

**MULTI-SULFUR AND SULFUR AND OXYGEN
FIVE- AND SIX-MEMBERED HETEROCYCLES**

**In Two Parts
PART TWO**

This is Part Two of the twenty-first volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Consulting Editor*



**MULTI-SULFUR AND SULFUR
AND OXYGEN FIVE- AND
SIX-MEMBERED HETEROCYCLES**

Part Two

David S. Breslow

Herman Skolnik

Hercules Research Center, Hercules Incorporated, Wilmington, Delaware

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C. C ₂ O ₂ Se-C ₄ O Furo[3, 4- <i>d</i>]-1, 3, 2-dioxaselenole	1273
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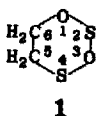
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$C_2O_2S_2$ RING SYSTEMS

Only one arrangement of heteroatoms is known in $C_2O_2S_2$ rings. The compounds are all related to carbyl sulfate, 1, 3, 2, 4-dioxadithiane 2, 2, 4, 4-tetroxide (2). Chemical Abstracts indexed this ring system under carbyl sulfate until 1936 and under 1, 3, 2, 4-dioxadithiane since that time.

I. $C_2O_2S_2$

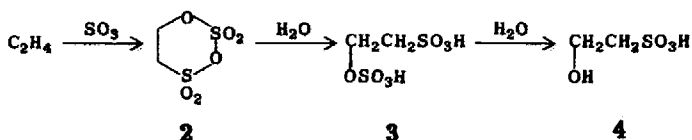
A. 1, 3, 2, 4-DIOXADITHIANE (1)



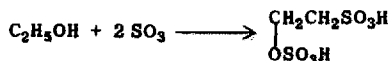
(RRI 180)

1. Preparation

In 1837 Regnault²⁹ passed ethylene and sulfur trioxide vapors through a U-tube. An exothermic reaction took place and white crystals, melting at about 80°, were formed. Magnus²⁴ named the compound carbyl sulfate (2) and indicated its structure by its hydrolysis to ethionic acid (3) and isethionic acid (4).

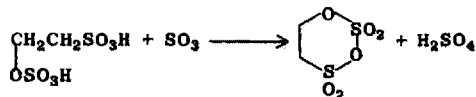


Thus, carbyl sulfate is the cyclic anhydride of ethionic acid (3). Magnus^{23,24} showed that carbyl sulfate is also formed in the reaction of ethanol with sulfur trioxide. However, carbyl sulfate is not a primary product of the reaction as indicated by Magnus, but is formed, according to Breslow and co-workers,^{8,9} by the dehydration of ethionic acid by sulfur trioxide. Thus, the reaction of one mole of ethanol with two moles of sulfur trioxide yields ethionic acid, while the reaction with three moles of sulfur trioxide yields carbyl sulfate.



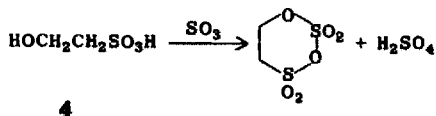
[For references, see pp. 624-625.]

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Since sulfuric acid is formed in the dehydration, this procedure is not recommended for the preparation of pure carbyl sulfate.

Carbyl sulfate has been prepared by the reaction of isethionic acid (4) with two moles of sulfur trioxide.²⁶



Carbyl sulfate is formed along with other products in the sulfonation of diethyl ether with sulfur trioxide;²⁰ diethyl sulfate was postulated as an intermediate. Absorption of ethylene by fuming sulfuric acid apparently also leads to the formation of some carbyl sulfate.^{27,28}

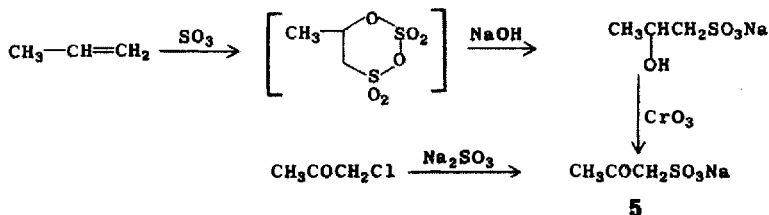
Carbyl sulfate is best prepared by the vapor phase reaction of ethylene with sulfur trioxide. Breslow and Hough⁹ found that carbyl sulfate could be obtained in 96% yield by a modification of the procedure of Regnault²⁹ and of Merley and Spring.²⁵ Gaseous sulfur trioxide was reacted with an excess of ethylene in a narrow tube and the liquid carbyl sulfate was allowed to flow into a receiver through a steam-heated condenser. Daimler and Platz¹³ claimed a 90% yield by carrying out the reaction in liquid sulfur dioxide, but it should be noted that a considerable excess of sulfur trioxide was used. This difficulty was apparently circumvented by carrying out the reaction in a special apparatus.¹⁷ Ethylene, sulfur trioxide, and sulfur dioxide were mixed in a nozzle under pressure at 20-70° and sprayed into a chamber, the vaporization of sulfur dioxide serving to cool the reaction. The procedure does not appear, however, to be suitable as a laboratory preparation.

It is quite remarkable, considering how long it has been known, that carbyl sulfate has been characterized only recently. Michael and Weiner²⁶ reported that carbyl sulfate melts at 80-85° and that it fumes and liquifies on exposure to air. Apparently this product, prepared by Regnault's procedure,²⁹ contains sulfur trioxide, since according to Breslow and Hough⁹ pure carbyl sulfate melts at 107.5-109°, does not fume in air, and liquifies only slowly on exposure to moisture.

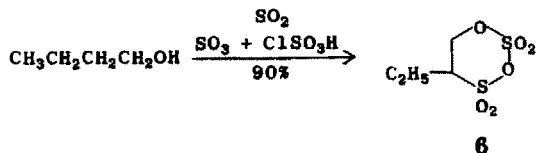
There is a large body of literature, predominantly patents, on the reaction of higher olefins with sulfur trioxide to form surfactants,^{2,35} and it has been generally assumed that a carbyl sulfate-type intermediate is involved. This, however, has been questioned (see section IB). Suter, Evans, and Kiefer³³ showed definitely by the following series of reactions that with a 1-olefin the sulfonic acid group is attached to the terminal carbon, since the same ketosulfonic acid (5) is formed by oxidizing the hydrolysis product from the reaction of propylene and sulfur

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trioxide as is obtained by the reaction of chloroacetone with sodium sulfite.

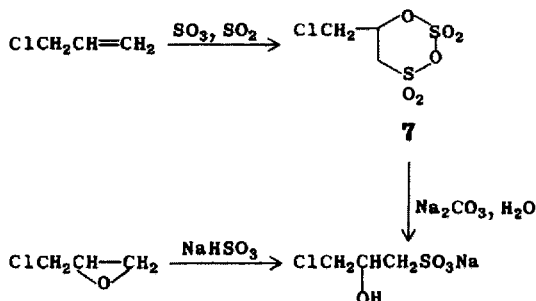


There are only a few instances, however, in which a substituted carbyl sulfate has been isolated. Daimler and Platz¹³ claimed that *n*-butanol yields crystalline 5-ethyl-1, 3, 2, 4-dioxadithiane 2, 2, 4, 4-tetroxide (6), but no properties were given.



