethyl xanthate to form

$$C_6H_{10}[SC(=S)OR]SK$$

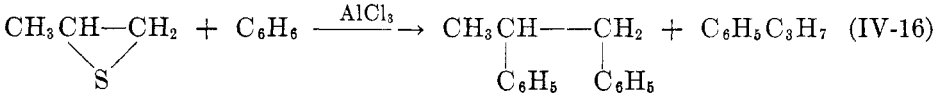
which goes to



is of the same type (109). Mercaptans do not add to tetramethylethylene sulfide (275a, 384).

Only primary alcohols give satisfactory yields in reaction IV-15, with boron fluoride as catalyst, and with saturated alcohols the primary mercaptan is the main product, although with cellosolve the tertiary mercaptan is the main product (384). It seems clear that, with substituted ethylene sulfides, the primary and secondary (or tertiary) carbon–sulfur bonds are broken at nearly the same rate, in contrast to the ethylene oxides. It is also notable that the ethylene sulfides do not seem to be hydrolyzed easily to β-hydroxymercaptans, possibly because they polymerize, again in contrast to ethylene oxides.

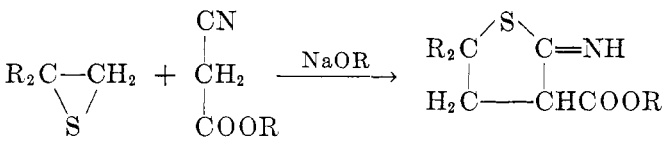
Propylene sulfide alkylates benzene in the presence of aluminum chloride



(IV-16)

at reflux temperatures; at lower temperatures the sulfide polymerizes, and apparently the alkylation reaction involves interaction of the polymer with benzene (399).

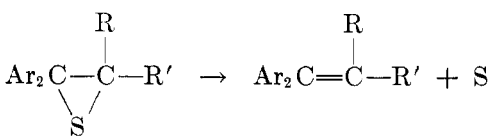
The olefin sulfides alkylate ethyl cyanoacetate, but not ethyl malonate or



(IV-17)

acetoacetate (382a); propylene and isobutylene sulfide resemble the corresponding oxides in undergoing cleavage at the primary carbon–sulfur bond by the nucleophilic anion derived from ethyl cyanoacetate (95, 382a).

Tetraarylethylene sulfides and some diarylethylene sulfides containing other negative groups lose sulfur on heating to about 200°C., or at much lower temperatures when heated with copper bronze (e.g., 356, 364, 365, 393, 394), the reaction leading in some cases to interesting ketene acetal derivatives.



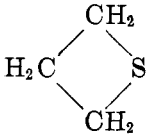
(IV-18)

R = R′ = aryl; R = Cl, R′ = *S*-aryl or *O*-aryl; R = R′ = *S*-aryl.

The driving force for the reaction is undoubtedly the tendency to form a conjugated system with the aromatic nuclei.

2. Higher ring homologs

The next higher homolog of ethylene sulfide, trimethylene sulfide, has been studied only slightly. It is reported to polymerize in the presence of nitric or hydrochloric acid (61), under conditions which do not affect tetramethylene sulfide, pentamethylene sulfide, or diethyl sulfide, and it is cleaved by the action of methyl iodide, perhaps through an intermediate cyclic sulfonium compound, although there is no evidence for this (18, 40, 179).

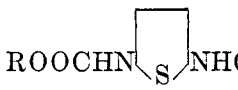


$$+ 2CH_3I \rightarrow [ICH_2CH_2CH_2\overset{+}{S}(CH_3)_2]I^- \quad \text{(IV-19)}$$

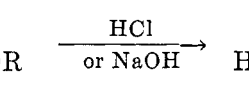
The compound is also reported to be cleaved by alcoholic ammonia at 200°C. to yield the aminothiol, $H_2NCH_2CH_2CH_2SH$ (179). Other cleavage reactions of the trimethylene sulfide by nucleophilic agents do not seem to have been studied.

The ease of cleavage characteristic of the three- and four-membered sulfur-containing rings above, which is of course well known for the three- and four-membered cyclic ethers (for trimethylene oxide, *cf.* 117) and for the corresponding carbocyclic compounds, is not exhibited by tetramethylene sulfide (thiophan). It forms a stable cyclic methiodide, which can be cleaved to an unsaturated open-chain sulfide by heating with base, and is also split by cyanogen bromide, but it does not polymerize with mineral acid (73). The next higher homolog, pentamethylene sulfide (tetrahydrothiapyran), behaves similarly and is stable to long treatment with dilute acids and bases.

2,5-Diaminothiophan, prepared by hydrolysis of the carbamate (78) or by the Hofmann reaction on the diamide (422), is rapidly hydrolyzed as follows (78):



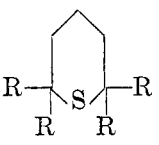
$$\xrightarrow[\text{or NaOH}]{\text{HCl}}$$



$$\rightarrow 2NH_3 + H_2S + OHCCH_2CH_2CHO \quad \text{(IV-20)}$$

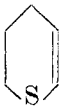
The presumed intermediate, 2,5-diaminothiophan, is analogous to an aldehyde ammonia or a hemiacetal (*cf.* page 70).

The 2,2,6,6-tetraalkylpentamethylene sulfides are cleaved by methyl iodide at 100°C., with the formation of trimethylsulfonium iodide (289).



$$+ 3CH_3I \rightarrow (CH_3)_3SI + \begin{pmatrix} R_2C(CH_2)_3CR_2 \\ | \qquad\qquad | \\ I \qquad\quad I \end{pmatrix} \quad \text{(IV-21)}$$

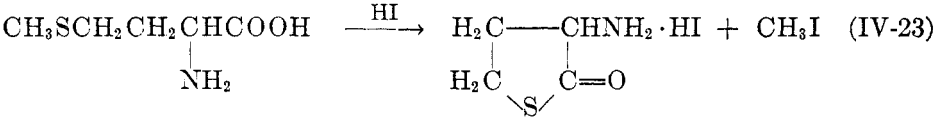
At lower temperatures the sulfonium salt of the cyclic sulfide can be isolated. Pentamethylene sulfide itself, which has primary carbons attached to the sulfur, does not give this result with methyl iodide, and the reaction is apparently to be attributed to the greater cationic stability of the tertiary carbon atoms compared to primary carbons. It is shown below that compounds containing the $-(CH{=}CHCH_2)_2S$ group yield trimethylsulfonium iodide when treated with methyl iodide; the allyl group is also stable as a cation (*cf.* page 25). The Δ^2-dihydrothiopyran apparently yields only trimethylsulfonium iodide when heated with methyl iodide at 100°C.; the Δ^3-compounds give mixtures of the cyclic and open-chain sulfonium compounds (290).



$$+ \ CH_3I \xrightarrow{100°C.} (CH_3)_3SI \qquad \text{(IV-22)}$$

C. DIALKYL SULFIDES WITH UNSATURATED GROUPS

Like the thiol compounds (*cf.* page 6) sulfides show a marked effect of unsaturated groups in the proper position on the rate of cleavage of the carbon–sulfur bond. Unsaturated groups attached to the γ-carbon are not apparently of much importance in affecting the behavior of the sulfide group. The principal example of this case is methionine, which has been studied in some detail to ascertain if the methylthiol group can be determined by the Zeisel methoxyl procedure. It is reported (21, 22) that methionine yields about 97 per cent of the theoretical amount of methyl iodide when refluxed several hours with hydriodic acid (sp. gr. 1.7), with formation of the thiolactone from homocysteine as the other product.



$$CH_3SCH_2CH_2CH(NH_2)COOH \xrightarrow{HI} H_2C{-}CHNH_2 \cdot HI + CH_3I \qquad \text{(IV-23)}$$

$$H_2C{-}C{=}O \quad (S)$$

Methionine

The behavior of this thiolactone on alkaline treatment is discussed below (page 55). Treatment of methionine with 18 *N* sulfuric acid at 125–135°C. gives a low yield of homocysteine and a little dimethyl disulfide. Hydrobromic and hydriodic but not hydrochloric acid also give some homocysteine (85). Systematic studies of the Zeisel procedure on various types of methylthiol compounds are described in reference 10.

Compounds of the type $RSCCHY$, where Y is a negative group, such as C=O, C=C, SO_2R' etc., as would be expected from the discussion above (page 6), are readily cleaved by bases, and in some cases also by acids, to yield RSH and an unsaturated compound.

Considering first the derivatives of cysteine, it is found that the rate of deamination, which undoubtedly involves the following steps (98),

$$RSCH_2\underset{\underset{NH_2}{|}}{C}HCOOH \xrightarrow{\text{base}} RSH + CH_2{=}\underset{\underset{NH_2}{|}}{C}COOH \xrightarrow{H_2O} CH_3COCOOH + NH_3 \quad \text{(IV-24)}$$

varies according to R in the following way:

$$\text{ethyl} < \text{benzyl} < SCH_2CH(NH_2)COOH < \text{phenyl}$$

The reactions are brought about by calcium hydroxide suspensions, or by alkaline plumbite solutions, and are accelerated by the presence of pyruvic acid or salicylaldehyde (98). The position of phenyl in the series may be attributable to the greater acidity of thiophenol compared to the other thiol compounds; the removal of RS^- in reaction II-9 may be expected to go more rapidly the greater the stability of RS^- relative to RSH.

Another interesting example is the alkaline cleavage according to reaction IV-24 of *S*-allylcysteine, which is obtained by reduction of alliine (*S*-allylcysteine sulfoxide), an antibiotic isolated from garlic (400).

Recently it has been found (148, 301) that some derivatives of cystine obtained by condensation of cysteine with mustard gas or related compounds can be cleaved by merely treating with silver or mercury salts in neutral solution, and then adding alkali to a pH of 8–10.

$$X(CH_2CH_2SCH_2\underset{\underset{NH_2}{|}}{C}HCOOH)_2 \xrightarrow[\text{then NaOH}]{AgNO_3} X(CH_2CH_2OH)_2 + 2HSCH_2\underset{\underset{NH_2}{|}}{C}HCOOH \quad \text{(IV-25)}$$

X = SO_2 or S.

The effect of the heavy metal on the alkaline cleavage may be attributed to coördination on the sulfur atom, forming a complex which is more vulnerable to a displacement of the R group by water or hydroxyl ion.

$$R{:}\overset{\delta+}{\underset{\underset{M}{|}}{\ddot{S}}}{:}CH_2CH(NH_2)COOH + OH^- \rightarrow ROH + M{:}\ddot{S}{:}CH_2CH(NH_2)COOH \quad \text{(IV-26)}$$

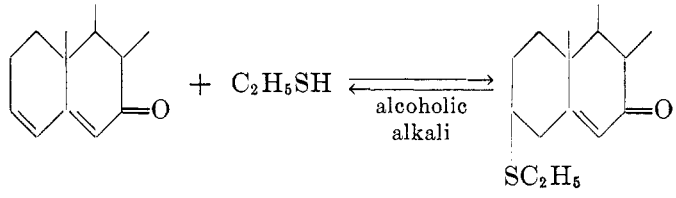
The heavy metals (mercury, silver) which catalyze the reaction are those which are known to form coördination compounds with sulfides.

Numerous examples of the following type of cleavage have been reported,

$$Ar\underset{\underset{O}{\|}}{C}CH_2\underset{\underset{SR}{|}}{C}HAr \xrightarrow{\text{base}} Ar\underset{\underset{O}{\|}}{C}CH{=}CHAr + RSH \quad \text{(IV-27)}$$

the cleavage occurring rapidly in most cases under very mild conditions, such as 0.1 *N* sodium carbonate at room temperature or lead acetate and 0.1 *N* sodium hydroxide (e.g., 38, 291). The starting compounds are readily obtained by addition of mercaptans or thiophenols to α,β-unsaturated ketones.

An interesting example of the behavior of the system RSCCC=CC=O is given by the 1,6-addition of ethyl mercaptan to a cholestadienone (323); the addition product is stable to acids but is split by bases, as would be expected.

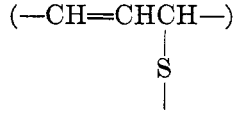


(IV-27a)

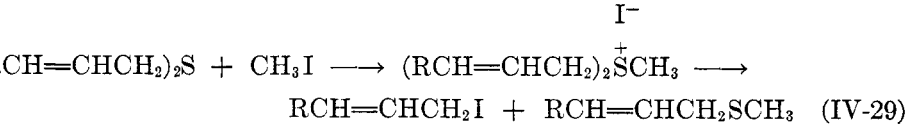
The compounds containing the group RSCHC=C show ready cleavage of the carbon–sulfur bond under conditions which do not affect the analogous saturated sulfides. One example of this difference is the action of methyl iodide on allylic sulfides, which under mild conditions yield trimethylsulfonium iodide (140, 269, 374, 395).

$$(RCH{=}CHCH_2)_2S + \underset{(excess)}{CH_3I} \rightarrow (CH_3)_3S^+I^- + 2RCH{=}CHCH_2I \quad \text{(IV-28)}$$

Free iodine may be formed from the substituted allyl iodide (374). The cleavage reaction is also shown by dicyclohexenyl sulfide, which has its double bonds in the same relative position (140), and, as shown below, is also given by benzyl sulfides (page 34). The reaction has been useful in studies on the nature of the sulfur combined with rubber during the vulcanization process; much of the sulfur is found to be removable by methyl iodide as trimethylsulfonium iodide, and hence is believed to exist in groups of the allyl sulfide type (375):



This cleavage probably proceeds through the formation of a sulfonium compound, which loses its allyl or other unsaturated groups through a series of reactions of the type suggested by Ray and Levine (312).



(IV-29)

The allyl group would split preferentially from the sulfonium salt instead of the methyl, because it is well known, especially from the elegant work of Ingold (174), that the group with the greatest cationic stability is the one which leaves

the sulfonium ion. Repetition of reaction IV-29 would lead to $(CH_3)_2S$ and then to the sulfonium compound, $(CH_3)_3SI$. It is quite possible, however, that the allyl sulfonium salt is never formed in reaction IV-29, even as an unstable intermediate; the reaction may involve a direct displacement of the allyl group by the methyl.

Another reaction which distinguishes between the allyl-type sulfides and saturated sulfides is the behavior on reduction with sodium and alcohol (140). The bis-α,β-unsaturated compounds yield a mixture of hydrogen sulfide and thiol; the mono-unsaturated sulfides yield a thiol, and the saturated sulfides are not affected.

$$(CH_2{=}CHCH_2)_2S \xrightarrow{Na,C_2H_5OH} \underset{(50\text{ per cent})}{H_2S} + \underset{(50\text{ per cent})}{CH_2{=}CHCH_2SH} \qquad \text{(IV-30)}$$

$$C_3H_7SCH_2CH{=}CH_2 \xrightarrow{Na,C_2H_5OH} \text{thiol, probably } \underset{(60\text{ per cent})}{C_3H_7SH} \qquad \text{(IV-31)}$$

The ease of hydrogenolysis of the benzyl group from nitrogen, oxygen, or sulfur is well known, and the cleavage of a substituted allyl group from oxygen and from sulfur by catalytic reduction has been reported (268, 287).

Of compounds containing negative groups other than the carbon–carbon double bond in the α,β-position, some work on β-sulfonyl-β-carbonyl sulfides can be mentioned. Exchange reactions of the following type have been observed on heating the components with sodium carbonate (169):

$$C_6H_5SO_2\underset{\displaystyle SCH_3}{\underset{|}{C}}HCOCH_3 + C_7H_7SO_2SC_2H_5 \longrightarrow C_7H_7SO_2\underset{\displaystyle SC_2H_5}{\underset{|}{C}}HCOCH_3 \ (+C_6H_5SO_2SCH_3) \qquad \text{(IV-32)}$$

It is interesting to point out that hydrolysis of the above type of β-substituted sulfide leads to cleavage of the acetyl group, instead of the sulfonyl group.

$$C_6H_5SO_2CH(SCH_3)COCH_3 \xrightarrow{\text{hydrolysis}} C_6H_5SO_2CH_2SCH_3 + CH_3COOH \qquad \text{(IV-33)}$$

Sulfides containing α,β-unsaturation in the form of the carboxyl group, $RSCH_2COOH$, have been studied in detail, mainly by Holmberg. It is found that CH_3SCH_2COOH is cleaved by heating with an aqueous solution of mercuric chloride (186), perhaps through the intermediate formation of the sulfoxide,

$$CH_3SCH_2COOH \xrightarrow[H_2O]{HgCl_2} \left[\begin{array}{c} O \\ \uparrow \\ CH_3SCH_2COOH \end{array}\right] \rightarrow CH_3SHgCl + CHOCOOH \qquad \text{(IV-34)}$$

which is shown to undergo the cleavage itself under the same conditions. Another possibility is that the coördination compound with mercuric chloride,

$$\begin{array}{c} CH_3SCH_2COOHgCl \\ \downarrow \\ HgCl_2 \end{array}$$

may be the intermediate instead of the sulfoxide, as suggested above for similar reactions (page 24). It is found, however, that there is a significant difference in the rate of cleavage of acids of the type $RSCH_2COOH$, depending on the nature of R; if R is a primary alkyl group, the acid is not affected by treatment with dilute mercuric chloride and hydrochloric acid in acetic acid, but if R is tertiary butyl, cinnamyl, or α-phenethyl, the cleavage is 30–70 per cent complete in 1 hr. (203), and yields in this case the mercapto acid. The acids which

$$RSCH_2COOH + HgCl_2\text{–}HCl \xrightarrow{H_2O} ROH + ClHgSCH_2COOH \quad \text{(IV-35)}$$

are cleaved by this mild treatment are the ones which can be prepared by the following process,

$$(CH_3)_3COH + HSCH_2COOH \xrightarrow{HCl} (CH_3)_3CSCH_2COOH + H_2O \quad \text{(IV-36)}$$

and it is to be noted that the R groups involved are those with a high degree of cationic stability which might well be expected to cleave in the complex

$$\begin{array}{c} RSCH_2COOH \\ \downarrow \\ HgCl_2 \end{array}$$

by an S_N1 process. It is also consistent with this picture that the acids

$$C_6H_5COCH_2SCH_2COOH$$

and $C_6H_5COCH_2SCH_2CH_2COOH$ are not cleaved under these mild conditions; the phenacyl group $C_6H_5COCH_2$ has very low cationic stability.

Compounds containing α,β-unsaturation on both sides, such as

$$C_6H_5COCH_2SCH_2COOH$$

above, are usually readily cleaved by aqueous alkali. The reaction has been recommended as a method of reducing benzoins,

$$ArCOCHOHAr$$

to desoxybenzoins, $ArCOCH_2Ar$ (39), because the benzoins react readily with thioglycolic acid to form the starting material for reaction IV-37. The reaction usually yields the following products, with the sulfenic acid as a possible intermediate (38, 39, 199, 414); the yields are usually good. However, compounds of the type $ArCOCH(R)SC_6H_4COOH$(*o* or *m*) are only slightly affected by boiling alkali (38).

$$\mathrm{ArCOCHSCH_2COOH} + \mathrm{NaOH} \rightarrow \mathrm{ArCOCH_2R} + (\mathrm{HOSCH_2COOH}) \rightarrow \mathrm{H_2S} + \mathrm{CHOCOOH} \quad \text{(IV-37)}$$

When R = H, the product is $(C_6H_5COCH_2)_2CHCOOH$, evidently produced by further condensation of the acetophenone formed initially, with the glyoxylic acid. The following alternative mechanism has also been suggested (414):

$$\mathrm{ArCOCHSCH_2COOH} \xrightarrow{2\mathrm{NaOH}} \mathrm{ArCO\overset{\ominus}{C}SCH_2COO^{\ominus}} \rightarrow \mathrm{ArCO\overset{\ominus}{C}HC_6H_5} + \mathrm{S{=}CHCOO^-} \quad \text{(IV-38)}$$

$$\mathrm{ArCO\overset{\ominus}{C}HC_6H_5} \xrightarrow{\mathrm{H_2O}} \mathrm{ArCOCH_2C_6H_5}$$

Compounds of the type shown below give carbon–carbon cleavage with alkali, like a β-keto ester (38, 414):

$$\mathrm{ArCOCHC_6H_5} \xrightarrow{\mathrm{NaOH}} \mathrm{C_6H_5COOH} + \mathrm{RSCH_2C_6H_5} \quad \text{(IV-39)}$$

R = C_6H_4COOH(*o*- or *m*-), C_2H_5.

The reason that there is no cleavage of the carbon–sulfur bond in these cases is probably that the C_2H_5SH or $HOSC_6H_4COOH$ which would be formed cannot be stabilized further by formation of a conjugated system, in contrast to the $HSCH_2COOH$ residue.

The cleavage shown in equation IV-39 does not occur with

$$\mathrm{C_6H_5COCHCH_2C_6H_5}$$
$$\mathrm{SC_6H_4COOH}\text{-}o$$

which is unchanged by refluxing for several hours with 2 *N* sodium hydroxide, so that it appears that the —COCHAr group is necessary.

A third type of reaction of these compounds has been observed (38) with formation of the α-hydroxyketone and, presumably, the thiol. This is probably

$$\mathrm{ArCOCH_2SR} \xrightarrow{\mathrm{NaOH}} \mathrm{ArCOCH_2OH} + \mathrm{RSH} \quad \text{(IV-40)}$$

Ar = 4-CH_3O-1-naphthyl; R = CH_2COOH.

an S_N2 reaction involving hydroxyl ion.

It is obvious that the possible reactions of compounds of the type

$$\mathrm{ArCOCH(SR)Ar}$$

are complicated, and the original literature (especially reference 38) should be considered for the details.

von Braun (74) observed that compounds of the type $C_6H_5(CH_2)_nSCH_2COCl$ gave the following reaction with aluminum chloride:

$$C_6H_5(CH_2)_nSCH_2COCl + AlCl_3 \rightarrow C_6H_5(CH_2)_nCl + C_6H_4\begin{cases} CO\text{——}CH_2 \\ (CH_2)_n\text{—}S \end{cases} \quad \text{(IV-41)}$$

Where $n = 1$ or 2, both products are obtained, but for $n = 3$, none of the cyclic compound, which would have an eight-membered ring, is obtained. The reaction is in interesting contrast to the behavior of analogous nitrogen compounds, which lose carbon monoxide and cyclize to tetrahydroisoquinolines and higher ring homologs ($n = 2$, 3, or 4) (68):

$$C_6H_5(CH_2)_nNHCH_2COCl \xrightarrow{AlCl_3} C_6H_4\begin{cases} CH_2 \\ NH \\ (CH_2)_n \end{cases} + CO \quad \text{(IV-42)}$$

The sulfur analogs do not give the loss of carbon monoxide (74).