This structure is questionable, since it is conceivable that the alcohol would be dehydrated to the olefin in refluxing sulfur dioxide. If it were, the product would be the 6-ethyl derivative by analogy with Suter's work.

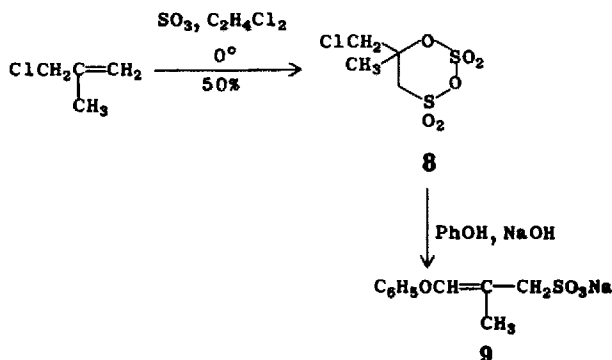
Ross³⁰ claimed that the reaction of allyl chloride with sulfur trioxide in refluxing sulfur dioxide gives crystalline 6-chloromethyl-1, 3, 2, 4-dioxadithiane 2, 2, 4, 4-tetroxide (7). Although no properties were given, he did prove that the sulfur was attached to the terminal carbon.



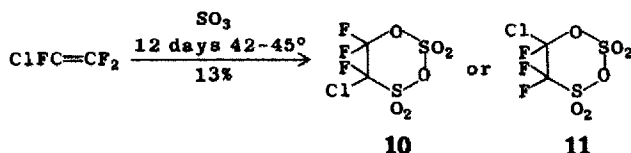
Only one crystalline compound other than carbyl sulfate has been isolated and adequately characterized. Suter and Bordwell³⁴ found that the reaction of two moles of sulfur trioxide dissolved in ethylene chloride with one mole of methallyl chloride at 0° gives a 50% yield of 6-methyl-6-chloromethyl-1, 3, 2, 4-dioxadithiane 2, 2, 4, 4-tetroxide (8) as colorless rosetts melting at 66-68° with decomposition. The compound is

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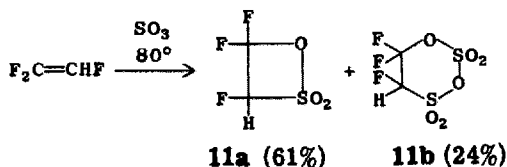
unusual in that it is a derivative of a tertiary alkyl ester of sulfuric acid, and no tertiary esters of sulfuric acid are known. It decomposes slowly at room temperature but is stable indefinitely at -5° . It hydrolyzes very readily in water, presumably to the expected hydroxysulfonic acid, while treatment with base yields an unsaturated sulfonic acid, in which respect it is similar to carbyl sulfate itself. Further proof of its structure was obtained by its reaction with phenol and excess alkali to form sodium 2-methyl-3-phenoxy-2-propene-1-sulfonate (9).



Jiang²¹ reacted chlorotrifluoroethylene with sulfur trioxide. At -20° he isolated what he considered to be a mixture of β -sultones, while at 45° he isolated a compound, b.p. 119° , n_D^{21} 1.3797, to which he tentatively assigned a carbyl sulfate structure, either 5-chloro-5,6,6-trifluoro-1,3,2,4-dioxadithiane 2,2,4,4-tetroxide (10) or the corresponding 6-chloro-5,5,6-trifluoro isomer (11).

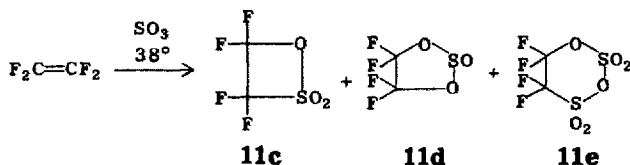


England, Dietrich, and Lindsey^{16a} investigated the reaction of a number of fluorinated olefins with sulfur trioxide. Trifluoroethylene reacted with freshly distilled sulfur trioxide to yield a mixture of β -sultone (11a) and a product, b.p. $156-157^{\circ}$, which analyzed as a 1 olefin : 2 SO_3 adduct. Inasmuch as they proved that 11a has an oxygen attached to the CF_2 group, they formulated the 1 : 2 adduct as 5,6,6-trifluoro-1,3,2,4-dioxadithiane 2,2,4,4-tetroxide (11b).

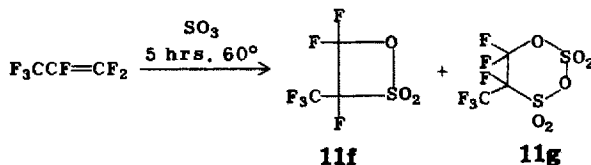


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Vinylidene fluoride yielded only an unstable 1:2 adduct, presumably a carbyl sulfate derivative. Under their conditions chlorotrifluoroethylene yielded only the mixture of β -sultones obtained by Jiang. Whereas tetrafluoroethylene formed only a β -sultone (11c) with freshly distilled sulfur trioxide, the use of commercial sulfur trioxide (Sulfan B) led to the formation of three products, the β -sultone (11c), 4,4,5,5-tetrafluoro-1,3,2-dioxathiolane 2-oxide (11d), and a 1:2 adduct assumed to be 5,5,6,6-tetrafluoro-1,3,2,4-dioxadithiane 2,2,4,4-tetroxide (11e), a fuming liquid boiling at 100-108°. 11e, b.p. 105-106°, n_D^{20} 1.3470, d_{20} 1.7407, was isolated, presumably as the sole product, by Dmitriev, Sokol'skii, and Knunyants^{14a} from the reaction of tetrafluoroethylene with dimeric sulfur trioxide, monomeric sulfur trioxide yielding only the sultone (11c).



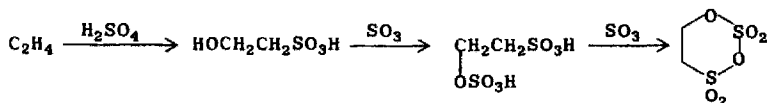
Similarly, England, Dietrich, and Lindsey found that perfluoropropylene yields a mixture of β -sultone (11f) and, presumable, 5-trifluoromethyl-5,6,6-trifluoro-1,3,2,4-dioxadithiane 2,2,4,4-tetroxide (11g), b.p. 114-115°, since the structure of 11f was proved unequivocally.



The authors attributed the difference between distilled and undistilled sulfur trioxide to the presence of polymer in the latter.

2. Mechanism of Formation

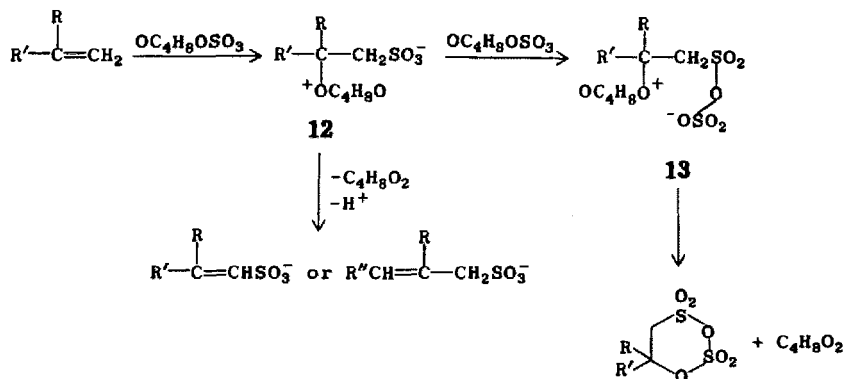
The mechanism of formation of carbyl sulfate from ethylene and fuming sulfuric acid or sulfur trioxide has been a subject of conjecture for some time. Wieland and Sakellarios³⁷ believed that sulfuric acid adds to ethylene as HO and SO₃H and that carbyl sulfate is formed subsequently.



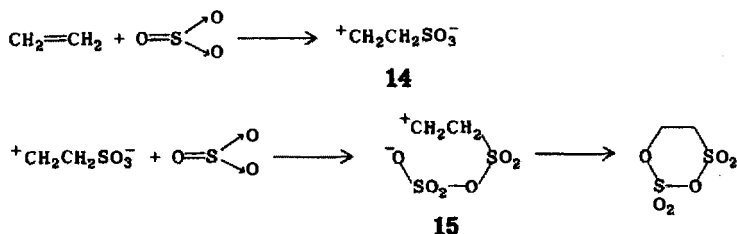
Since ethylene is known to react with sulfuric acid to form ethylsulfuric acid, and since carbyl sulfate can be formed with pure sulfur trioxide, this mechanism is obviously incorrect. Michael and Weiner²⁶ believed

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that the active sulfonating agent is S_2O_6 and that carbyl sulfate is the primary product of the reaction. Although they are undoubtedly correct in the second assumption, it has been pointed out by Suter, Evans, and Kiefer³³ that the dioxane-sulfur trioxide complex reacts with olefins to form carbyl sulfate-type products, and that there is no S_2O_6 in the complex. The latter statement has been questioned by Dombrovskii and Prilutskii.¹⁵ A mechanism which explains adequately the products of the reaction of olefins with the dioxane- SO_3 complex was postulated by Bordwell, Suter, and Webber.³ The reaction is initiated by the attack of the electrophilic sulfur of SO_3 on the terminal carbon of a 1-olefin, analogous to halogenation, or, alternatively, there is a nucleophilic displacement of dioxane from the dioxane- SO_3 complex by the olefin, to form intermediate **12**. If R and R' are hydrogens, or if R is hydrogen and R' is an alkyl group, the intermediate **12** attacks another molecule of dioxane- SO_3 , again by a nucleophilic displacement to give intermediate **13**, in which a nucleophilic displacement of dioxane by the negative sulfate group closes the ring to the substituted carbyl sulfate. If R and R' are alkyl or if either R or R' is phenyl, the second step does not take place and intermediate **12** loses dioxane and a proton to form an α, β - or β, γ -unsaturated sulfonic acid.



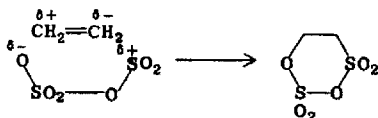
In the vapor phase reaction of ethylene with sulfur trioxide the mechanism should be quite similar:



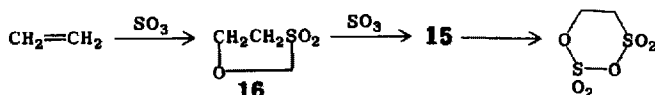
However, the existence of an unsolvated carbonium ion is dubious. The reaction might be concerted, involving the simultaneous attack of two SO_3 molecules on ethylene, but termolecular reactions in the vapor

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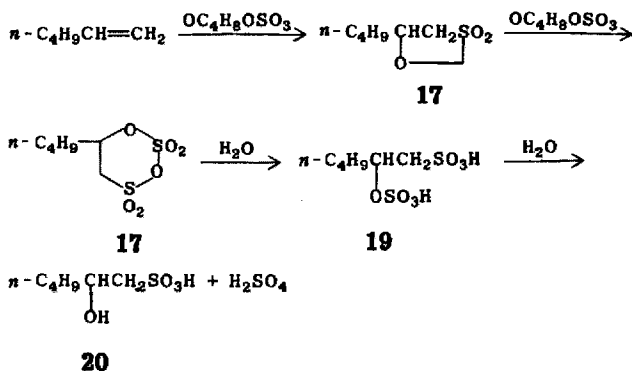
phase are very rare. It might involve S₂O₆, in agreement with Michael and Weiner,²⁶ although SO₃ is monomeric in the vapor state.²² Certainly the work of England, Dietrich, and Lindsey^{16a} and of Dmitriev, Sokol'skii, and Knunyants^{14a} (see section I A-1) seems to indicate that, at least under their conditions, fluorinated olefins yield carbyl sulfates by reaction with a dimer or higher polymer of sulfur trioxide.



A third alternative would involve the formation of a β -sultone (**16**). SO₃ would presumably attack the carbon-oxygen bond in **16** to give the intermediate **15**, since sulfate esters can undergo carbon-oxygen cleavage, although sulfur-oxygen cleavage by electrophilic attack of SO₃ cannot be ruled out.



Bordwell and co-workers in recent years have contributed considerable evidence that β -sultones are formed in the sulfonation of olefins with the dioxane-sulfur trioxide complex. Sulfonation of styrene with this complex yielded a product which showed the reactions expected of a β -sultone,⁵ and this possible intermediate was investigated more thoroughly.⁶ 1-Hexene was reacted at 0° with two moles of dioxane-SO₃. One mole reacted rapidly to give an intermediate, presumably the β -sultone **17**, which reacted slowly with a second mole to give the substituted carbyl sulfate (**18**) in 80-90% yield. This was not isolated, but hydrolysis with cold water gave the expected substituted ethionic acid (**19**). Heating the acid solution yielded the hydroxysulfonic acid (**20**) with liberation of the calculated quantity of sulfuric acid.