The reaction given below is an example of the cleavage of sulfides by bromine, presumably through the sulfoxide (209).

$$S(CH_2COOH)_2 + Br_2 \xrightarrow{H_2O} [OS(CH_2COOH)_2] \quad \text{(IV-43)}$$

$$\downarrow$$

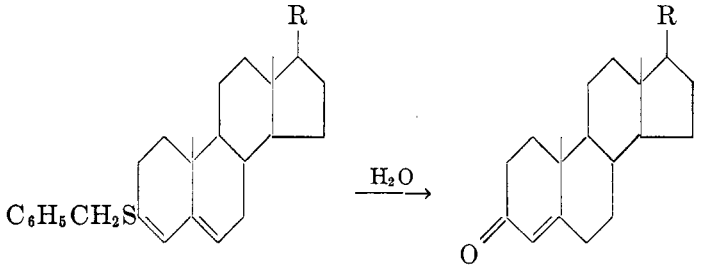
$$HOOCCH(SCH_2COOH)_2 \leftarrow HSCH_2COOH + OHCCOOH$$

There seem to be only a few compounds which contain the group RSC=C—. A series of β-alkylmercaptocrotonates, $CH_3C(SR)=CHCOOC_2H_5$, has been found to undergo more rapid cleavage than ordinary saturated sulfides (313); they are hydrolyzed by hot 10 per cent sulfuric acid and yield, when refluxed

$$CH_3C(SR)=CHCOOC_2H_5 \xrightarrow[H_2SO_4]{H_2O} RSH + CH_3COCH_3 + CO_2 + C_2H_5OH \quad \text{(IV-44)}$$

with phenylhydrazine, the pyrazolone and the mercaptan (*cf.* 376). Alkaline hydrolysis apparently attacks only the ester group, forming the corresponding β-alkylmercaptocrotonic acids (284, 313). It appears that the sulfur compounds are much more stable to acid hydrolysis than the corresponding oxygen compounds (*cf.* 11), but that the RSC=C— group, like the ROC=C— group, is more vulnerable to attack by acids, and also to replacement by nucleophilic groups, than is the corresponding saturated sulfide or ether.

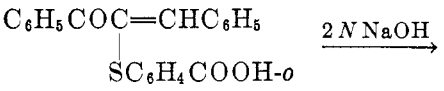
The ease of cleavage of the S—C=C bond is illustrated in the *S*-benzyl derivatives of the unsaturated steroids below (324); the sulfides are hydrolyzed by cadmium carbonate and mercuric chloride, and by very dilute aqueous hydrochloric acid, but are stable to base. If R = $OCOC_6H_5$, the *S*-benzyl group can be hydrolyzed without affecting the benzoxy group. A significant observation



(IV-45)

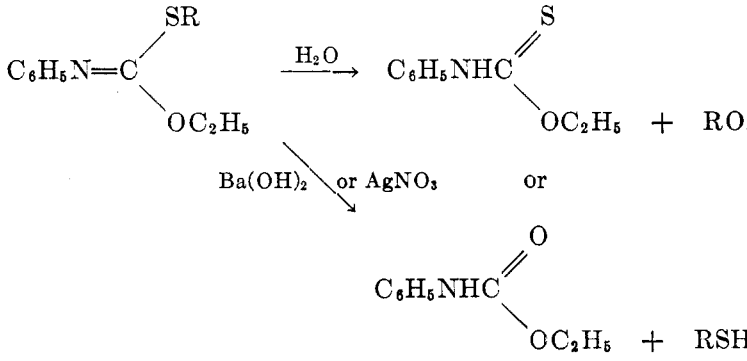
dealing with the Raney nickel desulfuration of the *S*-benzyl compound is that the use of fully active nickel (on the cholestadiene derivative, R = C_8H_{17}) leads to formation of the saturated hydrocarbon, with reduction of the double bonds; the use of nickel partially deactivated by boiling with acetone (386), however, gives desulfuration only to form $\Delta^{3,5}$-cholestadiene (324).

Compounds of the type $C_6H_5C(SR)=C(SR)C_6H_5$ are apparently readily cleaved, because all attempts to oxidize them yield benzil, $C_6H_5COCOC_6H_5$ (306). However, a somewhat similar compound is stable to alkali, at least, and undergoes a reverse aldol condensation rather than carbon–sulfur cleavage (38).



$$C_6H_5COCH_2SC_6H_4COOH\text{-}o + C_6H_5CHO \quad \text{(IV-46)}$$

Another type of compound, obtained by alkylation of the silver salt of phenylthiourethan with acetobromoglucose, followed by hydrolysis of the acetyl groups, may be mentioned here, although it might also be considered with the thiol esters (*cf.* page 47). The product can hydrolyze in two ways; alkaline hydrolysis or alcoholic silver nitrate gives thioglucose, and neutral hydrolysis yields ordi-



(IV-47)

R = $C_6H_{11}O_5$.

nary glucose (339). It would be interesting to know if this change in the point of attack is general. It is reported that $C_3H_5N{=}C(SC_2H_5)OC_2H_5$ is very stable to both acid and alkaline hydrolysis (338).

D. BENZYL SULFIDES

1. Benzyl alkyl sulfides, including benzhydryl and trityl compounds

A few benzyl compounds have been mentioned previously, but because of the number of compounds involved, it seems advisable to devote a separate section to them, including the more highly substituted compounds, such as α-phenethyl, benzhydryl, and trityl.

One of the most useful synthetic reactions involving carbon–sulfur bond cleavage is the reductive cleavage of the benzyl group from sulfur by sodium and liquid ammonia, which has been used particularly by du Vigneaud (e.g., 379) for the synthesis of thiol-containing amino acids and polypeptides. The thiol group is protected by benzylation at the beginning of the synthesis, and the protecting group is easily removed at the end, regenerating the thiol in good yield; this procedure was used in the synthesis of glutathione, for example (128). If the sodium–liquid ammonia process does not work, owing to insolubility, reduction with sodium and alcohol may be used (194).

Turning to the reactions (other than reductive cleavage) with which this review is primarily concerned, it appears from the information available that, in general, the ease of cleavage increases in the order $C_6H_5CH_2 < (C_6H_5)_2CH < (C_6H_5)_3C$. This order is not demonstrated very clearly in any one series but is implied in numerous scattered observations, and is in agreement with the behavior of arylmethyl compounds in general. The benzyl group in turn is usually much more readily cleaved than a saturated alkyl group, and resembles rather an allyl group. These relationships are the ones to be expected if the cationic stability of the hydrocarbon group is important.

In some cases, benzyl groups have been cleaved by aqueous halogen acid, although this behavior is by no means general. A recent example is the last step in a synthesis of penicillamine (377, 402), which is obtained in fair yield.

$$(CH_3)_2\underset{\displaystyle SCH_2C_6H_5}{\underset{|}{C}}CH(NHCOCH_3)COOH \xrightarrow[\text{reflux for 15 hr.}]{\text{HBr (d. = 1.49)}} (CH_3)_2\underset{\displaystyle SH}{\underset{|}{C}}CH(NH_2)COOH \quad \text{(IV-48)}$$

Penicillamine

Trityl methyl sulfide is cleaved under very mild conditions (by boiling acetic acid, or cold alcoholic silver nitrate, or cold concentrated sulfuric acid) to form methyl mercaptan and a triphenylcarbinol derivative (425); trityl phenyl sulfide

$$\underset{\text{Trityl methyl sulfide}}{(C_6H_5)_3CSCH_3} \xrightarrow{(H_2SO_4)} (C_6H_5)_3COH + CH_3SH \quad \text{(IV-49)}$$

is cleaved by alcoholic iodine, but the less highly phenylated compound, benzhydryl phenyl sulfide, $(C_6H_5)_2CHSC_6H_5$, is not affected by this reagent (408).

Cleavage reactions of a number of acids related to $ArCH_2SCH_2COOH$ have been examined, principally by Holmberg. One of the most interesting of these is the α-phenethyl derivative, which is cleaved by mercuric salts to α-phenethyl alcohol, by bromine to the corresponding bromide, and by sulfuryl chloride to the chloride (202).

$$\begin{array}{lcll} C_6H_5\overset{*}{C}H(CH_3)SCH_2COOH & + & HgCl_2 \rightarrow & C_6H_5CH(OH)(CH_3) \quad \text{(IV-50)} \\ & + & Br_2 & \text{(Br)} \\ & + & SO_2Cl_2 & \text{(Cl)} \end{array}$$

With the optically active acid, mercuric chloride racemizes the starting acid and gives inactive α-phenethyl alcohol; sulfuryl chloride gives an optically active chloride of a different sign of rotation, with no racemization of the starting material; and bromine gives an active bromide, also of different sign. The active halides can be converted back to the starting acid by treatment with

$$NaSCH_2COONa$$

and the acid formed has the same sign of rotation as the original, but the rotation is much smaller in amount, owing to partial racemization. If it is assumed, as seems reasonable, that this alkylation reaction goes with inversion, it is clear that reaction IV-50 also proceeds with inversion of the α-phenethyl group during the cleavage reaction to form the halide.

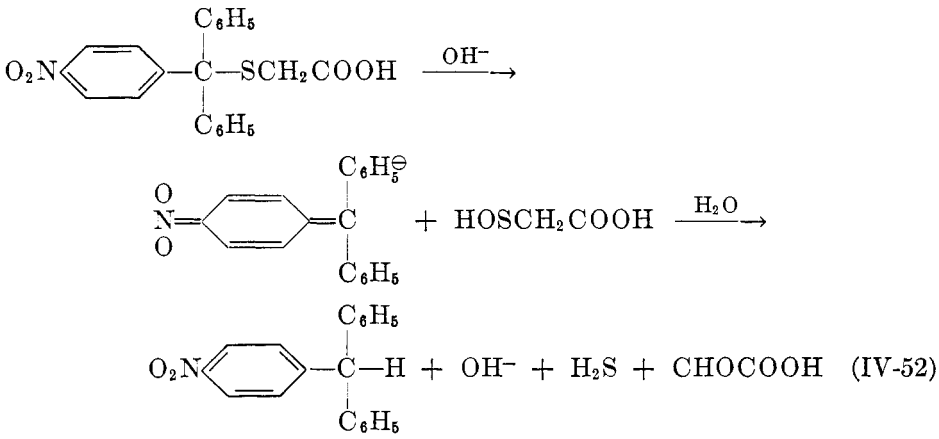
The racemization of the starting acid by mercuric chloride can be readily explained by the formation of a complex of the following type:

$$C_6H_5\overset{*}{C}H(CH_3)SCH_2COOH + HgCl_2 \rightarrow C_6H_5CH(\overset{\uparrow HgCl_2}{S})CH_2COOH \quad \text{(IV-51)}$$

The dipole present in the coördinate bond must be considered to be strong enough to form the corresponding carbonium ion, $C_6H_5(CH_3)\overset{+}{C}H$, at least to the extent necessary to cause racemization. The process is apparently similar to the racemization of active α-phenethyl halides by heavy metal salts, which occurs by formation of a similar complex (53), with racemization in the carbonium ion.

The stability of acids of the type $ArCH_2S(CH_2)_nCOOH$ to alkali is greatly diminished by a *p*-nitro group in the phenyl group. Thus, $C_6H_5CH_2SCH_2COOH$, $C_6H_5CH_2S(CH_2)_2COOH$, and $(C_6H_5)_3CSCH_2COOH$ are unchanged by boiling 1 hr. in 5 per cent alkali, but *p*-$O_2NC_6H_4CH_2SCH_2COOH$, *p*-$O_2NC_6H_4CH_2SCH_2CH_2COOH$, and *p*-$O_2NC_6H_4C(C_6H_5)_2SCH_2COOH$ are cleaved in 5 min.

(350). The effect of the nitro group is, obviously, to increase the susceptibility of the carbon attached to sulfur to attack by the hydroxyl ion, through the resonance stabilization.



The behavior of the other compounds mentioned above can be explained on a similar basis.

Tritylthioglycolic acid, $(C_6H_5)_3CSCH_2COOH$, is unaffected by aqueous alkali or by boiling with aqueous alcoholic hydrogen chloride, but is solvolyzed by concentrated sulfuric acid in the cold to give triphenylcarbinol. The next higher homolog, $(C_6H_5)_3CSCH_2CH_2COOH$, behaves similarly; both reactions are an illustration of the susceptibility of the trityl group to nucleophilic attack (220).

As would be expected from what has been said previously, dibenzyl sulfide, and the benzhydryl and trityl analogs, undergo a variety of cleavage reactions, the rate of which increases with increasing phenylation. Dibenzyl sulfide on pyrolysis (158) gives a complex mixture similar to that from dibenzyl disulfide (page 9).

Dibenzhydryl sulfide breaks down at 290°C. (at which temperature the oxygen analog, dibenzhydryl ether, is stable) as follows (359):

$$(C_6H_5)_2CHSCH(C_6H_5)_2 \xrightarrow{290°C.} (C_6H_5)_2C{=}S + (C_6H_5)_2CH_2 \quad \text{(IV-53)}$$

Dibenzhydryl sulfide

The presence of the thiobenzophenone is inferred from the blue color that appears and the formation of a complex with mercuric chloride when the reaction mixture is worked up, both of which are characteristic of this thioketone. Di-9-xanthyl sulfide gives the products analogous to those of reaction IV-53. The driving force in these reactions is apparently the increased resonance stabilization of the diaryl thioketone compared to the sulfide. The greater stability of the oxygen ethers to thermal decomposition may be a reflection of the higher carbon–oxygen bond strength (*cf.* page 10), because these high-temperature reactions probably go through a free-radical rupture of the carbon–sulfur bond.

Ditrityl sulfide, as would be expected, is decomposed under mild conditions,

such as heating below the melting point (181°C.). Treatment with hot alcoholic silver nitrate gives a quantitative yield of silver sulfide; cold concentrated sulfuric acid gives triphenylcarbinol, with a vigorous evolution of hydrogen sulfide; dry hydrogen chloride in boiling benzene gives two moles of trityl chloride and hydrogen sulfide, the trityl mercaptan initially formed being converted to trityl chloride and hydrogen sulfide (426).

A number of cleavage reactions of dibenzyl sulfide are known, in addition to the pyrolytic process mentioned above. Treatment of the sulfide with methyl iodide or other simple halide leads to the following process (311, 346),

$$(C_6H_5CH_2)_2S + \underset{\text{(excess)}}{CH_3I} \rightarrow (CH_3)_3SI + 2C_6H_5CH_2I \qquad \text{(IV-54)}$$

over several intermediate sulfonium compounds. The reaction depends on the preferential cleavage of the benzyl halide from sulfonium salts such as $[(C_6H_5CH_2)_2\overset{+}{S}CH_3]I^-$, for reasons discussed above (page 25). A reaction of similar type is the formation of a tribenzylsulfonium salt from dibenzyl sulfide, thionyl chloride, and ferric chloride (195).

$$3(C_6H_5CH_2)_2S + FeCl_3 \xrightarrow{SOCl_2} (C_6H_5CH_2)_3S^+FeCl_4^- \cdot (C_6H_5CH_2)_3SCl \qquad \text{(IV-55)}$$

The reaction may involve a cleavage of the dibenzyl sulfide, followed by addition of benzyl halide to unchanged sulfide, or it might proceed through a one-step bimolecular process, in which one molecule of sulfide (doubtless as a ferric chloride complex) alkylates a second molecule. The alkylation of sulfides by alkyl halides, to form sulfonium compounds, incidentally, is strongly catalyzed by ferric chloride (195) or mercuric iodide (189); in fact, if dibenzyl sulfide is treated with methyl iodide in the presence of mercuric iodide, the expected sulfonium salt, $[(C_6H_5CH_2)_2SCH_3]^+HgI_3^-$ is formed instead of the product indicated by equation IV-54 (189). The corresponding iodide, $[(C_6H_5CH_2)_2\overset{+}{S}CH_3]I^-$, cannot be obtained by the action of methyl iodide on dibenzyl sulfide, either one or two benzyl groups being replaced by methyl, as in equation IV-54.

A reaction similar to that of equation IV-55 has been observed with aluminum chloride and dibenzyl sulfide (256). A curious transformation of dibenzyl sulfide perchlorate has been described by Hinsberg (192); the product, $C_{21}H_{20}S$, is

$$(C_6H_5CH_2)_2S \cdot 2HClO_4 \xrightarrow{\text{base}} \underset{\displaystyle C_6H_5CH_2}{\overset{\displaystyle |}{C_6H_5CHSCH_2C_6H_5}} \qquad \text{(IV-56)}$$

$$(C_{21}H_{20}S)$$

obtained in two forms, but it has not been identified by synthesis, and a compound of the given structure is not reported in the literature. If the structure given is correct, the reaction closely resembles the Stevens rearrangement. This reaction, which was first observed with quaternary ammonium compounds, has been extended to sulfonium salts (415).

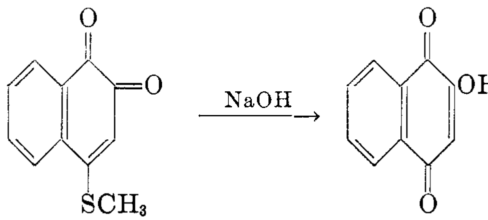
$$C_6H_5COCH_2\overset{+}{\underset{\displaystyle CH_2C_6H_5}{S}}CH_3 \xrightarrow{OH^-} C_6H_5CO\underset{\displaystyle CH_2C_6H_5}{C}HSCH_3 \qquad \text{(IV-57)}$$

It is possible that the perchlorate in equation IV-56 yields first tribenzylsulfonium perchlorate, which then rearranges by a process similar to that of equation IV-57. However, Hinsberg's results need further work to prove the nature of the product before much speculation is in order.

von Braun's cyanogen bromide cleavage of sulfides (*cf.* page 15) has been applied to substituted dibenzyl sulfides (70), which cleave less rapidly than benzylamines; all five of the compounds studied, which are methyl-substituted dibenzyl sulfides, are cleaved in 30 min. at 100°C. and it is found that the *o*-methyl-substituted ones cleave more slowly than the *m*- or *p*-isomers. This is doubtless due to a decrease caused by the ortho substituent, in the rate of formation of the probable intermediate:

$$(ArCH_2\underset{\displaystyle CN}{S}CH_2Ar')^+Br^-$$

The compound below, which is essentially a benzyl sulfide with α,β-unsaturation, gives replacement of the methylthiol group on treatment with aniline, yielding 1,2-naphthoquinone monoanilide or the dianilide, depending on conditions. It is cleaved by alkali as indicated (459).



$+ CH_3SNa$ (IV-58)

The sulfur is also removed by chlorination, forming 3,4-dichloro-1,2-naphthoquinone (459).

2. Benzyl aryl, and related sulfides

Because of the amount of information available on benzyl aryl sulfides, it seems advisable to consider them separately from the other alkyl aryl sulfides. This section also includes benzhydryl and trityl aryl sulfides.

A detailed study of the cleavage of benzyl phenyl sulfide (184) indicates that it is not cleaved to thiophenol by aqueous halogen acids, although the sulfide is completely decomposed in some cases; with hydrogen bromide in glacial acetic acid, under optimum conditions, a maximum of about 15 per cent of free thiophenol is formed, along with an equal amount of phenyl thiolacetate. Some cleavage is also obtained using aluminum chloride or zinc chloride with benzoyl chloride, with the formation of phenyl thiolbenzoate.

Aluminum bromide gives nearly quantitative cleavage of the sulfide accord-

ing to the equation:

$$\underset{\text{Benzyl phenyl sulfide}}{C_6H_5SCH_2C_6H_5} + AlBr_3 \rightarrow C_6H_5SAlBr_2 + C_6H_5CH_2Br \quad \text{(IV-59)}$$

$$C_6H_5SAlBr_2 \xrightarrow{H_2O} C_6H_5SH$$

Thiophenol

The benzyl bromide formed reacts with the solvent (chlorobenzene) to form a mixture of 3,3′- and 3,4′-dichlorodiphenylmethanes, the alkylation being accompanied by a halogen exchange (409). The reaction is complete after a few hours at room temperature in chlorobenzene as solvent, and requires a molar proportion of aluminum bromide; added water decreases the per cent of thiophenol formed, but it requires several moles of water to deactivate a mole of aluminum bromide, and the reaction is not affected by oxygen. Rate studies show that the reaction is first order in the sulfide, and is independent of the aluminum bromide concentration if that is present in greater than a mole-to-mole ratio. The activation energy is 25.8 kcal./mole.

$$\underset{\text{Benzyl phenyl sulfide}}{C_6H_5SCH_2C_6H_5} + AlBr_3 \xrightarrow{k_1} C_6H_5SCH_2C_6H_5 \xrightarrow{k_2}$$

$$C_6H_5SCH_2C_6H_5 \xrightarrow{AlBr_3} C_6H_5SAlBr_2 + C_6H_5CH_2Br \quad \text{(IV-60)}$$

$$C_6H_5SAlBr_2 \xrightarrow{H_2O} C_6H_5SH$$

The following mechanism is in agreement with the observations if k_2 represents the slow step. This mechanism also agrees with the observations that donor solvents (e.g., ether, nitrobenzene, nitroethane, alcohol) cut down the per cent of cleavage very sharply, presumably because they compete with the sulfide for the aluminum bromide.

It is found that the order of cleavage for $ArSCH_2C_6H_5$ is as follows: Ar = 3-bromophenyl > 4-chlorophenyl > phenyl (439). This is in agreement with the mechanism proposed, because step 2 would be favored by electron-attracting groups in the Ar group.