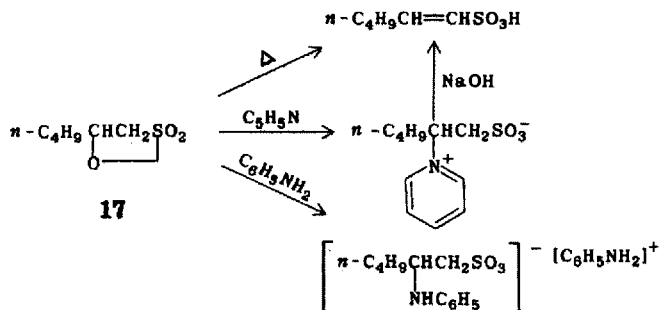


By reacting 1-hexene with an equimolar quantity of dioxane-SO₃ and determining the amount of sulfuric acid liberated on hydrolysis, it was

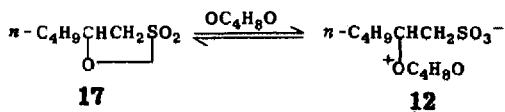
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shown that most of the hydroxysulfonic acid (20) was formed by hydrolysis of the β -sultone (17) and not by hydrolysis of the substituted carbyl sulfate. The same conclusion had been reached in the case of styrene.^{4,36} This casts considerable doubt on the general assumption that the formation of a hydroxysulfonic acid on hydrolysis is indicative of a carbyl sulfate-type intermediate.

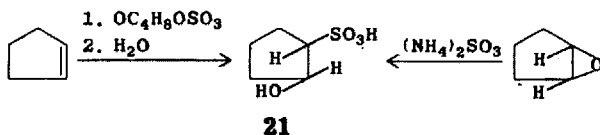
Several other reactions were carried out to show the similarity of the presumed β -sultone intermediate (17) with styrene β -sultone.



These reactions could, however, be explained just as readily on the assumption that the intermediate is the solvated zwitterion (12). That this was not the case was indicated by the fact that dioxane accelerated markedly the sulfonation of the intermediate, perhaps by formation of the solvated zwitterion.



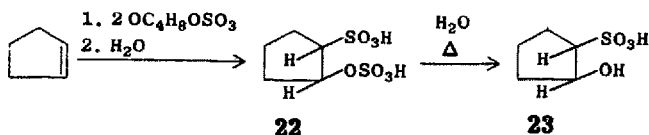
More direct proof of the formation of a β -sultone was obtained by studying the stereochemistry of the sulfonation of cyclopentene and cyclohexene.⁷ Treatment of cyclopentene with an equimolar quantity of dioxane-sulfur trioxide followed by hydrolysis yielded primarily *trans*-2-hydroxycyclopentanesulfonic acid (21). This acid was identical with one prepared by reacting cyclopentene oxide with ammonium sulfite. Since the oxide must be *cis* and since *trans* opening of epoxide rings by treatment with nucleophilic reagents is well established, both acids must be *trans*.



Reaction of cyclopentene with two moles of dioxane-sulfur trioxide gave different results. Hydrolysis of the reaction mixture with cold water yielded 2-hydrosulfatocyclopentanesulfonic acid (22), while further

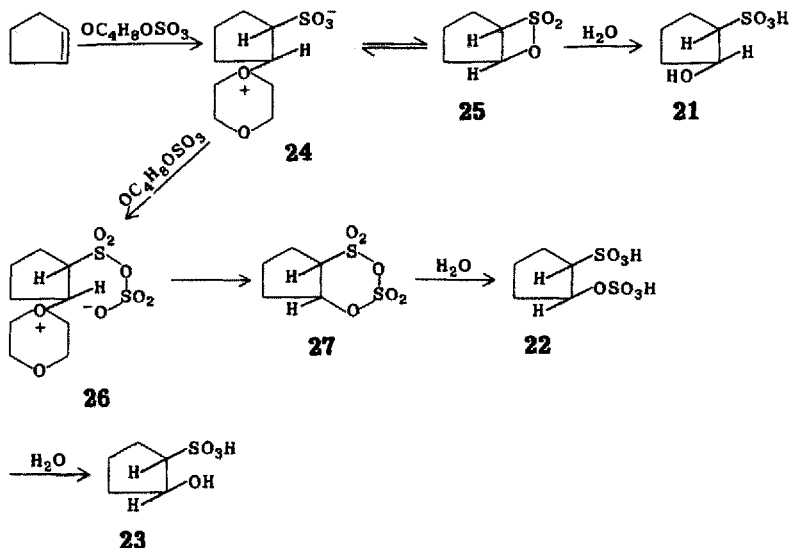
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hydrolysis formed a 2-hydroxycyclopentanesulfonic acid (**23**) isomeric with the *trans* compound. It must therefore be *cis*.



Sulfation of the *cis*-hydroxysulfonic acid (**23**) regenerated the ethionic acid (**22**), while sulfation of the *trans*-acid (**21**) yielded an isomeric product. Since acid-catalyzed hydrolysis of alkyl hydrogen sulfate esters is known to proceed by cleavage of the sulfur-oxygen bond,^{10,11} and since sulfation of secondary alcohols proceeds with retention of configuration,⁷ all the compounds in this series must have the *cis* configuration.

These results seem to be best explained on the basis of a β -sultone intermediate (**25**), probably in equilibrium with a solvated zwitterion (**24**). The β -sultone must be *cis* because of the smallness of the rings; reaction with water would proceed with inversion to give the *trans*-hydroxysulfonic acid (**21**). The zwitterion (**24**) would react with dioxane-SO₃ to give intermediate **26**. This would then ring close with inversion to give the substituted *cis*-carbyl sulfate (**27**), which on hydrolysis would lead to the *cis*-hydroxysulfonic acid (**23**).



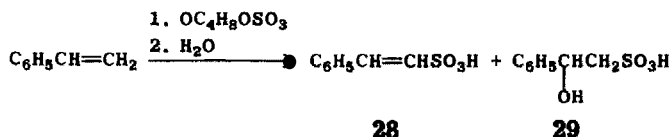
If the zwitterion were the only intermediate, it should exchange with dioxane and a mixture of *cis* and *trans* isomers would result on hydrolysis. If it exchanged, however, only by reaction of dioxane with the β -sultone, no inversion would take place and the stereospecificity would be

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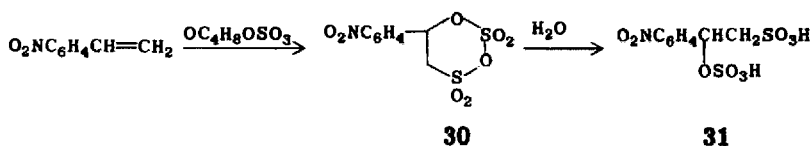
retained. A parallel series of experiments with cyclohexene showed that two moles of sulfonating agent yielded the corresponding *cis* derivatives. Sperling³¹ incorrectly assigned the *trans* configuration to these compounds. One mole of sulfonating agent gave only the unsaturated sulfonic acid.

After the completion of this work England, Dietrich, and Lindsey,^{16a} as well as Jiang,²¹ showed that fluorinated olefins, under certain conditions, yielded exclusively β -sultones on reaction with sulfur trioxide, whereas carbyl sulfate type compounds can be formed by varying the conditions (see section I A-1).

An interesting situation exists in the sulfonation of substituted styrenes with dioxane-SO₃. Bordwell and Rondestvedt⁴ found that styrene itself gives as the major products 2-phenylethene-1-sulfonic acid (**28**) and 2-phenyl-2-hydroxy-1-ethanesulfonic acid (**29**), presumably *via* the β -sultone.

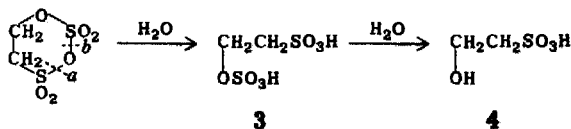


Truce and Gunberg³⁶ found, however, that sulfonation of *m*- and *p*-nitrostyrenes leads, after hydrolysis, to excellent yields of substituted ethionic acids (**31**), undoubtedly through the intermediate formation of substituted carbyl sulfates (**30**).



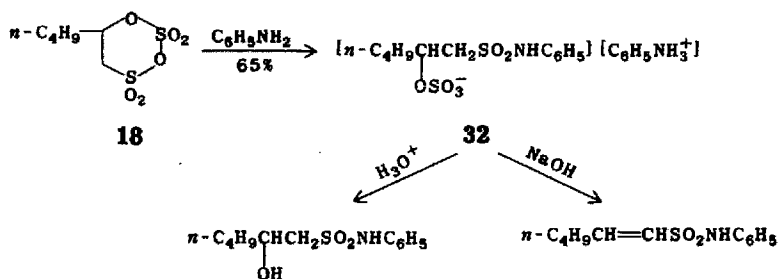
3. Reactions

As already mentioned, carbyl sulfate hydrolyzes readily in water, first to ethionic acid (**3**) and then, on heating, to isethionic acid (**4**).



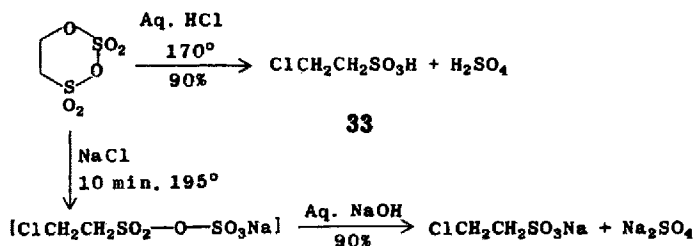
There is no direct evidence as to whether the hydrolysis takes place at *a* or at *b*. Bordwell and Peterson⁶ have shown that the reaction of 6-*n*-butyl-1, 3, 2, 4-dioxadithiane 2, 2, 4, 4-tetroxide (**18**) with aniline yields predominately the anilinium salt of 2-hydrosulfato-2-hexanesulfonanilide (**32**), undoubtedly by cleavage at *a*.

C₂O₂S₂ Ring Systems

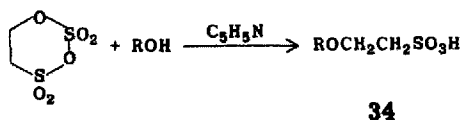


Carbyl sulfate itself has been shown to yield ethylenesulfonanilide on treatment with aniline followed by base, presumably through the same intermediates as shown above,¹⁶ and it has been inferred from this that carbyl sulfate probably hydrolyzes by breaking the sulfur-oxygen anhydride bond at α .⁶

Under certain conditions carbyl sulfate appears to act as an alkylating agent. Thus, Adams, Eatough, and Marvel¹ reported a 90% yield of 2-chloroethanesulfonic acid (**33**) from heating carbyl sulfate with concentrated hydrochloric acid at 170°. Catlin and Jenkins¹² obtained the corresponding sodium salt by heating carbyl sulfate with sodium chloride and treating the intermediate with aqueous base.

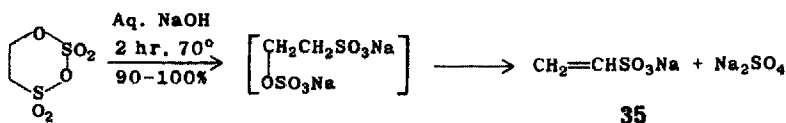


Carbyl sulfate has been reported to react with high molecular weight alcohols to form 2-alkoxyethanesulfonic acids (**34**)³² and with cellulose in the presence of pyridine to form a sulfoethyl ether.¹⁴



Thus, with certain reagents carbyl sulfate appears to act as an alkylating agent, undergoing carbon-oxygen cleavage like dialkyl sulfates.

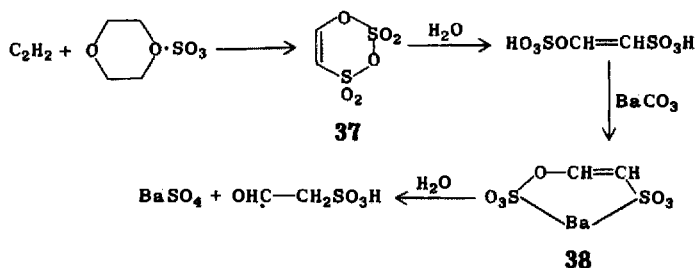
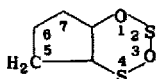
The most useful reaction of carbyl sulfate is its essentially quantitative conversion into sodium ethylenesulfonate (**35**) with aqueous base, presumably via the intermediate formation of sodium ethionate.⁹



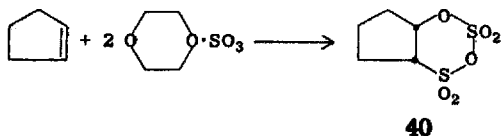
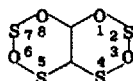
[For references, see pp. 624-625.]

B. 1, 3, 2, 4-DIOXADITHIIN (36)**36**

Dombrovskii and Prilutskii¹⁵ suggested the formation of 1, 3, 2, 4-dioxadithiin 2, 2, 4, 4-tetroxide (**37**) as an intermediate in the sulfonation of acetylene with the dioxane-sulfur trioxide complex. Although the compound was not isolated, they did obtain the barium salt (**38**) formed by its hydrolysis.

II. C₅-C₂O₂S₂ 5H-CYCLOPENTA-1, 3, 2, 4-DIOXADITHIIN (39)**39**

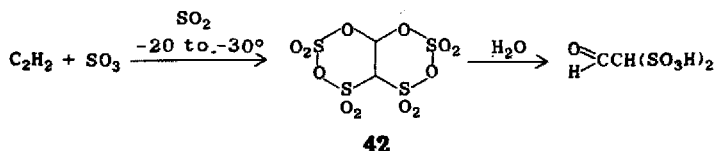
Bordwell and Peterson⁷ postulated the formation of *cis*-tetrahydro-5H-cyclopenta-1, 3, 2, 4-dioxadithiin 2, 2, 4, 4-tetroxide (**40**) by the sulfonation of cyclopentene with two moles of dioxane-sulfur trioxide; the compound was not isolated (see section IA-2).