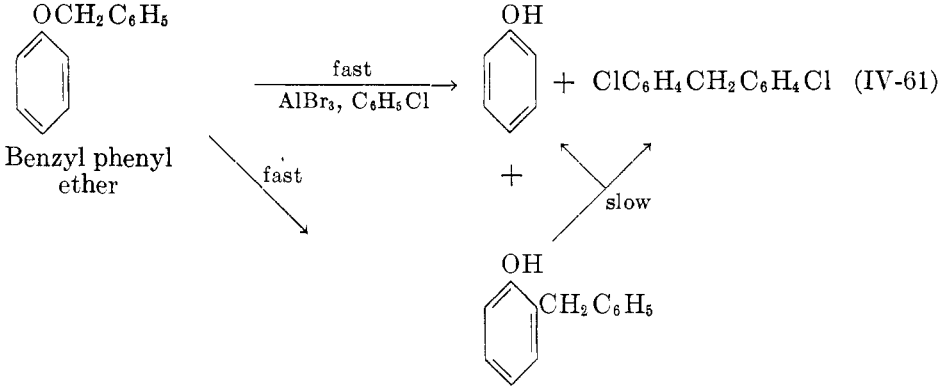
The reason for the failure of aqueous halogen acids to cleave the sulfide, which contrasts sharply with the rapid cleavage of analogous oxygen ethers (419), is not clear. It may be due to an unfavorable equilibrium in the reaction

$$C_6H_5SCH_2C_6H_5 + HX \rightleftarrows C_6H_5\overset{+}{S}(H)CH_2C_6H_5 \; X^-$$

since, as mentioned above (page 2), there is little evidence for hydrogen bonding involving sulfur, or it may be due to a slow cleavage (corresponding to k_2)

of the salt. It is possible that halogen acid cleavage of oxygen ethers in general involves a cyclic activated complex with two molecules of halogen acid, such as has been demonstrated for the cleavage of diethyl ether by hydrogen bromide in acetic acid (275), and that similar structures derived from sulfides are not stable.

The behavior of benzyl phenyl ether on treatment with aluminum bromide in chlorobenzene solution is quite different from that of the sulfide. The ether is converted extremely rapidly, even at −40°C., to a mixture of equal amounts of phenol, *o*-benzylphenol, and the same dichlorodiphenylmethanes which are obtained from the sulfide. The *o*-benzylphenol is converted slowly under these conditions to phenol and the dichlorodiphenylmethanes (409).



The action of chlorine on aryl benzyl sulfides leads to interesting results. Aryl methyl sulfides yield with chlorine the trichloromethyl derivatives, $ArSCCl_3$ (e.g., 457; for further discussion of this reaction, see page 41), but the benzyl analogs give benzal chloride and the sulfenyl chloride in anhydrous solution, or the sulfonyl chloride in water-containing solvents (24, 451, 457, 458).

$$ArSCH_2C_6H_5 + Cl_2 \xrightarrow[\text{water}]{\text{anhydrous}} \begin{matrix} ArSCl + C_6H_5CHCl_2 \\ ArSO_2Cl \end{matrix} \qquad \text{(IV-62)}$$

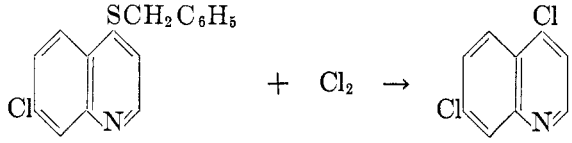
Bromine may also bring about the cleavage in some cases (452). The reaction may be considered to involve in general the formation of a halogen addition product as intermediate, which may be formulated as a sulfonium compound, and which decomposes as indicated below (24):

$$ArSR + X_2 \rightarrow \left[\begin{matrix} ArSR^+ \\ | \\ X \end{matrix}\right] X^- \rightarrow ArSX + RX \qquad \text{(IV-63)}$$

If R is benzyl, the chlorine addition product cannot be isolated, because the second step apparently takes place too rapidly (458), a result which is in agreement with the usual behavior of sulfonium compounds containing benzyl groups. If water is present, the sulfenyl halide can be oxidized to the sulfonyl halide.

An interesting extension of this reaction involves the cleavage of the carbon–

sulfur bond in the other direction (24); the explanation of this reaction is



(IV-64)

doubtless that the sulfonium intermediate of reaction IV-63 is decomposed by nucleophilic displacement by chloride ion of the sulfur from the 4-position of the quinoline nucleus; the susceptibility of the 2- or the 4-position in pyridine and quinoline to nucleophilic attack is well known.

The attack of metallic sodium on benzyl phenyl sulfide results in cleavage, in contrast to its action on the corresponding ether, which gives, in addition to cleavage, a rearranged product (368).

$$C_6H_5SCH_2C_6H_5 + Na \longrightarrow C_6H_5SNa + NaCH_2C_6H_5 \xrightarrow{H_2O}$$

Benzyl phenyl sulfide

$$C_6H_5SH + CH_3C_6H_5 \quad \text{(IV-65)}$$

$$C_6H_5OCH_2C_6H_5 + Na \longrightarrow C_6H_5ONa + NaCH_2C_6H_5$$

Benzyl phenyl ether

$$C_6H_5CHOHC_6H_5$$

A plausible mechanism for the oxygen compound involves the shift of an aryl group, without its pair of electrons, in the ion $C_6H_5OCHC_6H_5^{\ominus}$ to yield $^{\ominus}OCH(C_6H_5)_2$ (*cf.* the benzilic acid rearrangement), but a similar shift evidently does not occur in the sulfur series.

Study of more highly phenylated sulfides shows that the ease of cleavage increases with increasing number of phenyl groups, as would be expected. Thus, benzhydryl phenyl sulfide, $C_6H_5SCH(C_6H_5)_2$, is cleaved very rapidly to thiophenol by aluminum bromide in chlorobenzene at 0°C., the rate being much higher than that of benzyl phenyl sulfide; it is cleaved by boiling 32 per cent hydrogen bromide in glacial acetic acid, but not by boiling aqueous 48 per cent hydrobromic acid. It is also cleaved by alcoholic silver nitrate, but not by alcoholic iodine (408).

The following reaction is undoubtedly caused by tendency to form a conju-

$$4\,(C_6H_5)_2\overset{Cl}{\overset{|}{C}}SC_6H_5 + Hg \rightarrow 2\,(C_6H_5)_2C(SC_6H_5)\text{—}C(SC_6H_5)(C_6H_5)_2 \quad \text{(IV-66)}$$

$$\downarrow$$

$$(C_6H_5)_2C(SC_6H_5)_2 + (C_6H_5)_2C{=}C(C_6H_5)_2$$

gated system, by elimination of the phenylthiol groups (362); the case is somewhat analogous to the reversible loss of halogen from $(C_6H_5)_2C(Cl)C(Cl)(C_6H_5)_2$ to form $(C_6H_5)_2C{=}C(C_6H_5)_2$ (293).

Phenyl trityl sulfide is even more reactive; it is cleaved by alcoholic iodine, giving triphenylcarbinol, and, in contrast to benzyl phenyl sulfide, is split by

aluminum bromide in donor solvents, such as ether, alcohol, and nitrobenzene (408). It is also split rapidly by boiling 32 per cent aqueous hydrobromic acid, by dilute hydrochloric acid, by aqueous zinc chloride (408), and by cold concentrated sulfuric acid (220).

It has been shown (255) that phenyl trityl sulfide is dissociated thermally at 200°C. to form triphenylmethyl radicals, which are identified by their absorption

$$C_6H_5SC(C_6H_5)_3 \xrightarrow{200°C.} C_6H_5S\cdot + (C_6H_5)_3C\cdot \qquad \text{(IV-67)}$$

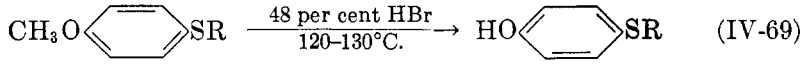
spectra; the fate of the phenylthiol radicals is not known. The oxygen analog, $C_6H_5OC(C_6H_5)_3$, apparently undergoes a similar reaction; at least, it is decomposed by heating at 241°C. for 2 hr. (450). Similar observations on bis(9-phenylthio-9-fluorenyl) show that this compound is decomposed to diphenyl disulfide and difluorenylethylene both thermally and photochemically (362).

The tendency of the carbon–sulfur bond in $C_6H_5SC(C_6H_5)_3$ to split with radical formation is emphasized by Ziegler's observation (450) that it is cleaved by sodium–potassium alloy, a reaction also shown by the oxygen analog.

$$C_6H_5SC(C_6H_5)_3 \xrightarrow{\text{Na–K alloy}} C_6H_5SK + KC(C_6H_5)_3 \qquad \text{(IV-68)}$$

E. ARYL ALKYL SULFIDES

There are a considerable number of observations which indicate the resistance of the $ArSCH_3$ group to cleavage by acidic reagents, compared to $ArOCH_3$. For instance, compounds of the type p-$CH_3OC_6H_4SR$ give only the following reaction with 48 per cent hydrobromic acid, with none of the thiophenol that would be formed by cleavage of the—SR bond, where R is CH_3 or some other simple primary alkyl group (403).



(IV-69)

Similar observations have been made on a series of 2-methyl-4-methoxyphenyl alkyl sulfides, except that in this case there is some decomposition to m-cresol, with the liberation of hydrogen sulfide (404).

The compound p-$CH_3C_6H_4SCH_3$ is found to be unchanged by treating with hydriodic acid in a sealed tube at 160°C.; hydrogen bromide–acetic acid or alcoholic potash in a sealed tube at 180–200°C. gives only traces of the thiol, as does aluminum chloride at 100°C. (15).

Studies on the application of the Zeisel methoxyl method to the determination of $—SCH_3$ on a number of benzene derivatives containing one or two $—SCH_3$ groups show that even with the addition of phenol to hydriodic acid (d = 1.7), the reaction is much slower than with the $—OCH_3$ compounds (303). The determination is further complicated by the fact that methyl mercaptan is formed, as well as methyl iodide, and the results tend to be low, especially with $C_6H_5SCH_3$ itself (303). After refluxing for 7 hr. with hydriodic acid, p-$CH_3C_6H_4SCH_3$ gives half the theoretical amount of methyl iodide, but the p-thiocresol has been decomposed completely (10). Mercuric iodide has been suggested as a catalyst

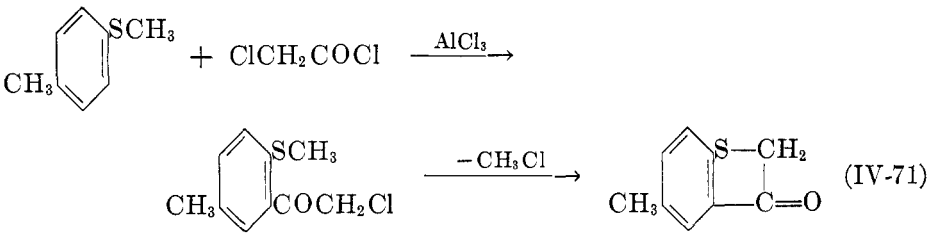
for the determination (328), but the results all in all look rather unsatisfactory as an accurate analytical method.

It is well known that phenyl alkyl ethers can be cleaved readily by Grignard reagents at temperatures above 100°C. (e.g., 385). The corresponding sulfides are not split under these conditions; methyl phenyl sulfide is metalated in the methyl group by butyllithium in ether (172), and in the nucleus by a Grignard reagent at 150°C. (173). At similar temperatures, butyllithium metalates the higher alkyl phenyl sulfides both in the side chain and in the nucleus, and splits the carbon–sulfur bond on both sides, the proportion of the products varying with the R group (173).

$$C_6H_5SR \xrightarrow[\text{then } CO_2]{C_4H_9Li,} C_6H_5COOH + RSH + C_6H_5SH + C_6H_4(SR)COOH\text{-}o \quad \text{(IV-70)}$$

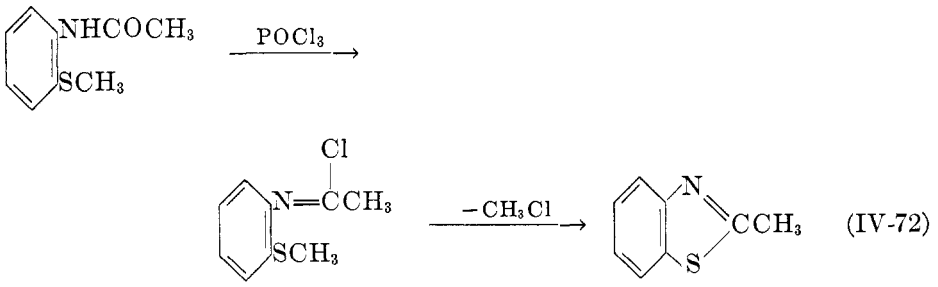
Cyanogen bromide does not seem to be effective in cleaving the —SCH_3 group (213).

There are a number of interesting cases in which methyl halide is eliminated from an —SCH_3 and an ortho-halogenated group, with ring-closure; this was first observed (15) in the acylation of methyl *p*-tolyl sulfide with chloroacetyl chloride, which yields a thionaphthene. The chloroacetyl derivative was not



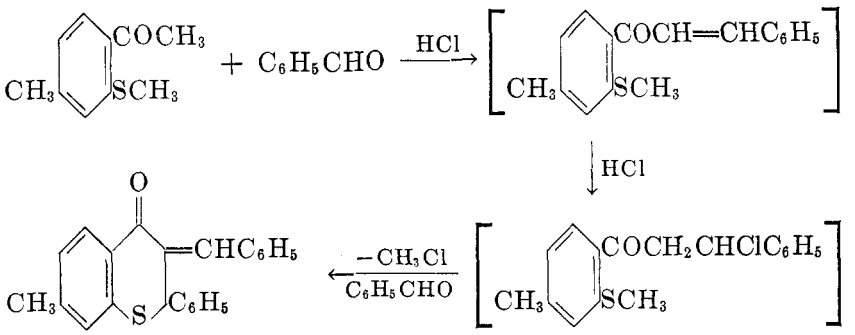
(IV-71)

isolated as an intermediate, but later work on the bromoacetyl compound (247, 248) showed that it loses methyl bromide very readily, forming the thionaphthene, presumably through the intermediate formation of a cyclic sulfonium salt (247). The cleavage thus occurs at the sulfonium stage. A similar reaction is the following, in which a benzothiazole is formed (460),



(IV-72)

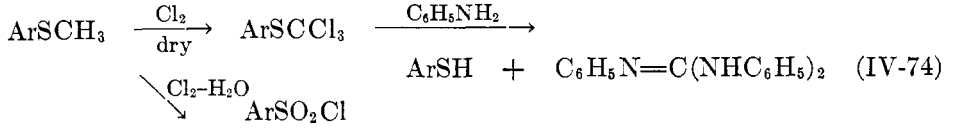
and the formation of a benzothiochromanone (16).



(IV-73)

The fact that reaction does not occur with the methoxy analog may indicate that the corresponding oxonium salt does not form sufficiently to allow the cleavage of the methyl group and cyclization to occur. The driving force in reactions IV-71 and IV-72 is probably the formation of the unsaturated heterocyclic ring, with consequent increase in stability (for another somewhat similar reaction, see reference 243).

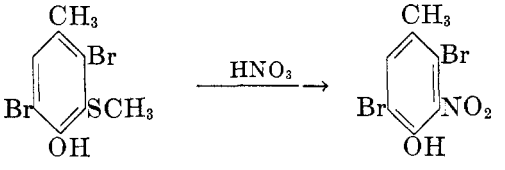
The action of halogens, and chlorine in particular, on compounds of the type $ArSCH_3$ (*cf.* page 37) has been studied; the first product of chlorination is usually the $—SCCl_3$ derivative (453, 455) and this can be converted to the thiophenol in several ways.



(IV-74)

In the presence of water, the sulfonyl chloride may be obtained (458).

The $—SCH_3$ group can be displaced from a benzene ring by a nitro group, if it is ortho or para to a hydroxyl group (454, 456). The reaction obviously is an electrophilic attack at a carbon with high electron density, and is different from



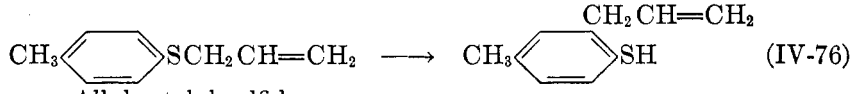
(IV-75)

those previously discussed in that the sulfur is removed from the aromatic ring.

It appears that in $2,4\text{-}(O_2N)_2C_6H_3SCH_2CH_2OH$ the sulfur may be removed by alkali from the ring by a nucleophilic attack (42), as would be anticipated from the presence of the nitro groups.

A few compounds of the structure ArSR, where R is a secondary alkyl group, have been cleaved in low yield with aluminum chloride (16) and acetic acid–zinc chloride (410), the products being mainly olefin and thiophenols.

The allyl phenyl sulfides rearrange to some extent on heating (218).



Allyl *p*-tolyl sulfide (IV-76)

The reaction is less than half complete after 4 hr. at 228–264°C., and is thus very much slower than that of the analogous oxygen compound, which gives 75 per cent rearrangement in less than 3 hr. at 200°C. (235). Nothing is known about the kinetics of the process represented by equation IV-76; it would be interesting to know the effect on the rate of substituents in the allyl group and in the nucleus, and to determine if the rearrangement of a crotyl group is accompanied by attachment of the γ-carbon to the aromatic nucleus. Treatment of allyl phenyl sulfide with zinc chloride–acetic acid seems to give a mixture of mono- and diallylated thiophenols (410).

There is a marked contrast, likewise, between allyl aryl ethers and sulfides in their behavior toward organometallic compounds; the sulfide shows the following behavior (266).

$$C_6H_5SCH_2CH{=}CH_2 + C_6H_5MgBr \xrightarrow[78°C.]{6\text{ hr.}}$$

Allyl phenyl sulfide

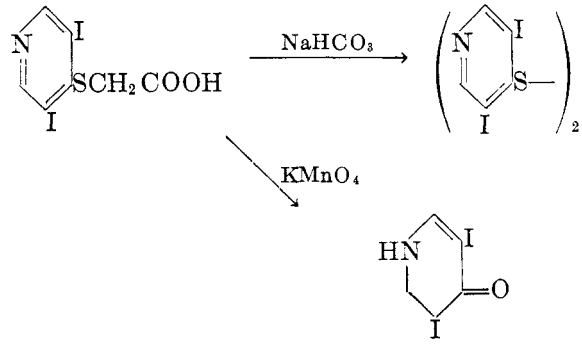
$$C_6H_5CH_2CH{=}CH_2 + C_6H_5SH + \text{starting material} \quad \text{(IV-77)}$$

(48 per cent) (35 per cent) (40 per cent)

The oxygen analog, on the other hand, is completely split by the phenyl Grignard at lower temperatures (264). The same contrast is observed between $C_4H_9SCH_2CH{=}CH_2$ and $C_8H_{17}OCH_2CH{=}CH_2$ (*cf.* page 25) (266).

Among the sulfides containing other unsaturated groups may be mentioned $C_6H_5SCH_2COCH_3$, which yields thiophenol after treatment with alcoholic potash (116), and 2-CH_3O-5-CH_3-$C_6H_3SCH_2COOH$, which is not affected by hydriodic acid below 150°C., and above that temperature yields methyl iodide and methyl mercaptan (170). The compound $CH_3C(SC_6H_5){=}CHCOOH$ is cleaved slowly by alkali, yielding thiophenol; the reaction is not complete after heating for several hours with concentrated alkali at 135°C. (133; *cf.* page 29).

An interesting example of the effect of unsaturation and of a negatively substituted heterocyclic nucleus in promoting carbon–sulfur cleavage is given by the pyridine derivative below, which goes to the corresponding disulfide rapidly upon heating in cellosolve or upon standing in sodium bicarbonate solution at room temperature (240).

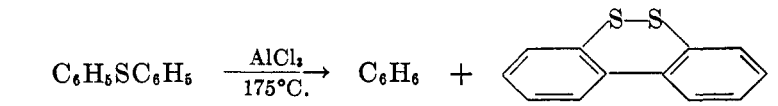


(IV-78)

The uniodinated compound does not show this behavior.

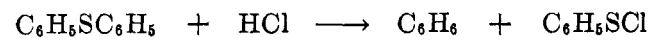
F. DIARYL SULFIDES

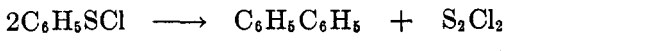
The diaryl sulfides, ArSAr′, are cleaved only with difficulty, as would be expected, except in special cases. The following reaction is reported (421),

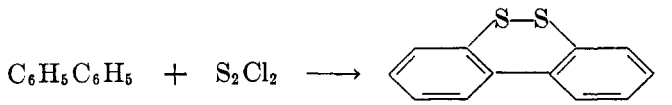


(IV-79)

and it is suggested to occur in the following steps:



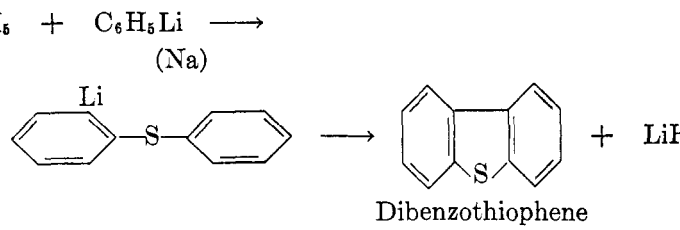




(IV-80)

However, none of the properties of the diphenylene disulfide isolated are given, so that it cannot be identified conclusively with the product later synthesized by an unambiguous method (26). Under milder conditions, diphenyl sulfide is acylated normally by acetyl chloride and aluminum chloride, without cleavage (121).

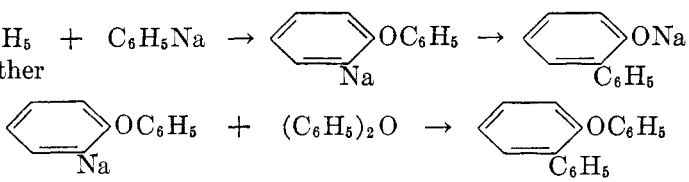
Phenyllithium and phenylsodium react with diphenyl sulfide to form dibenzothiophene; with phenyllithium, the formation of lithium hydride has been demonstrated, suggesting the following mechanism (266):



(IV-81)

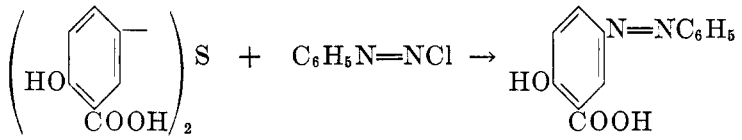
Dibenzothiophene

Diphenyl disulfide is reported to be formed by long treatment of diphenyl sulfide with phenylsodium or benzylsodium (163); the disulfide is also obtained by boiling the sulfide with sulfur (246). Diphenyl ether reacts differently with phenylsodium, giving cleavage of the ether linkage, and some arylation (265).