**40**III. C₂O₂S₂-C₂O₂S₂ 1, 3, 2, 4-DIOXADITHIINO[5, 6-*e*]-1, 3, 2, 4-DIOXADITHIIN (41)**41**

In 1898 Schroeter^{30a} reacted acetylene with fuming sulfuric acid and isolated, after hydrolysis, acetaldehydesulfonic acid. By substituting

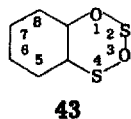
C₂O₂S₂ Ring Systems

sulfur trioxide for oleum and carrying out the reaction in liquid sulfur dioxide Gilbert and Otto^{19, 19b} were able to isolate a brown, resinous mass, which they formulated as dihydro-1, 3, 2, 4-dioxadithiino[5, 6-*e*]-1, 3, 2, 4-dioxadithiin 2, 2, 4, 4, 5, 5, 7, 7-octaoxide (**42**) because hydrolysis yielded acetaldehydedisulfonic acid.^{19a, 19b}



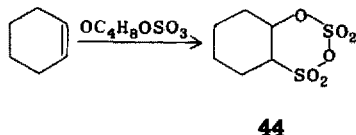
42 was reported to react with alkylbenzenes to form surface-active agents.¹⁸ Other reactions of acetaldehydedisulfonic acid have been described.^{19b}

IV. C₃O₂S₂-C₆ 1, 3, 2, 4-BENZODIOXADITHIIN (**43**)



(RRI 1492)

Sperling³¹ claimed that the reaction of cyclohexene with dioxane-sulfur trioxide yields hexahydro-1, 3, 2, 4-benzodioxadithiin 2, 2, 4, 4-tetroxide (**44**) as the primary product.



The compound was not isolated as such, but it was assigned the *trans* configuration. Bordwell and Peterson⁷ have shown, however, that the ring fusion is *cis* (see section I A-2).

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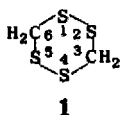
CHAPTER 7

C₂S₄ RING SYSTEMS

The existence of this ring system has been confirmed only recently. Only one arrangement is known, the symmetrical 1, 2, 4, 5-tetrathia compounds.

I C₂S₄

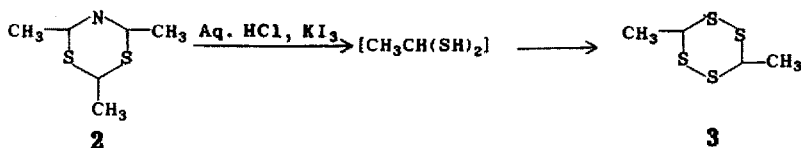
A. S-TETRATHIANE (1)



(RRI 182)

This ring system is indexed in Chemical Abstracts under the above name. It is also called 1, 2, 4, 5-tetrathiane or 1, 2, 4, 5-tetrathiacyclohexane. In the old literature the compounds are called duplodithioketones.

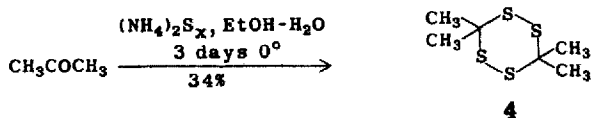
In 1887 Fasbender⁷ attempted to prepare 3, 6-dimethyl-s-tetrathiane (3), which he called diethylidene tetrasulfide, from thialdin (2).



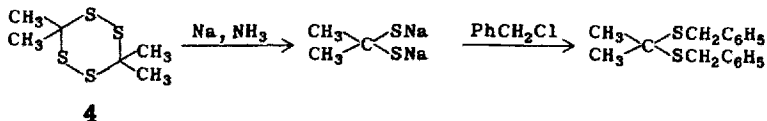
He obtained an amorphous, odorless powder, with a rather poor analysis. Although Fasbender assigned an s-tetrathiane structure to the material, it was undoubtedly a polymer.

In the same year Willgerodt¹² treated acetone with ammonium polysulfide and isolated a crystalline compound, melting at 98° and boiling at 243° with some decomposition. The compound had a characteristic unpleasant odor, was insoluble in water and was soluble in the common organic solvents. Although the compound analyzed as C₃H₆S₂, Willgerodt assumed it to be dimeric and named it duplodithioacetone (4). In 1958 Fredga⁸ repeated the preparation; he found that the reaction failed with higher homologs and with aromatic ketones. Magnusson^{10a} obtained a better yield by carrying out the reaction at a low temperature in aqueous alcohol.

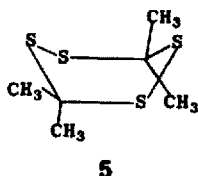
C₂S₄ Ring Systems



Reduction with sodium and ammonia followed by reaction with benzyl mercaptan gave the known acetone dibenzylmercaptol, thus confirming the proposed *s*-tetrathiane structure and eliminating the alternative 1, 2, 3, 5-tetrathiane structure.

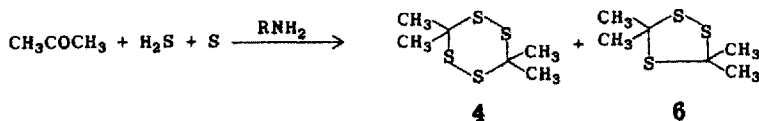


A preliminary crystallographic determination by Lindqvist and Rosenstein⁸ confirmed its structure as 3, 3, 6, 6-tetramethyl-*s*-tetrathiane (**4**). The molecule appears to exist in one of the two possible boat forms (**5**).

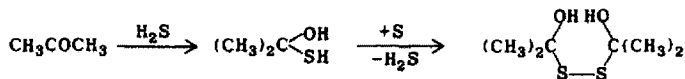


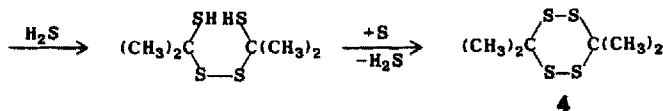
It is not readily apparent from an inspection of molecular models why this molecule should prefer the quite uncommon boat form.

Asinger and co-workers^{1,2,2a} isolated the same compound, m. p. 95°, as a by-product obtained in 11% yield from the synthesis of 3, 3, 5, 5-tetramethyl-1, 2, 4-trithiolane (**6**) from acetone, sulfur, and hydrogen sulfide in diisobutylamine as solvent (see Chapter 3, section II A). By increasing the amount of sulfur the yield of **4** was raised to 50%.

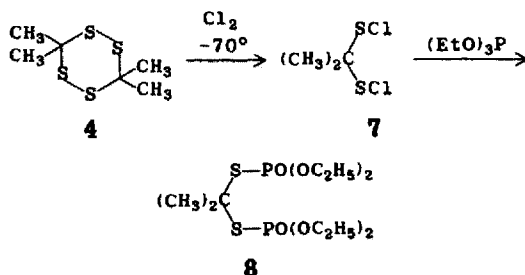


3, 3, 6, 6-Tetraethyl-*s*-tetrathiane, m. p. 44-46°, was prepared similarly from diethyl ketone. Asinger and Thiel^{2,2a} postulated the following mechanism to explain the formation, the hydroxyl group being replaceable by an amine function.



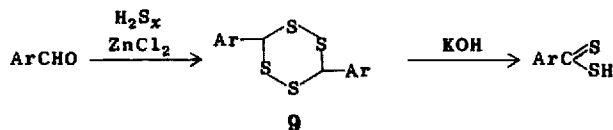


The only proof of structure offered by Asinger involved low-temperature chlorination of **4** to the *gem*-disulphenyl chloride (**7**), which reacted with triethyl phosphite to yield the known bis(thiophosphate ester) (**8**).



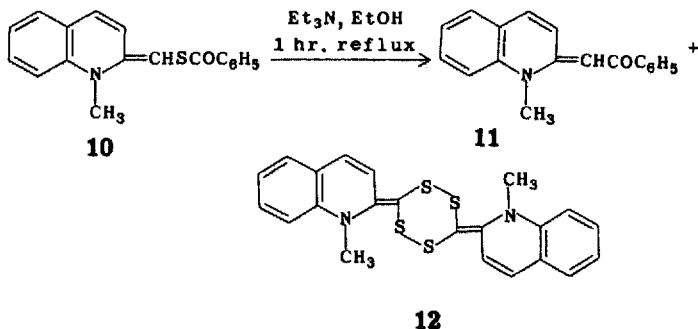
Asinger and co-workers^{2,2a} have shown that the reactions of ketones with amines and sulfur-containing compounds can lead to a variety of products, depending on the nature of the ketone, the reagents used, and the reaction conditions.

Bloch and co-workers^{3-5,9} reacted aromatic aldehydes with hydrogen persulfide (H_2S_x , where $x = 2$ or 3) in the presence of an acid catalyst and obtained an amorphous product which they formulated as a tetra-thiane (9). The reaction was carried out with benzaldehyde, salicylaldehyde, and anisaldehyde. None of the compounds was isolated pure. The benzaldehyde compound was investigated most thoroughly and the product analyzed approximately for $C_{14}H_{12}S_4$. It was a brownish, resinous material which melted at $80-90^\circ$ and decomposed at about 120° . It was also obtained by treating the crystalline adducts of benzaldehyde with H_2S_2 and H_2S_3 with zinc chloride. Since the only proof of structure given was the fact that reaction with alkali gave a better than 50% yield of dithiobenzoic acid, the structure of these compounds remains in doubt.



More recently, Knott¹⁰ decomposed 2-benzoylthiomethylene-1, 2-dihydro-1-methylquinoline (10) with triethylamine in ethanol and isolated a mixture of 1, 2-dihydro-1-methyl-2-phenacylidenequinoline (11) and an unknown compound which he formulated as 3, 6-bis(1, 2-dihydro-1-methyl-2-quinolyldiene)-s-tetrathiane (12).

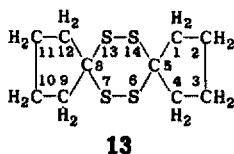
C₂S₄ Ring Systems



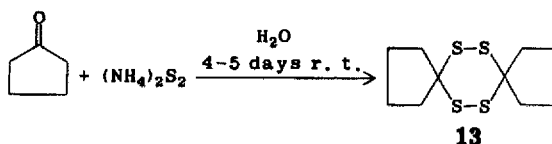
The compound was isolated as brown needles melting at 239° (with darkening at 227°); it was too insoluble for a molecular weight determination.

B. SPIRO DERIVATIVES

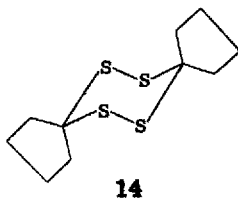
1. C₅-C₅-C₂S₄ 6, 7, 13, 14-Tetrathiadispiro[4. 2. 4. 2]tetradecane (13)

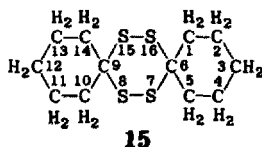


According to Fredga⁸ 13 was prepared in very low yield by Magnusson from cyclopentanone and ammonium disulfide.

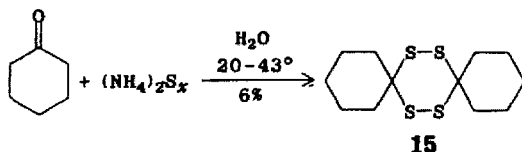


The compound melts at 151.5-153°. A preliminary crystallographic investigation by Lindqvist and Rosenstein indicated that the molecule exists in the chair form (14), in contrast to the boat form assumed by 3, 3, 6, 6-tetramethyl-s-tetrathiane.

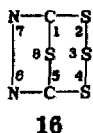


2. C₂S₄-C₆-C₆ 7, 8, 15, 16-Tetrathiadispiro[5. 2. 5. 2]hexadecane (15)

This compound was prepared by both Fredga⁸ and by Asinger and co-workers.^{1,2,2a} Fredga reported a melting point of 130. 5-131. 5° and



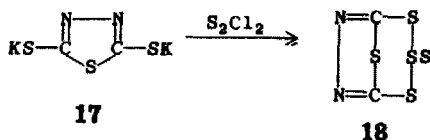
Asinger of 133°. Another instance of the effect of reaction conditions on the products formed in these reactions was indicated by Magnusson,^{10a} who isolated a 1, 2, 3, 5, 6-pentathiepane when the above reaction was carried out at 0-4° in aqueous ethanol.

II C₂N₂S-C₂S₄ 2, 3, 4, 8-TETRATHIA-6, 7-DIAZABICYCLO[3. 2. 1]-OCTANE (16)

(RRI 1062)

This ring system, which has been reported only in the 1, 5, 6, 7-tetrahydro form, is indexed in Chemical Abstracts as 2, 5-tetrathio-1, 3, 4-thiadiazole.

Chakravarti⁶ prepared a compound (18) which presumably contained this ring system by the reaction of sulfur monochloride with the dipotassium salt of 2, 5-dimercapto-1, 3, 4-thiadiazole (17).



The product was insoluble in all ordinary organic solvents and decomposed at about 80°. The analysis did not check this formula too well. The structure was assigned only on the assumption that S₂Cl₂ reacts

C_2S_4 Ring Systems

as $S=SCl_2$. Since it is now known that S_2Cl_2 more probably has the structure $Cl-S-S-Cl$,¹¹ and since branched sulfur chains very probably do not exist in organic compounds,^{7a,11a} the structure of **18** is questionable. Its physical properties indicate that it is actually polymeric.

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CHAPTER 8

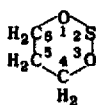
C₃O₂S RING SYSTEMS

Three basic ring systems are included in this category, the 1, 3, 2-, the 1, 3, 4-, and the 1, 3, 5-dioxathianes. The 1, 3, 2-dioxathianes consist primarily of the cyclic sulfite and sulfate esters of 1, 3-diols, while the 1, 3, 5-dioxathiane is the so-called monothioparaldehyde formed in the reaction of hydrogen sulfide with an acid solution of acetaldehyde. Little is known about 1, 3, 4-dioxathianes.