(IV-82)

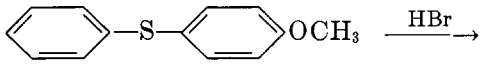
A series of diaryl sulfides containing a phenolic hydroxyl group either ortho or para to the sulfur has been found to undergo displacement of the sulfur by typical electrophilic reagents, such as chlorine, bromine, nitric acid, sulfuryl chloride, and benzenediazonium chloride (315, 316); the following reaction is representative.



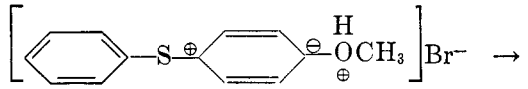
(IV-83)

The process is doubtless due to the high electron density in the positions ortho and para to the hydroxyl group; acetylation of the latter prevents the displacement in some cases (315). It is well known that a carboxyl, aldehyde, or sulfonate group which is ortho or para to a hydroxyl or amino group is frequently displaced by halogen or by other strongly electrophilic reagents (e.g., 149); apparently the sulfur in reaction IV-83 is displaced more rapidly than the carboxyl group. No data are given as to yields or the fate of the sulfur in the displacement reaction. Analogous reactions do not appear to have been observed in the oxygen series.

It has been observed that treatment of 4-methoxydiphenyl sulfide with hydrogen bromide in glacial acetic acid or with 48 per cent hydrobromic acid cleaves the aryl sulfide link, with formation of diphenyl disulfide and *p*-bromophenol (188). This reaction is obviously not an electrophilic displacement, but may take place through the oxonium salt as a nucleophilic attack.

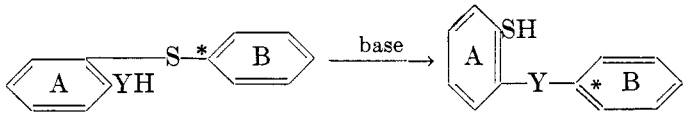


4-Methoxydiphenyl sulfide



$$C_6H_5SH + BrC_6H_4OH\text{-}p \quad \text{(IV-84)}$$

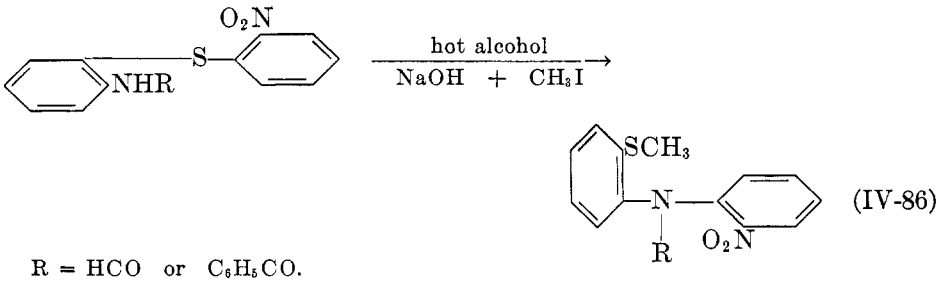
Diaryl sulfides with nitro groups ortho or para to the sulfur can give cleavage of the sulfide by attack of a nucleophilic reagent, as would be expected. The most interesting cases of this kind occur in molecules with an electron-donating group (hydroxyl, amino, or acylamino) in the ortho position to the sulfur, and represent a special case of the Smiles rearrangement (244, 428). The change can be represented as follows, in which Y is O, NH, NCH_3, $NCOCH_3$, NCOR,



(IV-85)

$NSO_2C_6H_5$, CONH, $CONC_6H_5$, etc.; the carbon with the asterisk must be made relatively positive by the presence in B of nitro groups or other strongly electron-attracting groups in the ortho or para positions. The sulfones rearrange more readily than the sulfides (135, 136), owing to the more positive character of C* in the sulfones, and similarly, the presence of three nitro groups in B makes the rearrangement more rapid (436). The presence of electron-donating groups in A also favors the shift by making Y more nucleophilic (135). The shift is base-catalyzed, and probably involves the anion from the group YH.

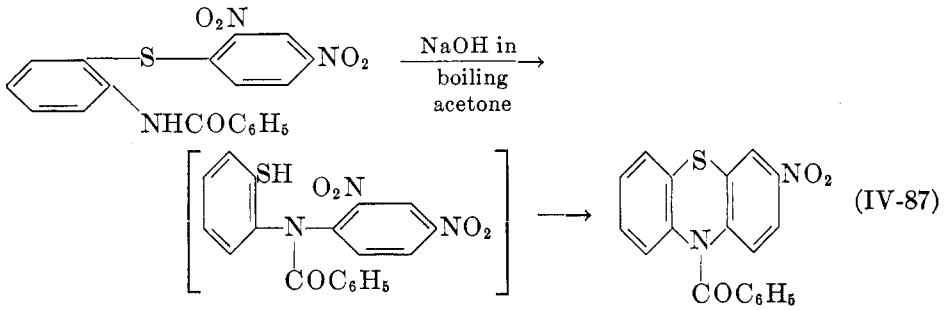
As specific examples, the following may be quoted (436):



(IV-86)

R = HCO or C_6H_5CO.

The dinitrophenyl sulfide rearranges under milder conditions, and the primary product loses nitrous acid to form a thiazone (436).



(IV-87)

All of the observations support the idea that the rearrangement is an intramolecular displacement of the sulfur from ring B by the nucleophilic center Y.

V. Thiol Acids, Dithio Acids, and Related Compounds

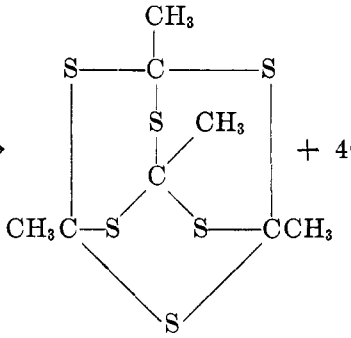
A. THIOL ACIDS

The thiol acids, RCOSH, are tautomeric with the thion acids, RCSOH; the free acids, according to spectroscopic evidence (183) are in the thiol form. In the ion, the thiol and thion forms would exist as the same resonance hybrid.

Thioformic acid is apparently unstable (13), but thioacetic acid is decomposed only at 180–200°C. in a sealed tube, to give hydrogen sulfide and sulfur (423). It does not appear that thiol acids are hydrolyzed quantitatively to carboxylic acids and hydrogen sulfide; it has been shown that thioacetic acid precipitates metallic sulfides and can be used for this purpose instead of hydrogen sulfide, but it seems probable that this is due to formation of the metal thiolacetates, CH_3COSM, and their subsequent decomposition, rather than to preliminary hydrolysis to hydrogen sulfide (314, 333). Thioacetic acid slowly forms hydrogen sulfide when heated with water at 100°C., but the reaction is evidently more complicated than a simple hydrolysis (398). Diphenylthioacetic acid, $(C_6H_5)_2$-CHCOSH, is reported to be hydrolyzed to diphenylacetic acid by boiling for 3 hr. in water, and to yield hydrogen sulfide in the cold in ethyl alcohol (412).

Thioacetic acid, when heated with zinc chloride, forms "tetraethenyl hexasul-

fide," which was originally assigned a highly improbable structure (159); its high melting point, stability, and crystallographic properties are in agreement with the hexamethylenetetramine-type structure below (152).



$$8CH_3COSH \xrightarrow{ZnCl_2} \text{"Tetraethenyl hexasulfide"} + 4CH_3COOH + 2H_2O \quad \text{(V-1)}$$

Thioacetic acid

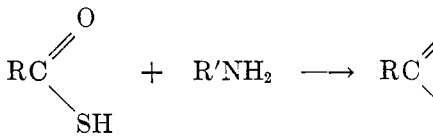
Thiol acids usually undergo esterification with alcohols to form oxygen esters, with elimination of hydrogen sulfide (317, 398), but the alternative process, with

$$CH_3COSH + ROH \rightarrow CH_3COOR + H_2S \quad \text{(V-2)}$$

$$CH_3COSH + ROH \rightarrow CH_3COSR + H_2O \quad \text{(V-3)}$$

the formation of thiol esters (equation V-3) occurs to some extent. At 77°C. both methanol and ethanol give 78 per cent of the oxygen ester (equation V-2) and 22 per cent of the thiol ester; 2-propanol gives 98 per cent of the oxygen ester, a result which is rather unexpected, and *tert*-butyl alcohol reacts very slowly, giving mainly decomposition products. Triphenylcarbinol at 100°C. gives only the thiol ester, $CH_3COSC(C_6H_5)_3$, which would be expected because of the great tendency of triphenylcarbinol to undergo carbon–oxygen cleavage to the triphenylmethyl carbonium ion.

The most interesting reactions of the thiol acids (from the standpoint of comparison to carboxylic acids) are those of amide formation.



$$RC(=O)SH + R'NH_2 \longrightarrow RC(=O)NHR' + H_2S \quad \text{(V-4)}$$

It is found that thioacetic acid reacts with primary and secondary amines very much more rapidly than acetic acid (300). Thiobenzoic acid likewise benzoylates amines much more rapidly than does benzoic acid (292, 432). Some compounds, such as anthranilic acid, which cannot be acetylated at all by acetic acid, are very rapidly acetylated by thioacetic acid (432). Thiobenzoic acid reacts fairly rapidly with aniline in chlorobenzene solution at 60°C. to form benzanilide, but there is no appreciable reaction between benzoic acid and aniline after a long period at 100°C. (292). Preliminary experiments show a striking accelerating effect of light on the reaction between thiobenzoic acid and aniline, and the

reaction may thus be a radical chain reaction (292). It has been noted that the reaction of sodium thiobenzoate and cyclohexylamine is promoted by iodine, a fact which may be evidence for a radical mechanism (4); the effect is probably not due to displacement of the equilibrium by removal of hydrogen sulfide.

It is probable that one factor which makes the thiol acids react with amines faster than the oxygen acids is the absence of hydrogen bonding between the thiol acids and amines. The hydrogen bonds between oxygen acids and amines would require several kilocalories of energy to break, which would make the activation energy greater for the oxygen acid reaction. It would be interesting to know if the thiol acids are esterified by alcohols faster than the corresponding carboxylic acids, but the requisite quantitative data do not seem to be available.

Thiol acids react with thiocyanates and isothiocyanates with cleavage of the carbon–sulfur bond in the thiol acid (434).

$$RSCN + C_6H_5COSH \rightarrow RSC(=S)NHCOC_6H_5 \qquad (V\text{-}5)$$

$$RNCS + C_6H_5COSH \rightarrow RNHCOC_6H_5 + CS_2 \qquad (V\text{-}6)$$

The reaction between an isothiocyanate and benzoic acid follows a course similar to that shown in equation V-6, but here also benzoic acid reacts more slowly (434).

Thioacetic acid is reported to yield hydrogen sulfide in liquid hydrogen fluoride, but the other presumed product of the reaction, acetyl fluoride, is not isolated (237). Thioacetic acid was shown by Kekulé in a very early paper to yield acetyl chloride and $PSCl_3$ when it was treated with phosphorus pentachloride (232).

B. THIOL ESTERS and THIOLACTONES

1. Thiol esters

Measurements of the equilibrium between mercaptans and carboxylic acids

$$R'COSR + H_2O \rightleftarrows RSH + R'COOH \qquad (V\text{-}7)$$

show that the equilibrium is much less favorable to the thiol ester than the corresponding one is to the oxygen esters. Table 3 gives the percentage ester present at equilibrium, starting with equal concentrations of acid and mercaptans, and includes data for the comparable oxygen esters (137). Similar measurements (234) on the isomeric butyl thiolbenzoates give the following percentages of ester at equilibrium, for the given R: *n*-C_4H_9, 14.4; *i*-C_4H_9, 13.6; *s*-C_4H_9, 8.9. *tert*-Butyl thiolbenzoate appears to decompose at 200°C., presumably to give isobutylene (234), and equilibrium values are not available.

The thiohydrolysis equilibrium reaction of a series of thiolacetates in liquid hydrogen sulfide at −77°C. has been measured conductimetrically (309) with

$$CH_3COSR + H_2S \rightleftarrows CH_3COSH + RSH \qquad (V\text{-}8)$$

the following results, which give the per cent of ester thiohydrolyzed in 0.1 *N* solution: CH_3, 4.5; C_2H_5, 10.1; *n*-C_3H_7, 49.3; *i*-C_3H_7, 30.8; *n*-C_4H_9, 68.0. The increase of thiohydrolysis with the increasing molecular weight seems hard to explain, unless it is due to increasing solubility of the ester in the solvent.

Recent studies (155a, 326, 332) give a detailed comparison of the rates of hydrolysis of a series of alkyl thiolacetates with those for the corresponding oxygen esters. Table 4 for alkaline hydrolysis gives the second-order rate constants,

TABLE 3

R	R′ = CH_3	R′ = C_2H_5	R′ = C_6H_5	OXYGEN ESTERS*
CH_3	16.2	15.6	18.7	69.5
C_2H_5	13.0	11.6	14.7	66.6
n-C_3H_7	12.8	11.3	14.1	66.8
$(CH_3)_2CHCH_2$	12.1	10.9	13.6	67.4

* R′ = CH_3.

TABLE 4

Alkaline hydrolysis of esters and thiol esters in 62 per cent acetone

THIOL ESTERS, CH_3COSR					ESTERS, CH_3COOR				
Temperature	R	k	E	$\log_{10}PZ$	Temperature	R	k	E	$\log_{10}PZ$
°C.		(moles/liter)$^{-1}$ min.$^{-1}$	kcal./mole		°C.		(moles/liter)$^{-1}$ min.$^{-1}$		
0	CH_3	0.466			0.4	CH_3	0.91		
			13.1	10.2				12.2	9.7
10	CH_3	1.06			10.8	CH_3	2.08		
10	C_2H_5	0.638			10.9	C_2H_5	0.908		
			14.4	10.9				12.0	9.2
20	C_2H_5	1.54			20.3	C_2H_5	1.75		
0	i-C_3H_7	0.086			10.4	i-C_3H_7	0.140		
			17.6	13.0				12.2	8.5
20	i-C_3H_7	0.818			20.2	i-C_3H_7	0.289		
10	i-C_4H_9	0.248			9.7	i-C_4H_9	0.314		
			18.5	14.0				12.4	9.1
20	i-C_4H_9	0.717			20.0	i-C_4H_9	0.676		
0	t-C_4H_9	0.0259			30.0	t-C_4H_9	0.0280		
			17.0	12.0				14.3	8.7
10	t-C_4H_9	0.0753			40.0	t-C_4H_9	0.0606		
−11.22	Allyl	0.217	17.9	14.3	−11.22	Allyl	0.246	9.9	7.7
0.00	Allyl	0.89	±0.5		0.00	Allyl	0.54	±0.5	
−11.18	Benzyl	0.18	16.0	13	−11.18	Benzyl	0.193	14.1	11.1
0.00	Benzyl	0.62	±1		0.00	Benzyl	0.59	±0.4	
−11.2	Trityl	3.4×10^{-2}	18 ± 2	14	0.00	Benz-hydryl	0.107		
0.0	Trityl	0.135							

k (in liters per mole per minute), the Arrhenius activation energies E (in kilocalories per mole), and the preëxponential term $\log_{10} PZ$ obtained from the equation $k = PZe^{-E/RT}$.

Inspection of table 4 shows that the rates of alkaline hydrolysis of the cor-

responding members of the two series are of the same order of magnitude, except for the *tert*-butyl compounds, for which the acetate is much slower than the thiolacetate. The activation energies for the thiol series show a steady increase with increasing branching of the alkyl group, while E for the oxygen series stays constant up to the *tert*-butyl acetate. This change in the activation energies is offset by a change in the $\log_{10} PZ$ term, so that the specific rate constants for the thiol esters are not very different. The larger values for the log PZ term in the thiolacetate series mean that the entropy of activation is more positive for the

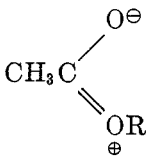
TABLE 5

Acidic hydrolysis of esters and thiol esters in 62 per cent acetone

THIOL ESTERS, CH_3COSR					ESTERS, CH_3COOR				
Temperature	R	$k \times 10^4$	E	$\log_{10}PZ$	Temperature	R	$k \times 10^4$	E	$\log_{10}PZ$
°C.		*min.*$^{-1}$			°C.		*min.*$^{-1}$		
30.0	CH_3	1.94	17.1	8.6	30.1	CH_3	52.0	15.7	9.00
40.0	CH_3	4.82			40.1	CH_3	120.0		
30.0	C_2H_5	1.34			30.1	C_2H_5	42.6		
			17.8	9.0				16.0	9.10
40.0	C_2H_5	3.49			40.0	C_2H_5	98.5		
30.0	i-C_3H_7	1.10			30.1	i-C_3H_7	20.0		
			19.7	10.2				16.3	9.00
40.0	i-C_3H_7	3.13			40.0	i-C_3H_7	47.1		
30.0	i-C_4H_9	0.996			30.1	i-C_4H_9	30.9		
			20.5	10.7				16.0	9.00
40.0	i-C_4H_9	3.19			40.0	i-C_4H_9	71.6		
30.0	t-C_4H_9	0.823			30.1	t-C_4H_9	8.00		
			20.7	10.8				23.2	13.6
40.0	t-C_4H_9	2.64			40.0	t-C_4H_9	27.0		
42.1	Allyl	6.3	16.3 ± 0.4	8.1	42.1	Allyl	68.7	17.3 ± 0.4	9.8
56.0	Allyl	18.3			56.0	Allyl	209.0		
40.0	Benzyl	2.6	19.8 ± 0.6	10.2	40.0	Benzyl	48.7	17.1 ± 0.1	9.6
56.0	Benzyl	12.1			56.0	Benzyl	186		
40.0	Trityl	76.5	29.7 ± 0.6	18.6					
56.0	Trityl	674							

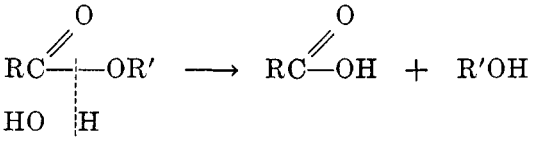
sulfur series than for the oxygen series; this can be interpreted as meaning that in entering the transition state, the oxygen esters lose more degrees of freedom, with the formation of rigid, exactly oriented structure, compared to the sulfur series. This is reasonable, in view of the larger size of the sulfur atom compared to oxygen and of the probability that the oxygen esters are solvated to a larger extent than the sulfur esters.

The results for the acidic hydrolysis, using hydrochloric acid, are given in table 5. It is evident that the thiolesters hydrolyze much more slowly than the oxygen esters under acid conditions, perhaps because the oxygen esters have much greater contributions from the resonance form



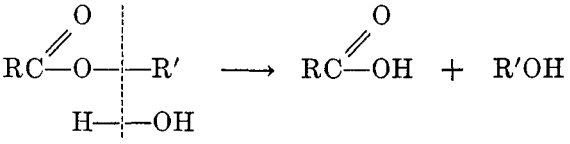
making the esters more susceptible to attack by a proton. As in the basic hydrolysis, the activation energies for the thiol esters increase with the increasing complexity of the alkyl group, while the activation energies for the oxygen esters stay essentially constant up to *tert*-butyl acetate.

It is well known that hydrolysis of esters normally proceeds by *O*-acyl cleavage.



(V-9)

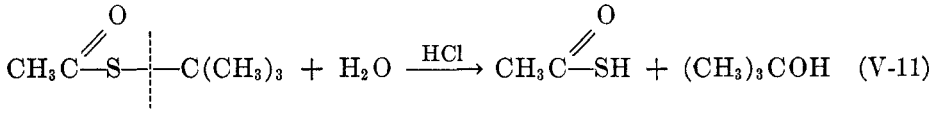
However, if the group R′ is one which possesses high cationic stability, such as allyl or substituted allyl, hydrolysis can occur by alkyl–oxygen cleavage (25, 100, 113).



(V-10)

The large increase in E and log PZ for *tert*-butyl and trityl acetates, compared to the other members of the series, makes it probable that, as suggested (100), these esters also hydrolyze by *O*-alkyl scission.

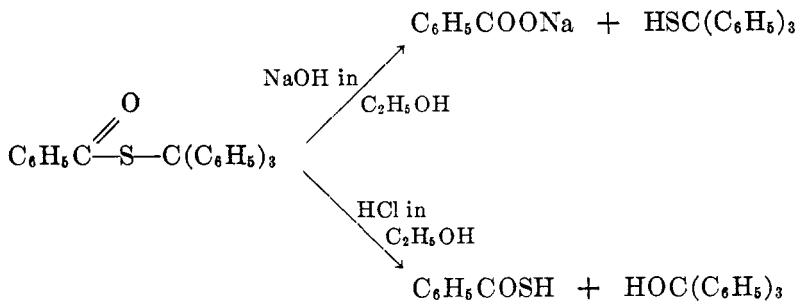
The hydrolysis of *tert*-butyl thiolacetate does not follow this course, because it is not possible to detect hydrogen sulfide in the hydrolysis mixture, which should be present if thioacetic acid is formed (326). This difference in mechanism



(V-11)

of hydrolysis of the two esters is undoubtedly due to the greater electronegativity of oxygen compared to sulfur, which would favor the formation of the *tert*-butyl carbonium ion from the oxygen ester.

The acid hydrolysis of trityl thiolbenzoate does lead to *S*-alkyl cleavage, however, a result to be attributed to the high cationic stability of the trityl group; alkaline hydrolysis leads to *S*-acyl cleavage, with the formation of trityl mercaptan (220, 221).



(V-12)

The esters of trityl mercaptan are split by concentrated sulfuric acid, as well as by alcoholic silver nitrate and by boiling acetic acid, observations which emphasize the ease of cleavage of the trityl group (425).

The thiolbenzoate below is hydrolyzed by alkali with *S*-acyl cleavage (350),

$$C_6H_5COSC(C_6H_5)_2COC_6H_5 \xrightarrow{NaOH} C_6H_5COONa + HSC(C_6H_5)_2COC_6H_5 \quad (V\text{-}13)$$

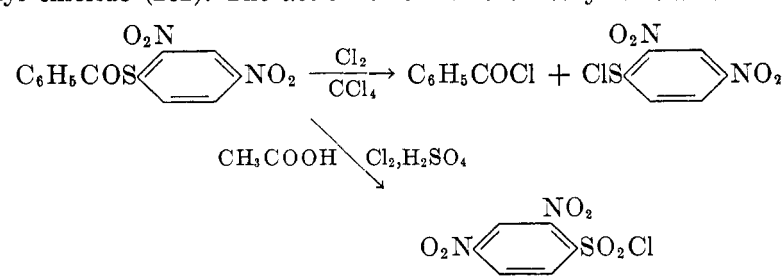
because of the lower cationic stability of the benzoylbenzhydryl group.

Thiol esters react normally with Grignard reagents to form tertiary carbinols (187), and they are reported to yield trialkylsulfonium iodides on long standing with alkyl iodide (302). The action of carbonyl reagents on unsaturated thiol esters of the type shown below yields the derivative of the corresponding carbonyl compound (20, 376):

$$CH_3(CH_2)_3CH{=}CHSCOCH_3 + H_2NNHCONH_2 \rightarrow CH_3(CH_2)_4CH{=}NNHCONH_2 + CH_3CONHNHCONH_2 \quad (V\text{-}14)$$

The group $-\overset{|}{C}{=}\overset{|}{C}-$ (SR) evidently undergoes a ready nucleophilic displacement, just as the corresponding oxygen function does.

Thiol esters can be converted by halogens or halogenating agents to sulfonyl halides or, under anhydrous conditions, to sulfenyl halides, similar to the reaction of sulfides described above (page 37). With chlorine in carbon tetrachloride, the sulfenyl chloride is formed quantitatively (154), while chlorination in concentrated sulfuric acid, followed by addition of aqueous acetic acid, gives the sulfonyl chloride (262). The action of chlorine on ethyl thiolacetate in water



(V-15)

gives ethanesulfonyl chloride in 71 per cent yield, and benzyl thiolbenzoate behaves similarly (124). Phosphorus pentachloride is reported to yield benzoyl chloride and diethyl disulfide from ethyl thiolbenzoate (392).

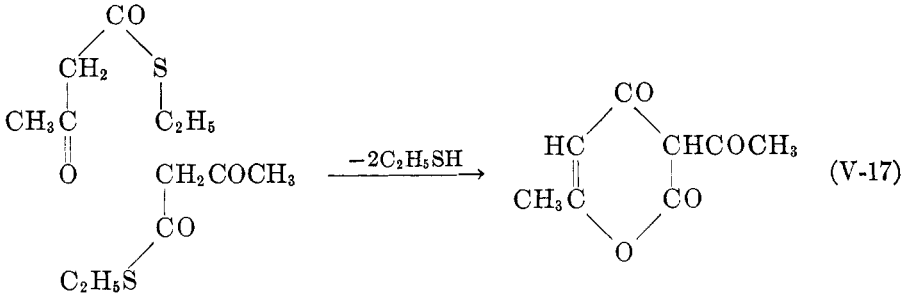
Peracetic acid oxidation of benzyl thiolbenzoate gives two moles of benzoic acid; butyl thiolbenzoate gives benzoic acid, and a small yield of butanesulfonic acid. With benzyl thiolacetate, the reaction apparently proceeds through a thiolsulfonate, because this can be isolated (92).

$$\underset{\text{Benzyl thiolacetate}}{CH_3COSCH_2C_6H_5} \xrightarrow[CH_3CO_3H]{\text{1 mole}}$$

$$C_6H_5CH_2SO_2SCH_2C_6H_5 \xrightarrow{CH_3CO_3H} C_6H_5CH_2SO_3H \quad \text{(V-16)}$$
(40 per cent)

If the α-ketosulfones or -sulfoxides, RCOSOR′ or $RCOSO_2R'$, are formed as intermediates in the oxidations, they evidently disproportionate or are cleaved by further oxidation.

Ethyl thiolacetate readily undergoes the Claisen condensation to form ethyl acetothiolacetate (23), $CH_3COCH_2COSC_2H_5$; this compound, like acetoacetic ester, forms metallic salts, but all except the copper derivatives decompose rapidly with precipitation of sulfides (or mercaptides?). The keto ester on heating forms dehydracetic acid, with much greater speed than acetoacetic ester.

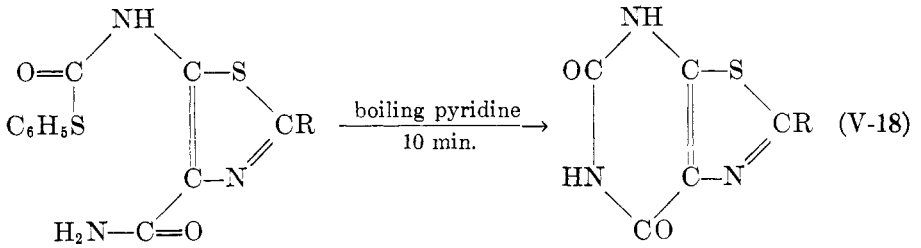


(V-17)

A mixture of equimolar amounts of $CH_3COOC_2H_5$ and $CH_3COSC_2H_5$ gives with sodium a mixture consisting of 98 per cent of $CH_3COCH_2COSC_2H_5$ and 2 per cent of acetoacetic ester. Unfortunately it is not known whether mercaptan or alcohol is eliminated in the condensation, so that speculation on the mechanism of the condensation is not warranted. However, treatment of ethyl thiolacetate with acetone and metallic sodium yields $CH_3COCH_2COSC_2H_5$ and no $CH_3COCH_2COCH_3$ (23). This might be due to one or both of the following reasons: (*1*) the anion $CH_2COSC_2H_5^{\ominus}$ is more stable (i.e., derived from a stronger acid) than $CH_2COCH_3^{\ominus}$; (*2*) the acylation of the former ion proceeds more rapidly than that of the latter.

The behavior of esters of thiophenol differs in some important respects from that of phenol esters; thus, treatment of a thiophenol ester, ArSCOR, with

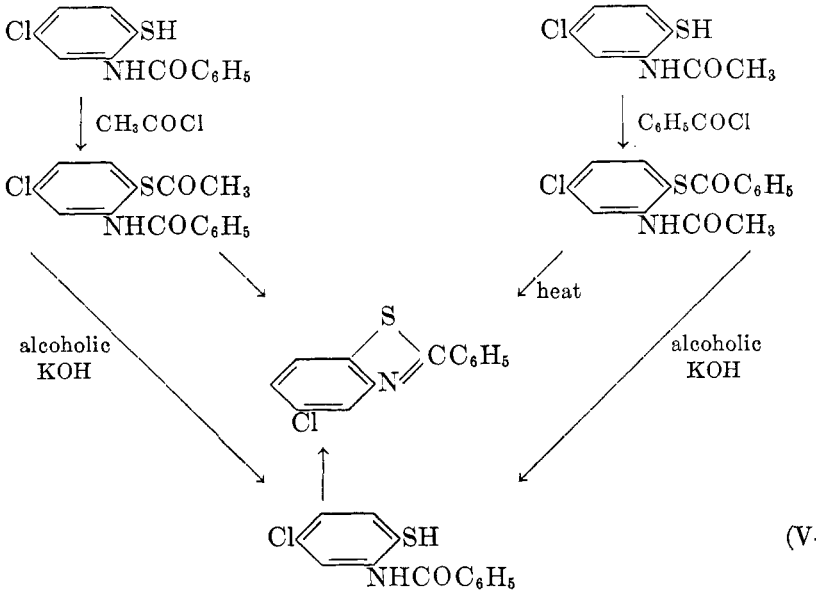
aluminum chloride does not lead to a Fries rearrangement to $Ar'(SH)COCH_3$ (1,2 or 1,4), but instead gives starting material or decomposition products (15, 83). The esters of thiophenols frequently do not seem to undergo cleavage as readily as their oxygen analogs, but in the case given below the cyclization proceeds very rapidly (103); the smooth cyclization is perhaps due to the fact



(V-18)

that the elimination of thiophenol is a reversible process, which is pushed to completion by pyridine.

Two isomeric mixed acyl derivatives can be obtained from the *N*-acyl derivatives of the aminothiophenol shown below (250, 251), whereas with aminophenols,

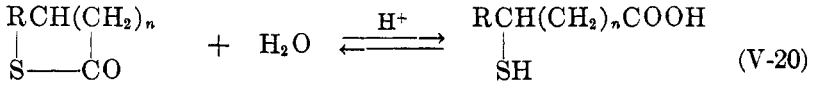


(V-19)

acyl interchange occurs during acylation and only one diacyl compound is obtained. The two diacylaminothiophenols do undergo an acyl interchange during saponification, because only one acylamino compound is formed. The isomeric diacyl derivatives, on heating or on saponification followed by recrystallization from alcohol, yield the same benzothiazole in all the cases examined, the removal of the acyl group being a function of the group and not of its attachment to nitrogen or sulfur (251).

2. *Thiolactones*

In addition to the usual scattered observations, which are as unilluminating as usual, the literature contains a very complete study of the rates and equilibria of hydrolysis for γ- and δ-thiolactones (335). For the equilibrium



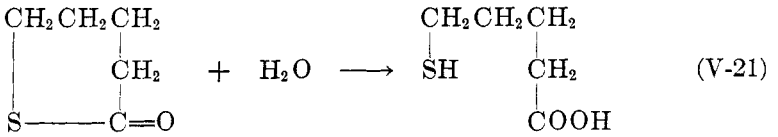
(V-20)

$n = 2,3.$

the rate constant for the hydrolysis is k_h and for lactonization is k_l; the equilibrium constant is $K = k_h/k_l$ = (acid)/(lactone). Measurement of the temperature coefficient of the reaction allows the calculation of the activation energy E and the preëxponential term $\log_{10}PZ$ for the hydrolysis and lactonization step, as well as the heat of the reaction. The values for the two rate constants and the equilibrium constant are found to be identical, in the case of the two γ-thiolactones studied with sulfur attached to a primary carbon, regardless of whether the equilibrium is approached from the side of the thiolactone or of the thiol acid. However, with γ-thiovalerolactone and its homolog, γ-thiocaprolactone (not given in table 6), the equilibrium and rate constants are markedly different, depending on the starting material. These thiolactones contain the sulfur on a secondary carbon, instead of a primary one, and it appears that some other process is occurring, in addition to the postulated equilibrium (equation V-20), such as polymerization of the lactone to form a linear polyester, loss of hydrogen sulfide, or replacement of the —SH group by hydroxyl or chlorine. The study of a thiol acid–thiolactone pair containing a tertiary thiol group would be of much interest.

The alkaline hydrolysis of the γ-thiolactones goes very rapidly, but the rate "constants" decrease rapidly as the reaction progresses, accompanied by disappearance of —SH, as determined by iodine titration. The rates of alkaline hydrolysis of γ-butyrolactone and γ-valerolactone have been measured and do not show similar anomalies (185).

The only δ-thiolactone investigated in this study (335) showed behavior markedly different from that of the γ-compounds. In water solution, the equilibrium is entirely on the side of the δ-thiol acid, although the latter can be lactonized, with loss of water, by heating.



(V-21)

The hydrolysis of the δ-thiolactone occurs in neutral solution as well as in acid solution, and the rate constant for the hydrolysis by neutral water molecules can be determined. The alkaline hydrolysis also takes place very rapidly. The corres-

ponding oxygen compound, δ-valerolactone, exists at equilibrium with the hydroxy acid to the extent of 25 per cent (197). Thus, as in the case of the mercaptan–carboxylic acid equilibria discussed above (page 47), the thiolactones at equilibrium show more of the open-chain form than their oxygen analogs do.

TABLE 6

Hydrolysis of thiolactones in aqueous acid

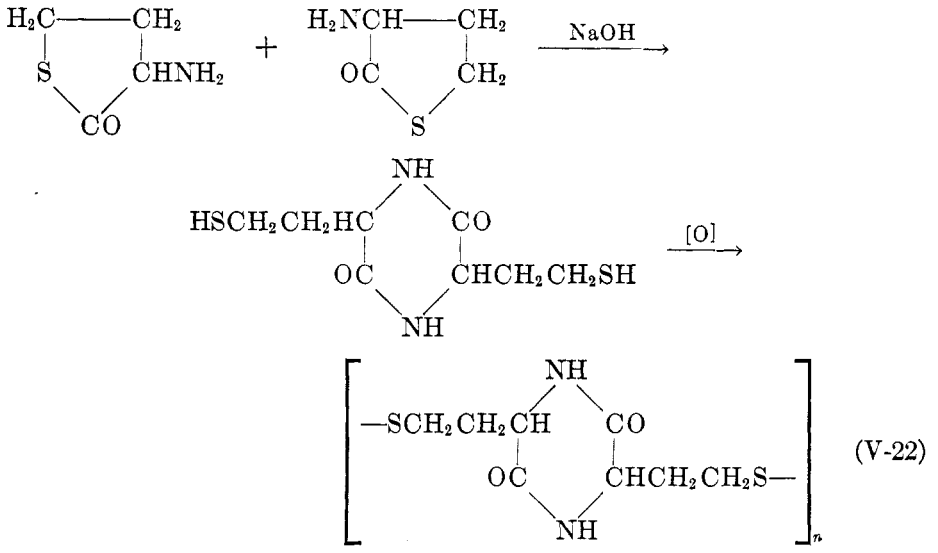
TEMPERATURE	$k_h \times 10^4$	$k_l \times 10^4$	K	E_h	$\log_{10}PZ$	E_l	$\log_{10}PZ$
1. $\underset{|}{C}H_2CH_2\underset{|}{C}H_2$ S——CO							
°C.							
25	7.24	8.46	0.856	18.5	10.4	17.7	9.91
35	19.9	22.3	0.892				
2. $\underset{|}{C}H_2CH(COOH)\underset{|}{C}H_2$ S——CO							
25	4.25	3.80	1.12	19.0	10.5	19.7	11.0
35	11.8	11.1	1.07				
3. $CH_3\underset{|}{C}HCH_2\underset{|}{C}H_2$ S——CO							
25*	22.7	9.9	2.29				
	9.6	20.1	0.48				
35*	53.5	23.7	2.26				
	25.4	53.5	0.48				

* The first value in each pair is that obtained from the lactonization reaction; the second is from the hydrolysis reaction.

Comparable to the observation above on the equilibrium between the δ-thiol acid and the δ-thiolactone is the fact that the ether thiol acid does *not* form a thiolactone (134); the ring in this case also would be a six-membered ring.

$$HSCH_2\underset{\displaystyle SH}{\underset{|}{C}}HCH_2OCH_2COOH$$

The α-amino-γ-thiolactone hydroiodide, obtained from methionine and hydriodic acid, is found on hydrolysis, followed by oxidation, to yield a polymer-like amorphous material. The reactions involved have been shown in an excellent study to be those indicated below (129), with first a condensation of two mole-

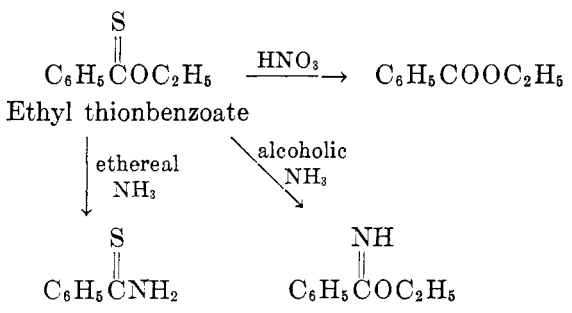


(V-22)

cules of the aminothiolactone to form a diketopiperazine with two free thiol groups, which, on oxidation, forms a polymeric disulfide.

C. THION ESTERS, THIOCARBONATES, AND XANTHATES

The thion esters, $RCOR'$, are much less stable than the isomeric thiol esters; the thiocarbonyl group is hydrolyzed rapidly to form hydrogen sulfide and the oxygen ester, $RCOOR'$. Thus, ethyl thionbenzoate is converted by cold aqueous silver nitrate to the oxygen ester with formation of silver sulfide (274), a reaction which can be used as the basis for a quantitative method of determining thion esters in the presence of thiol esters (229). The thion esters on saponification apparently yield the carboxylic acids, and presumably the first step in the hydrolysis is the formation of the oxygen ester $RCOOR'$ and hydrogen sulfide (49, 274). Other transformations of ethyl thionbenzoate are shown below (274):



(V-23)

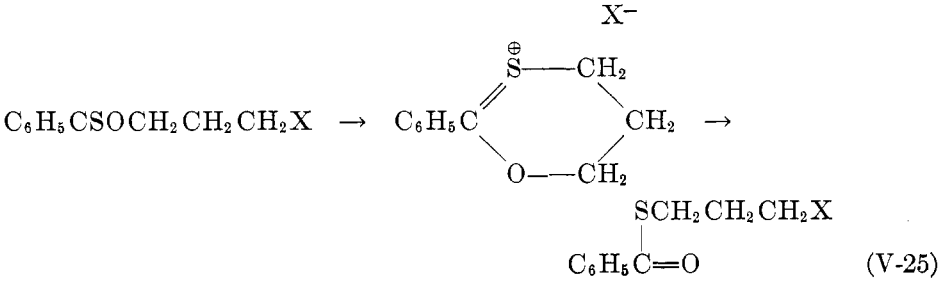
Phenylhydrazine behaves like ammonia (330). Methyl thionbenzoate is unaffected by oxygen at 100–120°C. after several hours, in contrast to the dithio ester

(392) (*cf.* page 63). The action of phenylmagnesium bromide on ethyl thionbenzoate leads to a small yield of benzophenone; hence this reaction must be accompanied by desulfuration (171).

The most interesting contrast between the thion and the thiol esters is the thermal rearrangement which some of the thion esters show, with the formation of the isomeric thiol esters. Although ethyl thionbenzoate, $C_6H_5CSOC_2H_5$, may be distilled at 240°C. without change, distillation of the γ-halopropyl thionbenzoates under reduced pressure leads to isomerization to the thiol structure (229); the reaction can be followed by the determination of thion sulfur. Treatment of the

$$C_6H_5CSOCH_2CH_2CH_2X \rightarrow C_6H_5COSCH_2CH_2CH_2X \qquad \text{(V-24)}$$

γ-halopropyl thionbenzoate with piperidine under mild conditions leads to isomerization along with the displacement reaction, to form the γ-piperidinopropyl thiolbenzoate, $C_6H_5COS(CH_2)_3N(CH_2)_5$ (229). The reverse of reaction V-24, the change from the thiol to the thion structure, does not seem to have been observed. It seems likely that the ready isomerization of the γ-halopropyl thion esters is due to the intermediate formation of a cyclic complex which undergoes cleavage at the oxygen atom (*cf.* 229, and the isomerization of β-haloethyl sulfides above, page 16).



(V-25)

The reaction may, however, be a bimolecular alkylation process. (It may be noted that the rate of replacement of hydroxyl by halogen using halogen acid in the series $RS(CH_2)_nOH$ is greatest for $n = 2,4$, and 5, where cyclic sulfonium salts may be formed (41)). The failure of the thiol esters to rearrange may be attributed to the small tendency for oxonium salt formation.

Diaryl thioncarbonates undergo a similar type of rearrangement at temperatures near 300°C. (367) and, in this case, intermediate sulfonium salt formation is not possible; this reaction, incidentally, offers a feasible method of converting phenols to thiophenols.

$$(ArO)_2C{=}S \xrightarrow{300°C.} ArOC(=O)SAr \qquad \text{(V-26)}$$

The monothiolcarbonates are easily hydrolyzed to yield a mercaptan, an alcohol, and carbon dioxide.

$$RSCOOR' + H_2O \rightarrow RSH + CO_2 + R'OH \qquad \text{(V-27)}$$

Hydrolysis appears to be catalyzed better by bases (180, 258, 295) than by acids (397). Hydrolysis at high temperatures can produce sulfide in addition to the mercaptan (295).

$$C_6H_5SCOOC_2H_5 \xrightarrow[130°C.]{\text{aqueous } NH_4OH} CO_2 + C_2H_5OH + C_6H_5SH + C_6H_5SC_2H_5 \quad \text{(V-28)}$$
$$\xrightarrow[H_2O,\ 230°C.]{}$$

Oxidation of arylthiocarbonates may yield the sulfonic acid (295).

$$C_6H_5SCOOC_2H_5 \xrightarrow[CH_3COOH]{KMnO_4} C_6H_5SO_3K \quad \text{(V-29)}$$

Dithiolcarbonates are subject to hydrolytic cleavage in much the same manner as the monothiolcarbonates. Bases catalyze the hydrolysis much better than acids (80, 193, 258, 337). The products are thiols and carbon dioxide.

$$C_2H_5SCOSC_2H_5 \xrightarrow{KOH} C_2H_5SH + K_2CO_3$$
$$\xrightarrow{NH_3} C_2H_5SH + H_2NCONH_2 \quad \text{(V-30)}$$

Thermal decomposition may take place at a high temperature, yielding desulfurized products (249).

$$C_6H_5CH_2SCOSCH_3 \xrightarrow{290°C.} \underset{\text{(60 per cent)}}{C_6H_5CH{=}CH_2} + \underset{\text{(25 per cent)}}{C_6H_5CH_3} \quad \text{(V-31)}$$

The xanthates are also easily hydrolyzed, especially when basic catalysts are present (180, 211, 258, 396). Cleavage of xanthates by phenylhydrazine is easier than the corresponding cleavage of dithiolcarbonates (81),

$$C_6H_5NHNH_2 + ClC_6H_4CH_2OC(=S)SCH_2C_6H_5 \xrightarrow[\text{alcohol}]{\text{boiling}}$$
$$ClC_6H_4CH_2OC(=S)NHNHC_6H_5 + C_6H_5CH_2SH \quad \text{(V-32)}$$

$$C_6H_5NHNH_2 + C_6H_5CHS_2C(=O)SCH_2C_6H_4Cl \longrightarrow \text{starting material, recovered unchanged}$$

and may be used to distinguish xanthates from dithiolcarbonates. The products obtained vary with the experimental conditions (180).

$$C_6H_5COCH_2SCSOCH_2COOH \xrightarrow[\text{distill}]{\text{steam}} HOCH_2COOH + CO_2 + H_2S + HSCH_2COC_6H_5 \quad \text{(A)}$$

$$\xrightarrow[\text{cold}]{2\ N\ Na_2CO_3} HOCH_2COOH + CO_2 + H_2O + (C_6H_5COCH_2S)_2CS \quad \text{(B)} \quad \text{(V-33)}$$

$$\xrightarrow{\text{alcoholic KOH}} \xrightarrow{H^+} HSSCOCH_2COOH \quad \text{(C)}$$

Reaction A gives the expected products of hydrolysis. The products in reaction B arise from the additional reaction between the mercaptan and starting material.

$$C_6H_5COCH_2SH + C_6H_5COCH_2SCSOCH_2COOH \rightarrow (C_6H_5COCH_2S)_2CS \quad \text{(V-34)}$$

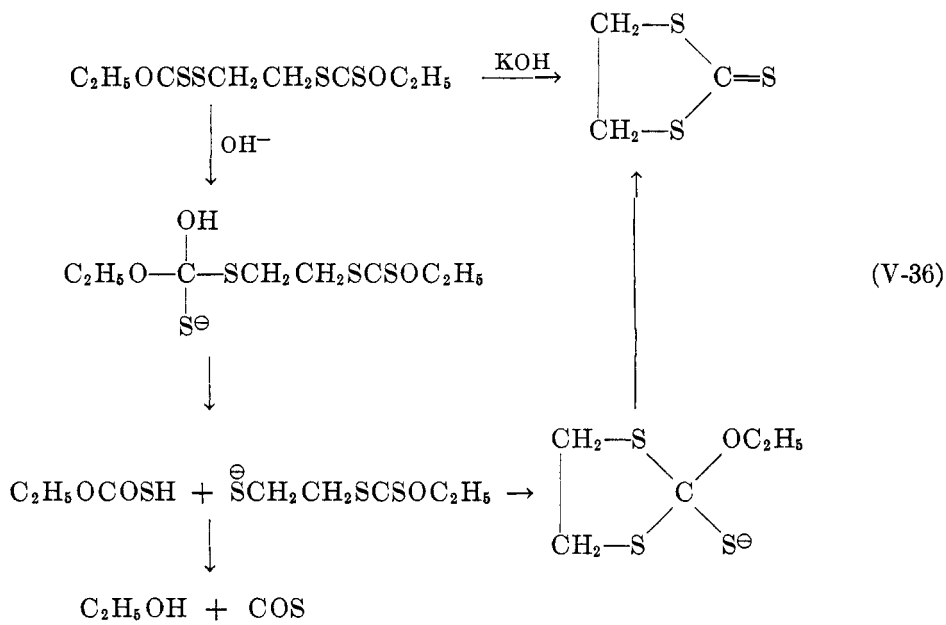
In reaction C one would have expected to obtain the trithiocarbonate as in B. However, one must consider the reaction of the hydrogen sulfide with the potassium hydroxide to yield SH^-, which would be an active reagent in the displacement reaction and yield the product obtained. Holmberg (206) showed that the decomposition of xanthates in excess water followed equation A, and that with limited amounts of water, reaction B held.

Use of amines as cleavage agents can give additional reaction products to those mentioned above, but the reactions follow similar mechanisms (206, 210, 211).

$$ROCSSCH_2COOH + H_2NR' \rightarrow ROCSNHR' \quad \text{(V-35)}$$

Reaction V-35 probably indicates the analogous intermediate step involved in hydrolysis in reaction V-33A. In addition, the above reaction indicates that the RS—C— linkage is attacked in this case instead of the RO—C— linkage.

An interesting extension of reaction B is the following (151):

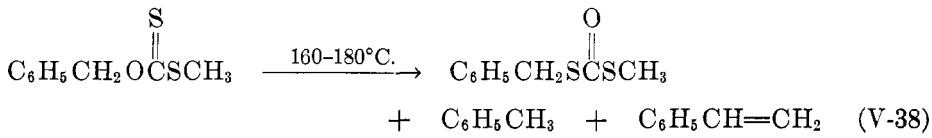


(V-36)

The thermal decomposition of xanthates is the basis for the Tschugaeff method of dehydrating alcohols (416, 420).

$$RCH_2CH_2OCSSCH_3 \xrightarrow[\text{distillation}]{\text{dry}} RCH{=}CH_2 + COS + CH_3SH \quad \text{(V-37)}$$

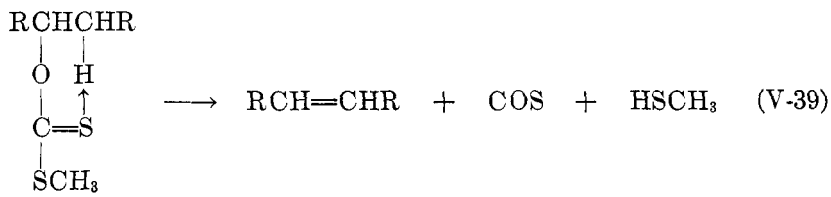
In some cases, the xanthates rearrange on heating to the dithiolcarbonates (82,



(V-38)

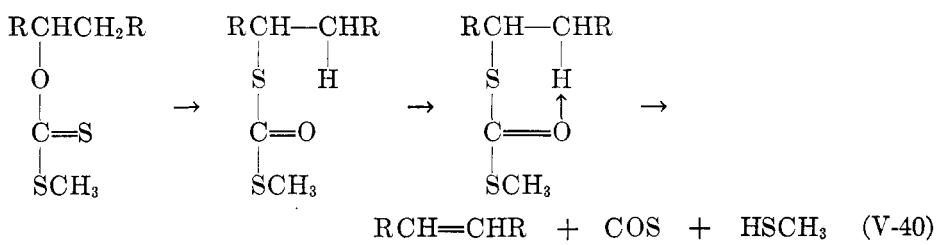
153, 249), a reaction similar to the rearrangement of thion esters above (page 57). The styrene and toluene are evidently due to further decomposition of the dithiolcarbonate.

The following mechanism has been proposed for the xanthate decomposition in the Tschugaeff process (396).



(V-39)

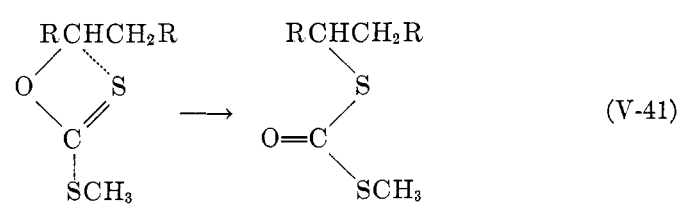
The decomposition is supposed to be preceded by attack on the hydrogen β to the oxygen, by the thion sulfur. This seems improbable to us, because of the very slight tendency of sulfur to coördinate with hydrogen. It appears possible that the xanthate may first rearrange to the dithiolcarbonate, which then allows attack of the carbonyl *oxygen* on the β-hydrogen, followed by decomposition.



(V-40)

This mechanism, in addition to the greater hydrogen-bonding power of oxygen, has the further point in its favor that sulfur is known to be more effective than oxygen in activating an α-hydrogen (268, 325) and presumably also a β-hydrogen.

The elimination of water *via* the Tschugaeff procedure is believed to take place *cis* (3, 214); if that is correct, the isomerization of the xanthate to the dithiolcarbonate would have to take place by a front-side attack without inversion,—the S_N1 mechanism (105). Possibly, however, the Tschugaeff process involves



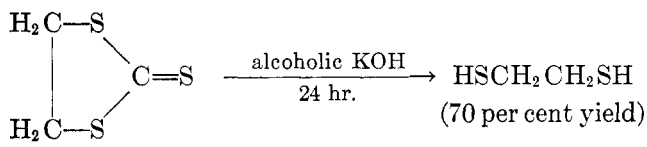
(V-41)

inversion, followed by *trans* elimination, which would give the overall result of *cis* elimination.

A puzzling feature of the xanthate series is the occurrence of labile and stable forms of the xanthates, considered to be identical except for stability to heat (81). Possibly the xanthates can decompose by a chain process, and the stable form has been purified sufficiently to remove the chain initiator.

Like the monothio- and dithiocarbonates, the trithiocarbonates are readily hydrolyzed, especially in the presence of base (151, 180, 198, 331).

$$(RS)_2CS + KOH + H_2O \longrightarrow 2RSH$$



(V-42)

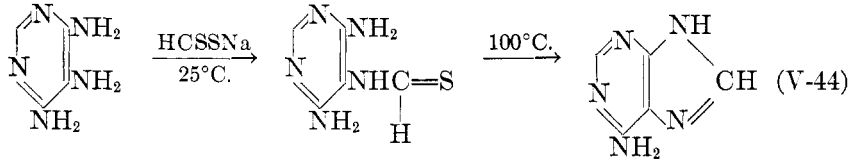
Monothiocarbamates are easily decomposed with alkali.

$$C_6H_5SCONHR + Pb(OH)_2 + \underset{(0.1\ N,\ \text{cold})}{\text{alkali}} \rightarrow Pb(SC_6H_5)_2 + RNH_2 \quad \text{(V-43)}$$

Lead acetate in 70 per cent alcohol will also effect cleavage of the above compound on heating for 5 min. (131). This ease of cleavage has led to the suggestion that phenylmercaptocarbonyl chloride be used as a group-protecting agent.

D. DITHIO ACIDS AND ESTERS

The dithio acids, RCSSH, resemble the thio acids in the speed with which they react with amines to form thioamides. Dithioformic acid, HCSSH, has proved to be very useful for the formation of thioformamido compounds under very mild conditions; the latter may be used as intermediates in the synthesis of thiazole or purine derivatives (267, 417). The very mild conditions under which



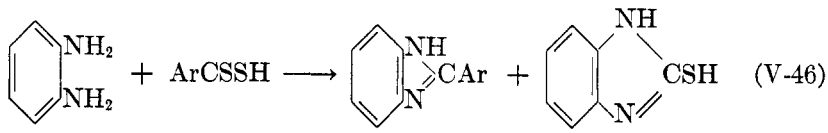
(V-44)

the thioformamido group will eliminate hydrogen sulfide with an *o*-amino group to form the imidazole ring is of great value in nucleoside syntheses (267).

Dithioformic acid reacts readily with phenyl isocyanate and phenyl isothiocyanate to form thioformamido derivatives (417) (*cf.* page 47).

$$\underset{(C_6H_5NCS)}{C_6H_5NCO} + HCSSH \longrightarrow C_6H_5NHC(=S)H + \underset{(CS_2)}{COS} \quad \text{(V-45)}$$

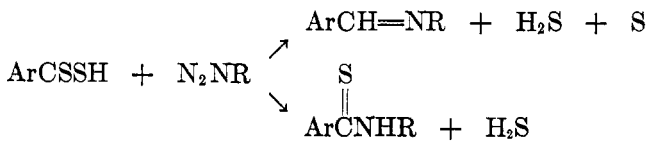
Aromatic dithio acids are reported to react with *o*-phenylenediamine to form benzimidazole and 2-mercaptobenzimidazole at 25°C.; the latter is presumably



(V-46)

formed by decomposition of the dithio acid to carbon disulfide, followed by combination of this with *o*-phenylenediamine (449).

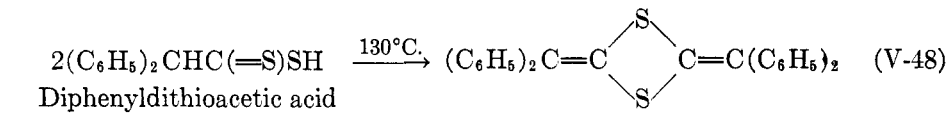
Aromatic dithio acids may react with compounds such as phenylhydrazine and semicarbazide in two ways, with the formation of a thioacyl derivative or of an aldehyde derivative (447).



(V-47)

The semicarbazones can be hydrolyzed to the aldehydes, and the method has been proposed as a way of synthesizing aromatic aldehydes, because the dithio acids can be readily obtained by the action of carbon disulfide on the corresponding Grignard reagent. However, a critical study (382) shows that other methods, particularly the ethoxymethyleneaniline procedure, are preferable as ways of converting aromatic Grignard reagents to aromatic aldehydes.

The action of hydrazine on aromatic dithio acids can lead to various heterocycles, including tetrazines, triazoles, and thiodiazoles (448). Diphenyldithioacetic acid is reported to yield dimeric thiodiphenylketene, on heating to 130°C. (361a). The same product is obtained by heating the thion ester, $(C_6H_5)_2CHCSOC_6H_5$ (366).



Diphenyldithioacetic acid

(V-48)

The structure of the dimer has not been proved.

The dithiocarbamic acids are obtained in the form of their salts from primary or secondary aliphatic amines and carbon disulfide. Aromatic amines do not yield stable salts of this type unless a stronger base than the aromatic amine is

$$2R_2NH + CS_2 \rightarrow R_2NCSSH \cdot HNR_2 \qquad \text{(V-49)}$$

present; instead, they form the diarylthiourea or the isothiocyanate. Reagents which react with hydrogen sulfide, such as iodine in pyridine (162) or lead salts (110), favor these reactions.

$$2ArNH_2 + CS_2 \rightarrow ArNHCSNHAr + H_2S \qquad \text{(V-50)}$$

$$ArNH_2 + CS_2 \rightarrow ArNCS + H_2S$$

It has recently been shown that sodium dialkyldithiocarbamates condense with primary or secondary amines in the presence of oxidizing agents to form dithiocarbamylsulfenamides, which lose sulfur slowly to form thiourea deriva-

tives (381). This interesting observation has prompted the suggestion that the

$$R_2NCSSNa + HNR'_2 \xrightarrow[NaOCl]{I_2\ or} R_2NCSSNR'_2 \rightarrow R_2NCSNR'_2 + S \quad (V\text{-}51)$$

oxidative condensation of dithio acids with cyclohexylamine yields first an unstable sulfenamide, RCSSNHR′, which loses sulfur to form the thioamide RCSNHR′ (4).

The dithiocarbamates (dithiourethans) of the type NH_2CSSR decompose slowly on standing, and rapidly when distilled, into RSH and HCNS. The R′NHCSSR type decomposes more slowly, giving RSH and R′NCS. The completely substituted series, R'_2NCSSR, is stable (66).

The dithio esters, RCSSR′, seem to be more unstable than the thion or thiol esters. Methyl dithiobenzoate is attacked slowly by oxygen at 100°C., with the formation of some sulfur dioxide (392), and acid hydrolysis of $(C_6H_5)_2CHCSSC_6H_5$ yields diphenylacetic acid and thiophenol (366).

The same ester, which is reported to exist in two tautomeric forms, the colorless "enethiol" and the orange normal form, is converted to diphenylthioketene dimer by heat (365, 366).

$$2(C_6H_5)_2C{=}\underset{\underset{SH}{|}}{C}SC_6H_5 \longrightarrow 2(C_6H_5)_2CH\underset{\underset{S}{\|}}{C}SC_6H_5 \xrightarrow{250°C.}$$

$$(C_6H_5)_2C{=}C\begin{array}{c}S\\ \diagup\ \diagdown\\ \diagdown\ \diagup\\ S\end{array}C{=}C(C_6H_5)_2 + 2C_6H_5SH \quad (V\text{-}52)$$

The reactions shown below occur under mild conditions (444).

$$C_6H_5CSSCH_2C_6H_5 + NH_3{-}H_2O \rightarrow C_6H_5CONH_2 + C_6H_5CH_2SH \quad (V\text{-}53)$$

$$\downarrow \begin{array}{l}Na_2S\\ alcohol\end{array}$$

$$C_6H_5CSSNa + C_6H_5CH_2SH$$

The dithiolactone below is obtained by treating the oxygen lactone with phosphorus pentasulfide; in the presence of hot alkali the thiocarbonyl group is hydrolyzed, giving the thiolactone.

$$CH_3\underset{\underset{S\text{——}C{=}S}{|}}{C}HCH_2\underset{\underset{S\text{——}C{=}S}{|}}{C}H_2 \xrightarrow[alkali]{hot} CH_3\underset{\underset{S\text{——}C{=}O}{|}}{C}HCH_2\underset{\underset{S\text{——}C{=}O}{|}}{C}H_2 \quad (V\text{-}54)$$

$$\downarrow CH_3ONa$$

$$CH_3\underset{\underset{S\text{——}C{=}S}{|}}{C}HCH_2C{=}\underset{\underset{S\text{——}CHCH_3}{|}}{C}CH_2\underset{\underset{S\text{——}CHCH_3}{|}}{C}H_2 + H_2S$$

With sodium methoxide, the dithiolactone undergoes a Claisen-type condensation

to form the bis product, with the elimination of hydrogen sulfide (155). This seems to be one of the few cases in which a thiocarbonyl group gives an aldol-like condensation, although it is possible that this reaction proceeds by hydrolysis of the thiocarbonyl group to a carbonyl, followed by condensation with elimination of water. Butyrolactone itself undergoes an exactly analogous condensation to form a bis product (147).

VI. Thiocarbonyl Compounds

For an excellent review on the preparation and reactions of these compounds the reader is referred to the paper by Campaigne (87). In this paper only those reactions involving cleavage of the carbon–sulfur bond will be discussed, with the hope that suitable correlations can be made between the reactions of the thiocarbonyl compounds and the reactions of other sulfur compounds wherein a carbon–sulfur bond is broken.

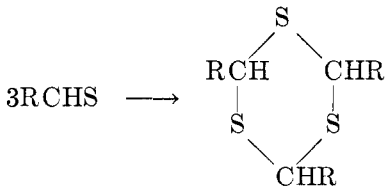
In this section only the compounds of the type RCR' (where R′ may be H)
$\|$
S

will be considered. The reader is referred to the sections on the dithio acids (page 61), the dithio esters (page 63), the thion esters (page 56), and the thiocarbonates (page 57).

A. Aliphatic Thiocarbonyl Compounds

Although there are several papers in the literature concerning aliphatic thioaldehydes, few of these give convincing evidence that the authors were dealing with pure compounds. In the preparation of thioaldehydes, the monomers are rarely isolated (273, 369), the products isolated being polymers, generally the trimers (*cf.* Section VII, C), along with dimers, tetramers, and higher polymeric forms. Another difficulty encountered is that the trimers exist in two isomeric forms (33, 440).

The main reaction of thioaldehydes involving a cleavage of the carbon–sulfur bond is polymerization, generally to the dimers or trimers.



(VI-1)

Polymerization can occur between thioaldehydes and oxygen aldehydes, yielding products such as $(CH_3CHO)_2(CH_3CHS)$ and $(CH_3CHO)(CH_3CHS)_2$ (253). After polymerization, the resulting compounds no longer show the properties of an aldehyde, but show the properties of the more stable (less reactive) mercaptals or sulfides (*cf.* Section VII, C).

Few of the aliphatic thioketones have been isolated as the monomers. Among the exceptions to this generalization are those compounds which have a strong tendency to enolize, namely $S(CH_2\overset{\overset{S}{\|}}{C}R)_2$ (76) and those of the type $R\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{S}{\|}}{C}R$ (76, 286). The per cent of enolization for several of these compounds has been determined (286) (table 7). As already pointed out (page 2), the —SH group has little or no tendency to form hydrogen bonds. Consequently, the enol form of thioacetoacetic ester should be more polar with respect to its keto form than the enol form of acetoacetic ester is to its keto form. Increased polarity of the enol should lead to greater solubility of the enol in polar solvents such as ethanol.

TABLE 7

Enolization of aliphatic β-keto esters

COMPOUND	PER CENT ENOL IN ETHANOL SOLUTION			
	Y = S			Y = O
	30°C.	40°C.	60°C.	25°C.
$CH_3\overset{\overset{Y}{\|}}{C}CH_2COOC_2H_5$	41.0		38.7	9–11
$CH_3\overset{\overset{Y}{\|}}{C}CHCOOC_2H_5$ (CH₃)	62.8	61.9	60.0	5.1
$CH_3\overset{\overset{Y}{\|}}{C}CHCOOC_2H_5$ ($CH_2CH(CH_3)_2$)			64.4	9.0–9.5
$CH_3\overset{\overset{Y}{\|}}{C}CHCOOC_2H_5$ ($COOC_2H_5$)	61.1		58.5	

As the per cent of enolization is related to the solubility of the enol and keto forms, one would expect greater enolization of the sulfur analogs of acetoacetic ester, in agreement with the data of table 7.

Reaction of thioacetoacetic ester compounds with carbonyl group reagents, with 10 per cent potassium hydroxide, or with 10 per cent sulfuric acid evolves hydrogen sulfide and liberates the oxygen ketone, which, in the case of the carbonyl group reagents, undergoes further reaction. Reaction with base and alkyl halide leads to unsaturated sulfides, while reaction with iodine or other mild oxidizing agent gives the corresponding unsaturated disulfides (286).

Thiocarbonyl compounds that readily enolize have been used to convert oxygen aldehydes to thioaldehydes (285).

$$\text{—C(=S)—CH}_2\text{COOR} \underset{}{\overset{K_1}{\rightleftharpoons}} \text{—C(SH)=CHCOOR} + \text{RCHO} \overset{K_2}{\rightleftharpoons}$$

$$\text{RCHS} + \text{—C(OH)=CHCOOR} \overset{K_3}{\rightleftharpoons} \text{—C(=O)—CH}_2\text{COOR} \qquad \text{(VI-2)}$$

Because the β-oxo ester is less enolized than the β-thio ester, $1/K_3 > K_1$ (table 7), the equilibrium is in favor of the formation of the thioaldehyde ($K_2 > 1$).

Hydrolysis of monomeric thioketones with acid, base (282), or water (91) results in the oxygen carbonyl compound.

B. AROMATIC THIOCARBONYL COMPOUNDS

Attempts to obtain aromatic thiocarbonyl compounds as the monomers have met with more success. Polymerization of the aromatic thioaldehydes occurs, however, almost as easily as with the aliphatic thioaldehydes (238) and, as before, the trimers are favored.

Heating the monomeric (or the polymeric) aromatic thioaldehydes leads to stilbene-type substituted ethylenes (283, 443, 445).

$$(\text{C}_6\text{H}_5\text{CHS})_7 \xrightarrow[\text{heat}]{\text{CHCl}_3} \text{H}_2\text{S} + \text{stilbene} \qquad \text{(VI-3)}$$

The yields of stilbene-type products are increased by metallic catalysts such as iron powder (320) or copper powder (44, 239, 270). Occasionally the disulfide is also isolated from the pyrolysis of a thioaldehyde with a metallic catalyst (44).

The monomeric thioaldehydes give the typical carbonyl group reactions (445) with such reagents as 2,4-dinitrophenylhydrazine.

The isolation of monomeric aromatic thioketones has met with success in all cases, but even here, the tendency still exists to form dimers, trimers, and higher polymeric forms (88).

Reactions of thioketones wherein a carbon–sulfur bond is broken and which are analogous to reactions of oxoketones are (*1*) conversion to the dihalide (347),

$$\text{Ar}_2\text{C=S} + \text{SOCl}_2 \rightarrow \text{Ar}_2\text{CCl}_2 \qquad \text{(VI-4)}$$

(*2*) pinacol-type dimerization (360),

$$\text{Ar}_2\text{C=S} + \text{MgMgI}_2 \rightarrow \text{Ar}_2\text{C(SMgI)—C(SMgI)Ar}_2 \qquad \text{(VI-5)}$$

(*3*) reduction (139),

$$\text{Ar}_2\text{C=S} + \text{H}_2 + \text{catalyst} \rightarrow \text{Ar}_2\text{CHSH} \qquad \text{(VI-6)}$$

and (*4*) reactions with the usual carbonyl group reagents (168), e.g.:

$$\text{Ar}_2\text{C=S} + \text{NH}_2\text{OH} \rightarrow \text{Ar}_2\text{C=NOH} \qquad \text{(VI-7)}$$

Reactions of thioketones involving a carbon–sulfur bond cleavage which have

no analogy in the oxoketone reactions are a result of the ability of divalent sulfur to undergo further oxidation (353, 354, 390),

$$Ar_2C{=}S + O_2 + \text{light} \rightarrow S + SO_2 + Ar_2C{=}O \qquad \text{(VI-8)}$$

$$Ar_2C{=}S + H_2O_2 \rightarrow Ar_2C{=}O \qquad \text{(VI-9)}$$

the greater donor capacity of the sulfur atom (12, 167, 168, 352, 361, 388, 389),

$$Ar_2C{=}S + (C_2H_5)_3P + O_2 \rightarrow Ar_2C{=}O + (C_2H_5)_3PS \qquad \text{(VI-10)}$$

$$Ar_2C{=}S + Cu \xrightarrow{\text{heat}} Ar_2C{=}CAr_2 \qquad \text{(VI-11)}$$

$$Ar_2C{=}S + C_6H_5NCO \xrightarrow[20\text{ hr.}]{170^\circ\text{C.}} Ar_2C{=}NC_6H_5 + COS \qquad \text{(VI-12)}$$

$$(C_6H_5)_2C{=}C{=}O + Ar_2C{=}S \rightleftarrows (C_6H_5)_2C(\text{—}S\text{—})CO\text{—}C(C_6H_5)_2 \qquad \text{(VI-13)}$$

or the greater ease of nucleophilic attack at the thiocarbonyl group (62, 168, 363, 393).

$$Ar_2C{=}S + \text{10 per cent KOH} \rightarrow Ar_2CO \qquad \text{(VI-14)}$$

$$Ar_2C{=}S + C_6H_5N_3 \rightarrow N_2 + S + (C_6H_5)_2C{=}NC_6H_5 \qquad \text{(VI-15)}$$

$$Ar_2C{=}S + (C_6H_5)_2CN_2 \rightarrow Ar_2C(\text{—}S\text{—})CAr_2 + N_2 \qquad \text{(VI-16)}$$

It is of interest to note in passing that the equilibrium reaction (VI-13) has been used as a method of purification of thiobenzophenone. In reaction VI-14, if stronger bases are used one gets the disulfide (389).

VII. Mercaptals and Mercaptoles

A. Mercaptals

Considerable literature is available wherein the carbon–sulfur bonds of mercaptals have been broken. Several reagents have been used to effect the cleavage, but the most generally useful appears to be mercuric chloride–hydrochloric acid. Hydrochloric acid alone is not effective generally (146, 298, 341, 401), in contrast to its action with acetals, but mercuric chloride alone often is effective; the rate of the cleavage reaction with mercuric chloride is greatly increased by the addition of hydrochloric acid (37, 259, 441). A possible explanation is that the cleavage reaction is a displacement of an unfavorable equilibrium.

$$RCH(SR')_2 \underset{H^+,\,H_2O}{\overset{K_1}{\rightleftarrows}} RCHO + R'SH \underset{H^+}{\overset{K_2\ \ HgCl_2}{\rightleftarrows}} (R'S)_2Hg \qquad \text{(VII-1)}$$

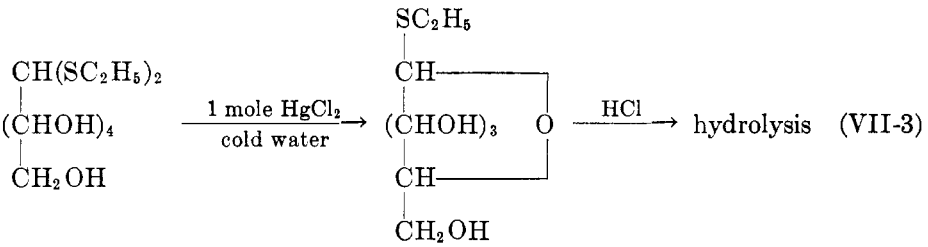
The acid presumably functions as a proton donor to form the onium salt, which then decomposes to the aldehyde and mercaptan. Hydrogen chloride alone is not effective on the mercaptals because it does not coördinate with the sulfur, as was

also the case in the cleavage of sulfides (*cf.* page 35). Hydrochloric acid hydrolyzes oxygen acetals rapidly, but here onium salt formation can occur (405). Evidence for reaction VII-1 is gained from the observation that formaldehyde can displace benzaldehyde (209).

$$C_6H_5CH(SCH_2COOH)_2 + CH_2O \xrightarrow[3\text{ days}]{HCl,\ 25°C.} CH_2(SCH_2COOH)_2 + C_6H_5CHO \quad \text{(VII-2)}$$

It has been demonstrated that the mercaptals of formaldehyde and glyoxylic acid are very resistant to hydrolysis as compared to the mercaptals of benzaldehyde (203). Either K_1 (equilibrium constant for cleavage of the mercaptal) or K_2 for regeneration of the mercaptan from the mercaptide) can be the controlling factor.

Further evidence for an equilibrium mechanism (reaction VII-1) is afforded by the following reaction (340):



(65 per cent yield)

In addition, most reagents that give insoluble mercaptides, such as silver nitrate and cadmium sulfate, also effect cleavage (145, 209). These reagents would have no affect on an alcohol, and the rate of cleavage of oxygen acetals is so great that additional catalysts are not needed. This is the outcome of the greater ease of protonation of oxygen ether linkages over sulfur ether linkages.

The ease of cleavage appears to be influenced more by the nature of the aldehyde than by the nature of the mercaptan (203, 209, 325).

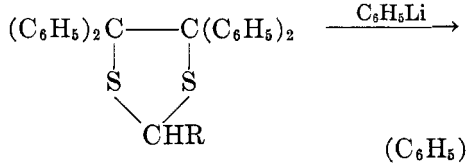
Quantitative methods have been developed for following the cleavage reaction (208, 209). These methods make use of a modified iodimetric titration, or an alkalimetric titration of the acid produced by cleavage with mercuric chloride.

$$R'CH(SR)_2 + HgCl_2 + H_2O \rightarrow 2RSHgCl + 2HCl + R'CHO \quad \text{(VII-4)}$$

Certain mercaptals are resistant to cleavage by mercuric chloride–hydrochloric acid. Glucose mercaptals are cleaved readily by this reagent, but the pentaacetyl glucose mercaptals are cleaved only with difficulty (75). Using anhydrous formic acid, the pentaacetyl glucose mercaptal was cleaved to an extent of 50 per cent if the mercaptan was distilled from the mixture (further evidence of an equilibrium reaction mechanism). In contrast, the dipropylidene derivative of glucose mercaptal was cleaved easily by mercuric chloride, although not by 0.5 *N* sulfuric acid (111).

α-Thioglucosides (ethyl and methyl) are split rapidly by mercuric chloride, but the β-forms cleave only slowly (341). If this is a stereo-specific effect, then the results in the preceding paragraph could be a result of steric influences. No conclusive evidence is available.

Although most mercaptals are stable to base (38) the following exception was noted (349, 351):



The stability of the mercaptal toward the base decreases as one changes R from R = H to R = COOR′ to R = CH_3. All of these mercaptals decompose thermally.

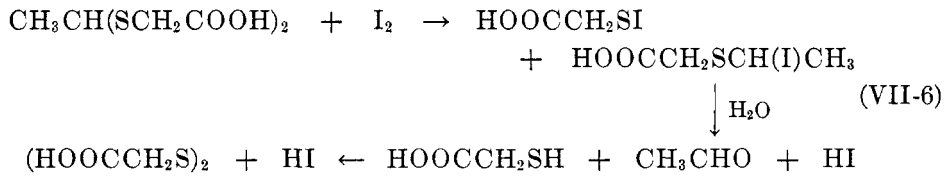
TABLE 8

Per cent decomposition of mercaptals by mercuric chloride

$RCH(SCH_2COOH)_2$

R	DECOMPOSITION	R	DECOMPOSITION
	per cent		*per cent*
H	57.3	HOOC	65.2
CH_3	100.1	C_6H_5	99.0
CH_3CH_2	99.4		

Mercaptals can also be cleaved oxidatively. The mechanism involved may be similar to that in the mercuric chloride–hydrochloric acid reaction, here the mercaptan being removed from the equilibrium as the disulfide. If strong oxidizing agents are used, oxidation of the mercaptal to the disulfone may occur before the mercaptal hydrolyzes to the aldehyde and mercaptan. As mild oxidizing agents, bromine (96, 141, 252), nitric acid (141), iodine (209), and potassium peroxydisulfate (201, 204) have been used. In the case of iodine, the following mechanism was proposed (209):



No data are available to test the hypothesis that the intermediate sulfenyl halide would react with the mercaptan rather than the water. (The specific rate constant of the former reaction may well be greater, but in the reaction conditions used, the water is in excess.)

Cleavage with peroxydisulfate has been known to give some unexpected products (201, 204).

$$C_6H_5CH(SCH_2COOH)_2 \xrightarrow[1\,N\,NaOH]{K_2S_2O_8} C_6H_5\underbrace{CHSCH_2COO} \quad \text{(VII-7)}$$

It would be of interest to know whether the same product was obtained using equimolar quantities of benzaldehyde and thioglycolic acid.

Hemimercaptals are infrequently mentioned in the literature. It is stated that they readily dissociate into their components (371).

$$CH_2O + HSCH_2CONHC_6H_5 \rightleftharpoons HOCH_2SCH_2CONHC_6H_5 \quad \text{(VII-8)}$$

Iodine readily displaces the above equilibrium to the left by removing the mercaptan as the disulfide.

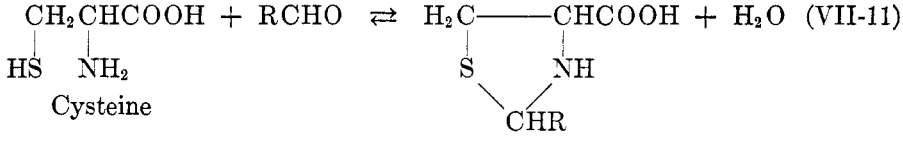
Monothiomercaptals are rather stable compounds except in the presence of acids (430).

$$C_2H_5SCH_2OCH_3 \xrightleftharpoons{H^+} CH_2(OCH_3)_2 + CH_2(SC_2H_5)_2 \quad \text{(VII-9)}$$

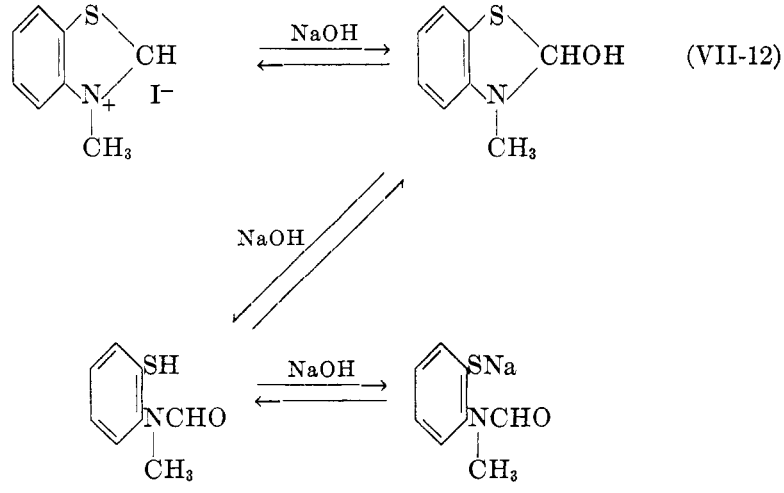
With ethylmagnesium bromide the above compound gives the mercaptan and the oxygen ether.

$$C_2H_5SCH_2OCH_3 + C_2H_5MgBr \xrightarrow[5\text{ hr.}]{100°C.} C_2H_5SH + C_2H_5OCH_2CH_2CH_3 \quad \text{(VII-10)}$$

The grouping N—CHR—S—, which is analogous to the hemimercaptals, undergoes reversible cleavage (*cf.* page 67); the grouping occurs in the thiazolidines, and it has been shown (310, 371) that the thiazolidines formed from cysteine by condensation with aldehydes are in equilibrium with the two components.



The grouping S—CH(OH)N— is present in the pseudo-bases derived from thiazolium salts, and it goes to the mercapto formamido compound (280).

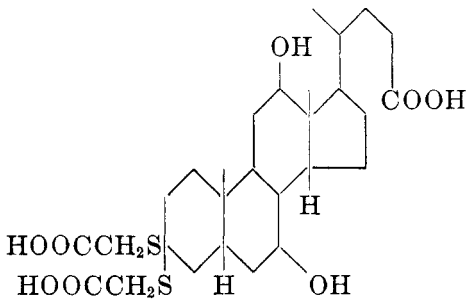


(VII-12)

This reaction is shown by the thiazolium nucleus in thiamin, and was of importance in determining the structure of this vitamin (438); it is not given by thiazolium salts which lack the hydrogen in the 2-position (438).

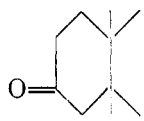
B. MERCAPTOLES

As in the case of the mercaptals, the mercaptoles are generally stable to bases, and can be cleaved by dilute mineral acids (133, 166, 226, 364).



$$\xrightarrow[\text{boiling}]{5\ N\ \text{NaOH}} \text{no reaction} \qquad \text{(VII-13)}$$

$$\xrightarrow{\text{dilute HCl}}$$



etc.

Although quantitative data are lacking, it appears that mercaptoles are more easily hydrolyzed than mercaptals. This is in accord with an equilibrium viewpoint, for one might expect the equilibrium between a ketone and a mercaptan to be less in favor of the mercaptol than the equilibrium between an aldehyde and a mercaptan in favor of the mercaptal (347).

Occasionally mercuric chloride or cadmium sulfate in acidic media is employed to effect cleavage of a mercaptole (209).

Certain mercaptoles have been found subject to basic cleavage. These mercaptoles are of type where a particularly acidic hydrogen is attached alpha to the carbon bearing the thio linkages (*cf.* reaction II-9) (14, 133, 296, 305).

$$(C_6H_5S)_2CCH_2SO_2C_6H_5 \xrightarrow[\text{heat}]{\text{concd. aqueous KOH}} \underset{\displaystyle CH_3}{\overset{\displaystyle (C_6H_5S)_2C}{|}}CH_2SO_2C_6H_5$$

$$CH_3SO_2C_6H_5 + C_6H_5SK + KOOCCH_3 \qquad \text{(VII-14)}$$

$$CH_3C(SR)_2CHCOOR'' \xrightarrow[H_2O]{\text{alkali}} \underset{\displaystyle SR}{\overset{\displaystyle CH_3C}{|}}{=}CHCOOH \qquad \text{(VII-15)}$$

$$\underset{\displaystyle R'}{|}$$

In reaction VII-15 if R is benzyl, no cleavage of the mercaptole linkage occurs, but the ester is hydrolyzed. Considering the smaller acidity of benzyl mercaptan as compared to other aliphatic mercaptans, one might expect the equilibrium to lie much more in favor of the mercaptole and be harder to displace by base. Although work has been done on the mercaptoles of compounds of the type —$COCH_2CO$—, the basic cleavage is not mentioned (304, 321, 322).

Reductive cleavages of mercaptoles have been reported using Raney nickel (89), sodium powder (355), sodium amalgam, and tin–hydrochloric acid (133). The following is probably a reductive cleavage also (281):

$$(ArS)_2CCOC_6H_5 + Zn + CH_3COCl \xrightarrow{\text{ether}} ArSC{=}CC_6H_5 \quad \text{(VII-16)}$$
$$\quad\; C_6H_5 \qquad\qquad\qquad\qquad\quad C_6H_5\;\; OCOCH_3$$

Thermal decomposition of mercaptoles leads to a mixture of products, chief of which are tars (30). Products isolated and identified have been thioketones and sulfides (31, 357).

$$(CH_3)_2C(SC_2H_5)_2 \rightarrow (CH_3)_2C{=}S + (C_2H_5)_2S \quad \text{(VII-17)}$$

$$Ar_2C(SCH_2C_6H_5)_2 \rightarrow Ar_2C{=}S + (C_6H_5CH_2)_2S \quad \text{(VII-18)}$$

The thioketones produced in these reactions were identified merely by color reactions. The nature of the aromatic group affects the temperature at which thermal decomposition takes place (357). Similarly, in compounds of the type $RR'C(SR'')_2$ the nature of R′ and R influences the temperature of decomposition (357a, 362), although no regularities are apparent.

A study of mercaptole formation from various mercaptans (305) shows that the order of rate of mercaptole formation is the following: $C_6H_5CH_2SH > C_2H_5SH > n\text{-}C_5H_{11}SH \gg C_6H_5SH$. This series is also that of decreasing stability of the mercaptoles, the phenyl derivative being least stable, and is the order of increasing acidity.

Hemimercaptoles are easily cleaved by heating in aqueous solution, generating the component ketone and mercaptan (28, 29, 60, 358). Cold alkali effects cleavage in some cases (29).

$$C_6H_5SCHCCl_3 \xrightarrow[\text{cold}]{OH^-} C_6H_5SH + CHCl_3 + HCOOH \quad \text{(VII-19)}$$
$$\quad\;\; OH$$

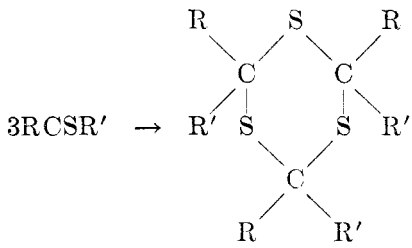
The cleavage in reaction VII-19 might well be cleavage of the thioformate.

$$C_6H_5SCHCCl_3 + OH^- \rightarrow [C_6H_5SCH(OH)_2] + CHCl_3$$
$$\quad\;\; OH$$

$$[C_6H_5SCHO] + H_2O \xrightarrow{OH^-} C_6H_5SH + HCOOH \quad \text{(VII-20)}$$

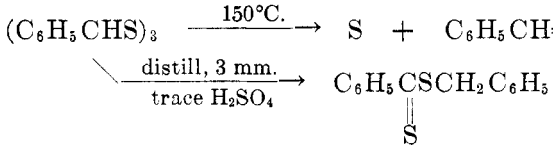
C. POLYMERIC THIOCARBONYL COMPOUNDS

Special types of mercaptals and mercaptoles are the polymeric thiocarbonyl compounds (32, 86, 272, 348).

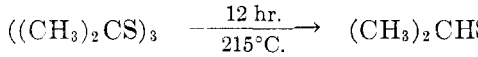


(VII-21)

The carbon–sulfur bonds of these compounds can be broken by thermal cleavage, the products being of various kinds, but usually derived from the monomeric thiocarbonyl group compound (34, 56, 245, 444).

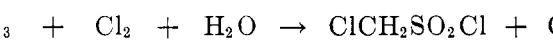


(VII-22)

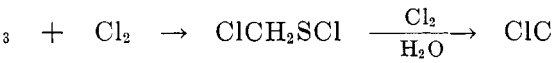


(VII-23)

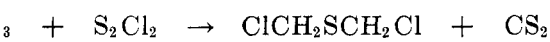
Halogens and sulfur halides readily break the carbon–sulfur bonds of this type of compound (50, 126, 257, 271).



(VII-24)



(VII-25)



(VII-26)

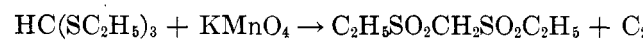
In the cleavage of *s*-trithianes with anhydrous chlorine, a difference in reaction products is noted if the *s*-trithiane is derived from an aliphatic or an aromatic thiocarbonyl compound (125). *s*-Trithianes from thioformaldehyde, thioacetaldehyde, thiopropionaldehyde, thiobutyraldehyde, and thioacetone give 1-chloroalkylsulfenyl chlorides, while *s*-trithianes from thiobenzaldehyde and from thiobenzophenone eliminate sulfur, replacing the sulfur atom with two chlorine atoms. (Compare the corresponding cleavage of sulfides, page 37.)

Polymeric thiocarbonyl compounds are also cleaved (presumably *via* sulfonium salt intermediates) by use of alkyl halides (302).

For polymeric compounds involving mixed carbon–sulfur and carbon–oxygen linkages the reactions are similar to those outlined above (253).

D. ORTHO THIOESTERS

Oxidative elimination of a thiomercaptal group can occur in special compounds, chief of which are the ortho thioesters (19, 205).



(VII-27)

The elimination is not due to the instability of the α,α,α-trisulfone, for this compound has been prepared from tetramethylthiomethane (17).

$$C(SCH_3)_4 + 0.4\ N \text{ perphthalic acid in ether} \xrightarrow{0°C.} HC(SO_2CH_3)_3 \quad \text{(VII-28)}$$

If the elimination were due to steric hindrance, one would have expected elimination of two thio groupings from the tetramethylthiomethane.

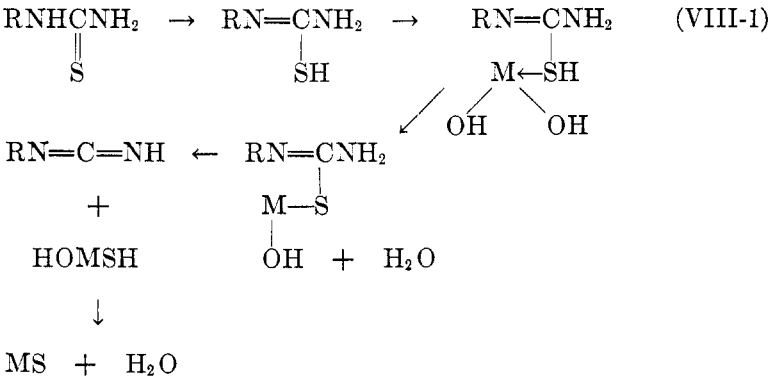
VIII. Miscellaneous Compounds

A. THIOUREAS

1. Sulfur unalkylated

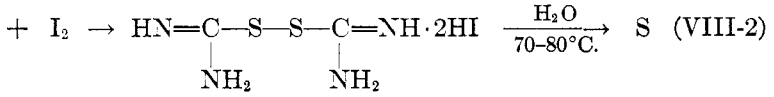
Many reactions which would be included in this category on first glance probably involve an alkyl–sulfur intermediate, and consequently are dealt with later.

Desulfuration of thioureas using lead hydroxide has been known for many years (122). From the results obtained, it is apparent that the degree of substitution on the nitrogens determines to a large extent the ease of the desulfuration. Qualitatively, four general groups can be made (122): (*a*) all monosubstituted thioureas appear desulfurizable; (*b*) symmetrical disubstituted thioureas are desulfurizable if either group is unsaturated (except *N*,*N*′-diallylthiourea); (*c*) trisubstituted thioureas are desulfurized with great difficulty; (*d*) tetrasubstituted thioureas are not desulfurized even with mercuric oxide. Recently (329) a mechanism has been proposed which accounts for the above observations on the basis of the *N*-hydrogens participating in the intermediate stages of the desulfuration.



Desulfuration does not take place in acid solution because of salt formation at the amino or imino group.

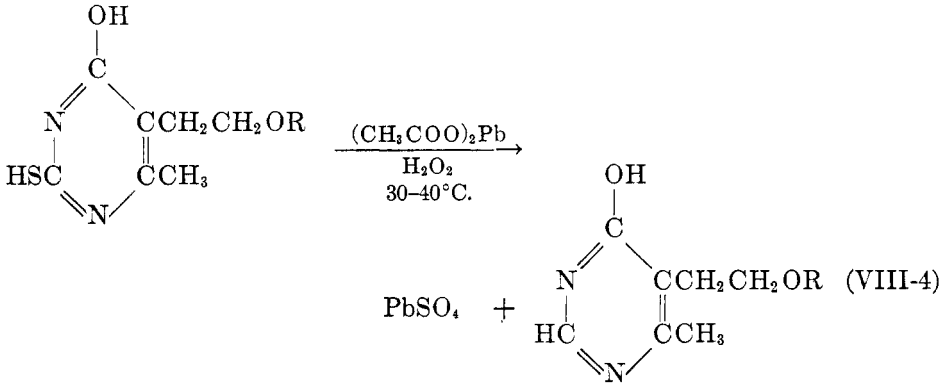
Oxidation of thioureas to disulfides has also been known for a long time (431). The resulting disulfides are often unstable and/or form periodides when iodine is used as the oxidizing agent (224, 279, 431).



Oxidation leading to desulfuration can also occur (297).

$$C_6H_5NHC(=S)NHC_6H_5 + HgO \rightarrow C_6H_5NHCONHC_6H_5 + HgS \quad \text{(VIII-3)}$$
$$+ Br_2 \rightarrow (BrC_6H_4NH)_2CO$$

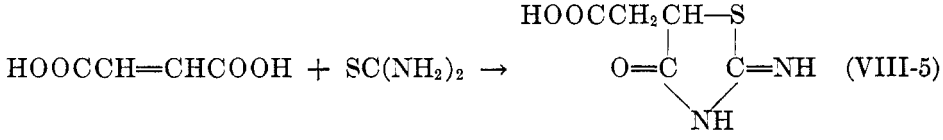
A well-known extension of the ease of oxidative desulfuration of "thioureas" occurs in the heterocyclic field (228, 261, 308, 418).



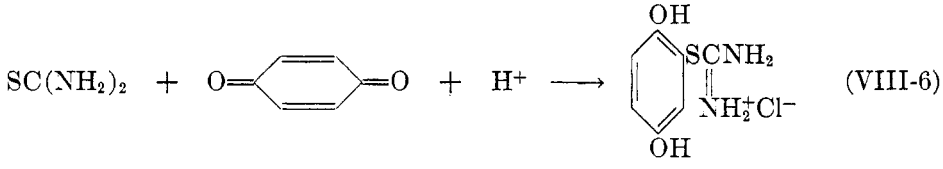
(VIII-4)

No attempt was made to review carbon–sulfur bond cleavages in the heterocyclic field; nonetheless, it should be pointed out that reductive cleavage with Raney nickel is often as useful as the above oxidative desulfuration (9).

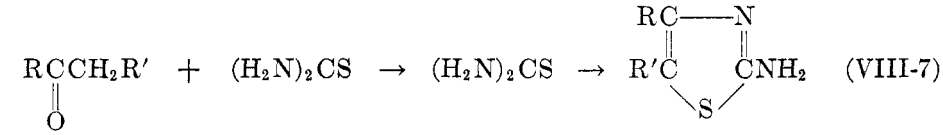
Thiourea and *N*-alkylated thioureas can condense with other systems forming two carbon–sulfur single bonds rather than the carbon–sulfur double bond. These reactions are promoted by acidic reagents (123, 132, 329, 370).



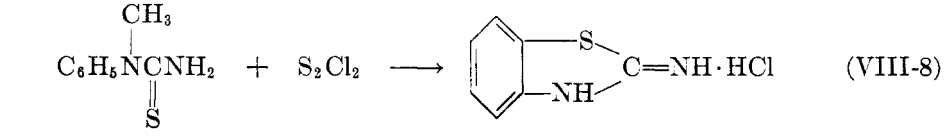
(VIII-5)



(VIII-6)

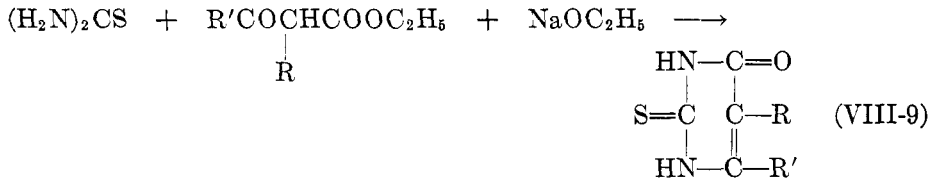


(VIII-7)



(VIII-8)

If basic reagents are used, condensation can occur on the nitrogens, producing a substituted thiourea, for example (6):

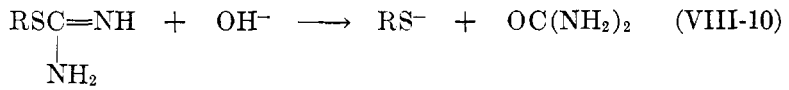


(VIII-9)

2. S-Alkylthioureas

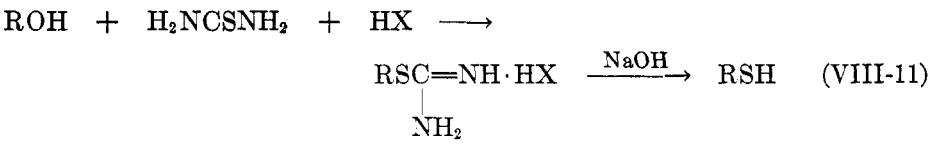
a. Nitrogen unsubstituted

Probably the most familiar reaction of the *S*-alkylthioureas is the cleavage with base to give mercaptans.



(VIII-10)

This reaction proceeds well even when R is tertiary butyl (19). Innovations in the method have been made (150) such that an alcohol can be used as starting material.



(VIII-11)

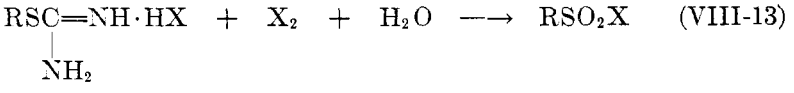
The intermediate *S*-alkylisothiourea need not be isolated.

It has been suggested that the *S*-alkylisothiourea picrates be made as derivatives to characterize alkyl bromides and iodides (77). This method is not applicable to the chlorides because of the unreactive nature of the halogen, and not applicable to tertiary halides because of an *S*-alkyl interchange which occurs with the solvent (260).

(VIII-12)

The interchange occurs very rapidly when R equals butyl, less readily when R equals other branched chains, and to no appreciable extent when R equals *n*-alkyl.

Oxidative halogenation of *S*-alkylisothioureas to sulfonyl halides also illustrates cleavage reactions wherein the alkyl group–sulfur linkage can be broken rather than the sulfur–urea carbon residue linkage.

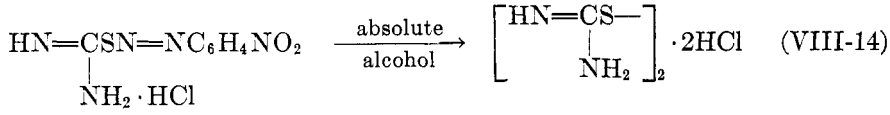


(VIII-13)

Good yields of sulfonyl halide are obtained when R is benzyl. If R is branched,

however, considerable sulfur is obtained as sulfate, indicating preliminary cleavage between the alkyl group and the sulfur atom. Tertiary butyl, for example, gives no sulfonyl chloride, only sulfate (*cf.* page 5) (386a).

One can find other *S*-substituted thioureas in which the group substituted on the sulfur is more weakly linked to the sulfur than is the carbon urea residue (84).

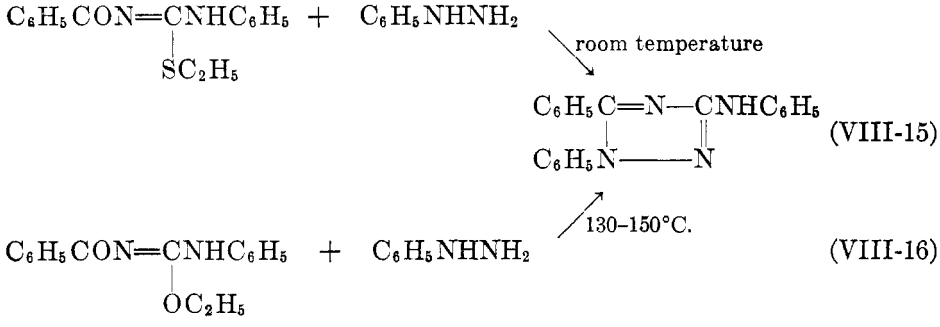


(VIII-14)

b. Nitrogen substituted

There appears to be little effect produced by substitutions on the nitrogens on the ease of cleavage of the carbon–sulfur bond in *S*-alkylisothioureas; at least the effect is not as great as variations in the *S*-alkyl group (84).

A comparison between *S*-alkylisothioureas and *O*-alkylisoureas can be obtained from the following reported reactions (225):



(VIII-15)

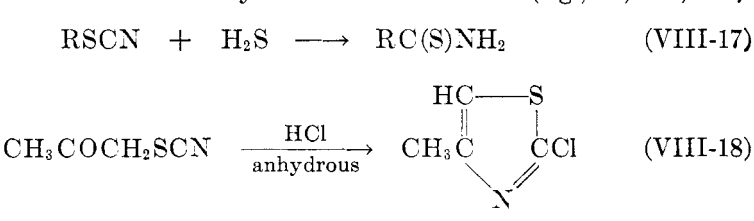
(VIII-16)

Other examples of similar nature have been reported (106).

The decreased reactivity of phenylthiourea toward *S*-alkylisothiourea picrate formation (77) is probably due to steric hindrance in formation and not to increased instability of the product formed, the picrate.

B. THIOCYANATES

Addition reactions of thiocyanates generally do not lead to compounds wherein the carbon–sulfur bond of the thiocyanate has been broken (e.g., 59, 411, 433).



(VIII-17)

(VIII-18)

(VIII-19)

The resultant compound may cleave under different conditions (72a):

$$RSC(S)NH_2 + KOH \xrightarrow{heat} RSH \quad \text{(90 per cent yield)} \qquad \text{(VIII-20)}$$

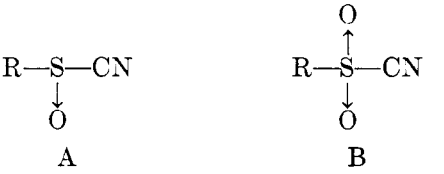
This section will discuss only those reactions wherein the carbon–sulfur bond of the thiocyanate is broken; the reader is referred to other sections of this paper for carbon–sulfur bond cleavages of the products resulting from addition reactions of the thiocyanates.

Oxidative reactions involving thiocyanates invariably lead to cleavage of the carbon–sulfur bond, the chief product being the corresponding sulfonic acid (59, 230, 277, 288).

$$RSCN + HNO_3 \rightarrow RSO_3H \qquad \text{(VIII-21)}$$

In addition to the expected sulfonic acids, other oxidized sulfur acids have been claimed, but their isolation and the proof of their structure are unconvincing (288). The other products resulting from reaction VIII-21 are probably nitrogen and carbon dioxide (277). Electrolytic oxidation also yields the sulfonic acid (144). Oxidation by chlorine and water gives the sulfonyl chloride (223).

No reference was found concerning compounds of type A or type B, the stability of which might give pertinent information as to the mechanism of the oxidative cleavage of thiocyanates.



A B

Reduction of thiocyanates generally leads to the corresponding mercaptan.

$$RSCN \xrightarrow{(H)} RSH \qquad \text{(VIII-22)}$$

Several reducing agents have been used, among which are zinc and hydrochloric acid (397), hydrogen iodide and phosphorus (175), and zinc and sodium carbonate (231). Reaction VIII-22 forms the basis for a useful method of introducing the mercapto group into an aromatic ring system.

$$Ar \rightarrow ArSCN \rightarrow ArSH \qquad \text{(VIII-23)}$$

It is claimed that reduction of allyl thiocyanate with sodium amalagam leads to allyl cyanide, but the compound isolated was not demonstrated conclusively to be allyl cyanide (46).

$$CH_2{=}CHCH_2SCN + Na(Hg) \rightarrow Na_2S + CH_2{=}CHCH_2CN \qquad \text{(VIII-24)}$$

One might postulate the formation of allyl cyanide as resulting from a displacement reaction of the —SCN (or —SH) by —CN, combined with an allylic shift (*cf.* also page 81).

Thiocyanates are cleaved by both basic and acidic reagents.

$$RSCN + \text{base} \rightarrow RSSR \qquad \text{(VIII-25)}$$

$$RSCN + \text{acid} \rightarrow RSH \qquad \text{(VIII-26)}$$

Although quantitative data are lacking, qualitative examples indicate that basic reagents bring about cleavage more rapidly than acidic reagents (120).

$$BrC_6H_4SCN + 10\%\ KOH \rightarrow (BrC_6H_4S)_2 + \text{some } BrC_6H_4SH \qquad \text{(VIII-27)}$$

$$BrC_6H_4SCN + 10\%\ H_2SO_4 \rightarrow \text{no reaction} \qquad \text{(VIII-28)}$$

$$BrC_6H_4SCN + 75\%\ H_2SO_4 \xrightarrow{\text{heat 1 hr.}} CO_2 + BrC_6H_4SH \qquad \text{(VIII-29)}$$

In reaction VIII-27, the mercaptan could have been formed from basic cleavage of the disulfide (*cf.* page 10). More probable, however, is the following mechanism (*cf.* reaction VIII-39):

$$RSCN + OH^- \rightarrow \left[\begin{array}{l} RSC{=}N \\ \quad | \\ \quad OH \end{array}\right]^- \rightarrow RS^- + HOCN \qquad \text{(VIII-30)}$$

$$2RS^- + HOCN + 2H_2O \rightarrow RSSR + NH_3 + CO + 2OH^- \qquad \text{(VIII-31)}$$

Cleavage with acid would proceed less rapidly, as it would involve protonation of the weakly basic —CN group, direct protonation of the sulfur being unlikely (*cf.* page 2). In acid solution the mercaptan produced is less likely to be oxidized by the cyanic acid.

$$HOCN + H_2O + H^+ \rightarrow CO_2 + NH_4^+ \qquad \text{(VIII-32)}$$

Of the basic cleavage reagents, it should be pointed out that the use of anhydrous ammonia gives the addition product (a substituted thiourea), while aqueous or alcoholic ammonia gives the expected scission product (64, 94, 222a, 242).

$$C_2H_5SCN + \text{anhydrous ammonia} \rightarrow C_2H_5SC(NH_2)NH \qquad \text{(VIII-33)}$$

$$C_2H_5SCN + NH_4OH \rightarrow (C_2H_5S)_2 + NH_4CN + (NH_2)_2CO \qquad \text{(VIII-34)}$$

The thiourea is known to cleave with base to yield the mercaptan and not the disulfide (*cf.* page 76); therefore reaction VIII-34 presumably is the basic cleavage reaction (VIII-27), followed by reaction of the ammonium and cyanate ions.

Use of potassium sulfide on a thiocyanate generally leads to the sulfide rather than the disulfide (114).

$$CH_3CH_2SCN + K_2S \rightarrow (CH_3CH_2)_2S + KSCN \qquad \text{(VIII-35)}$$

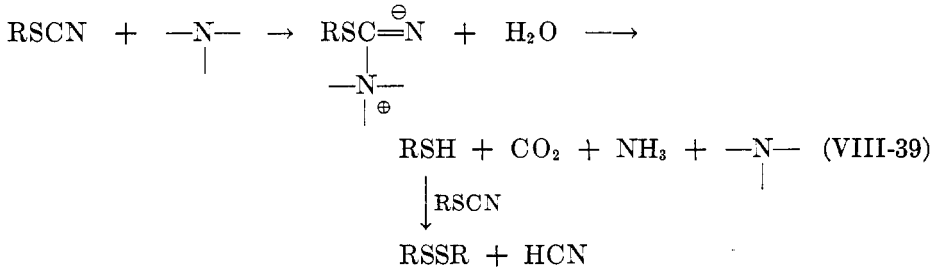
$$NCSCH_2CH_2SCN + K_2S \rightarrow \begin{array}{l} CH_2{-}CH_2 \\ \quad \diagdown\ \diagup \\ \quad\ S \end{array} \qquad \text{(VIII-36)}$$

Presumably the mechanism involved is a displacement on carbon.

$$CH_3CH_2SCN + K_2S \rightarrow CH_3CH_2S^- + KSCN + K^+ \quad \text{(VIII-37)}$$

$$CH_3CH_2S^- + CH_3CH_2SCN \rightarrow CH_3CH_2SCH_2CH_3 + SCN^- \quad \text{(VIII-38)}$$

When tertiary amines are allowed to react with thiocyanates, an intermediate salt is formed, the hydrolysis of which leads to a mercaptan and regeneration of the tertiary amine. It is reported that the mercaptan may then react with additional thiocyanate to give a disulfide.

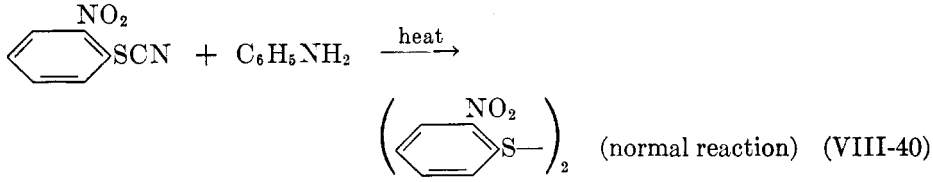


(The disulfide might well arise from an oxidation by the cyanic acid, as in reaction VIII-31.) This mechanism accounts well for the products obtained, and for the observed qualitative order of reactivity (196).

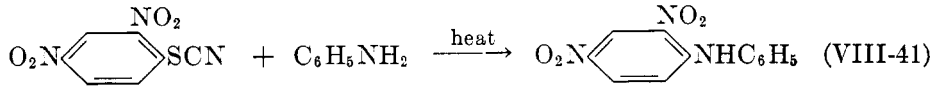
$$p\text{-}O_2NC_6H_4SCN > p\text{-}CH_3C_6H_4SCN > p\text{-}ClC_6H_4SCN > C_6H_5CH_2SCN \gg C_{12}H_{25}SCN$$

Earlier (254) it had been claimed that the reaction of methyl thiocyanate with trimethylamine gave tetramethylammonium thiocyanate, $(CH_3)_4N^+SCN^-$. Methyl isothiocyanate, it was also claimed, gave the same product but required a higher temperature and a longer time for reaction. This intermediate salt would not account for the products of hydrolysis. Also, the thermal conversion of thiocyanates into isothiocyanates is known (*cf.* page 81), the reverse reaction not having been observed.

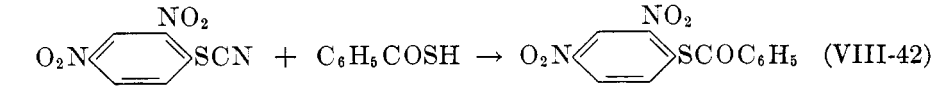
In certain negatively substituted aromatic thiocyanates, the —SCN group undergoes the expected displacement reaction (94, 434).



(normal reaction) (VIII-40)



(VIII-41)



(VIII-42)

Reaction VIII-42 is in contrast to the expected addition reaction (VIII-19) to give the thiocarbamate.

Chlorination of methyl thiocyanate under anhydrous conditions leads to a mixture of $CSCl_4$, $CSCl_2$, CCl_4, and SCl_2 (79, 222).

Thiocyanates react with the Grignard reagent to give a mixture of products resulting from two main reactions (1):

$$RSCN + RMgBr \rightarrow RSR + MgBrCN \qquad \text{(VIII-43)}$$

$$RSCN + RMgBr \rightarrow RSMgBr + RCN \xrightarrow{RMgBr} RCOR \qquad \text{(VIII-44)}$$

$$\downarrow$$

$$RSH$$

When R is alkyl in the thiocyanate, both reactions VIII-43 and VIII-44 proceed about equally to give a mixture of products. When R is aromatic in the Grignard reagent, then the latter reaction (VIII-44) predominates.

Allyl thiocyanates isomerize on heating to yield the isothiocyanates (42a). No rearrangement of the carbon skeleton is observed.

$$C_6H_5CH{=}CHCH_2SCN \rightarrow C_6H_5CH{=}CHCH_2NCS \qquad \text{(VIII-45)}$$

This isomerization may account for the observation given in reaction VIII-24. Reactions of the isothiocyanates are not included in this paper, but it may be pointed out that allyl isothiocyanate gives some allyl cyanide on standing for a long time in water (437) or when desulfurized over hot zinc (372).

IX. References

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