I 1, 3, 2-DIOXATHIA COMPOUNDS

A. C₃O₂S

1. 1, 3, 2-Dioxathiane (1)



1
(RRI 219)

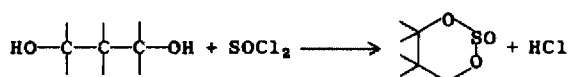
This ring system includes the cyclic sulfite and sulfate esters of 1, 3-diols. Chemical Abstracts indexes the ring system as 1, 3, 2-dioxathiane. An alternative name is 1, 3-dioxo-2-thiacyclohexane. However, the compounds are generally found under the parent hydroxy compounds, and these names are seldom used.

a. Sulfite Esters

(1) Preparation

The monocyclic sulfite esters which have been reported in the literature are listed in Table 1.

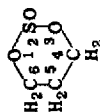
The esters are prepared by treating a 1, 3-diol with thionyl chloride at room temperature or somewhat above.



Although excellent yields have been reported in some cases, the reaction does not appear to be as clean as it is with 1, 2-glycols. Thus, Majima and Simanuki³⁹ reported that trimethylene glycol reacts with thionyl chloride to form principally 1, 3-dichloropropane plus a small

[For references, see pp. 671-674.]

TABLE 1. 1, 3, 2-Dioxathiane 2-Oxides



Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
None	15.5		49-50	4	$n_D^{25} 1.4500$	57b
			74-76	14		39
			69-69.5	15	$n_D^{20} 1.4560, d_4^{20} 1.3406$	5, 6
	42		76	15	$n_D^{20} 1.4567, d_4^{20} 1.3225$	22a
			76-77	17		64
			90-91	38	$n_D^{25} 1.4498$	16
			89	39	$n_D^{25} 1.4509$ (95% pure)	12, 62a
	30		88	39	$n_D^{20} 1.4530$	62
4-CH ₃ -			54	6	$n_D^{25} 1.4430$ (96.3% pure)	12
			68.5-69	7		37a
			63	10	$n_D^{25} 1.4447, d_4^{25} 1.234$	49
			59	10	$n_D^{25} 1.4437$	16
cis(?) -5-Cl	11	62	96	12		16

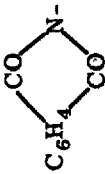
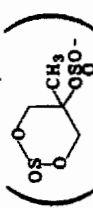
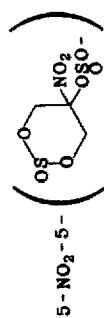
<i>trans</i> (?)-5-Cl	50	42	67-73	12	16
5-Cl			70-90	15	8, 8a
5-C ₆ H ₅ O-	76		81-82	9	8
5-(<i>o</i> -CH ₃ C ₆ H ₄ O-)	76		101-102	30	8
NH ₂ · HCl		158-160			57a
(CH ₃) ₂ N- · HCl		147			57a
		195			57a
5-(C ₅ H ₁₀ N-) · HCl		153-154			15
		148			14b
5-(7-theophyllinyl)	86	278-279			8a
4, 6-(CH ₃) ₂	70		75-77	13	36, 37a
5, 5-(CH ₃) ₂	70		89	33	41
	70		95	40	62
			74-74.5	16	37a

TABLE 1. 1, 3, 2-Dioxathiane 2-Oxides (contd)

Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
4- <i>n</i> -C ₃ H ₇ -5-C ₂ H ₅ -			93-94	3	<i>n</i> _D ²⁵ 1.4543, <i>d</i> ₄ ²⁵ 1.092	49
5-CH ₃ -5-ClCH ₂ -			120	22		18
5-CH ₃ -5-HOCH ₂ -	89		118	3	<i>n</i> _D ²⁴ 1.4786, <i>d</i> ₄ ²⁵ 1.498	63
5, 5-(ClCH ₂ -) ₂	100	30	113-115	4-5		52
	70-73					53, 55
5, 5-(BrCH ₂ -) ₂	77.5	28-30				33a
5-CH ₃ -5-NO ₂	100	110-112				53, 54
5-C ₂ H ₅ -5-NO ₂	5	95-96				38
5-CH ₃ -5-NH ₂ · HCl		68-70				57a
5-ClCH ₂ -5-(CH ₃) ₂ N · HCl		179-181				32a, 62b
5-ClCH ₂ -5-NO ₂		130-131				30
5-HOCH ₂ -5-NO ₂		86-89				57a
		104				21
	28	105-106				31
						21
5-CH ₃ -5- 		96				18



5-NO ₂ -5-	48. 5				38
5, 5-(C ₆ H ₅ -) ₂	60	103-104	190	3	41
D L- <i>cis</i> -4-(p-O ₂ NC ₆ H ₄ -)-5-CH ₃ CONH-	43	143-144			4
	17	143 (dec.)			20a
		dec. 150			43
D L- <i>trans</i> -4-(p-O ₂ NC-)-5-CH ₃ CONH-	20	163-165 (dec.)			4
	64	dec. 187			43
		165-167			47
(+)- <i>trans</i> -4-(p-O ₂ NC ₆ H ₄ -)-5-CH ₃ CONH-		118-121 (dec.)			3
					47
D L- <i>trans</i> -4-C ₆ H ₅ -5-Cl ₂ CHCONH-		118-119			
D L- <i>cis</i> -4-(p-O ₂ NC ₆ H ₄ -)-5-Cl ₂ CHCONH-	77	187 (dec.)			4
	47	189. 5			20
		dec. 193			43
D L- <i>trans</i> -4-(p-O ₂ NC ₆ H ₄ -)-5-Cl ₂ CHCONH-		175-176			45, 47
	42	180			20
	82	dec. 182			43

$[\alpha]_D^{20} + 83. 3^\circ$

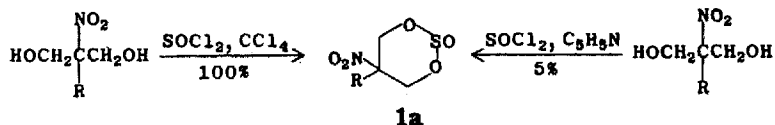
TABLE 1. 1, 3, 2-Dioxathiane 2-Oxides (contd)

Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
(-)- <i>trans</i> -4-(ϕ -O ₂ NC ₆ H ₄ -)-5- Cl ₂ CHCONH-	62	171-172			[α] _D - 101°	45, 47 4
D,L- <i>cis</i> -4-(ϕ -O ₂ NC ₆ H ₅ -)-5- C ₆ H ₅ CONH-		177-178 (dec.)				20a
5-C ₆ H ₅ -5-CH ₃ NH- · HCl	62	157-158				59a
5-(<i>o</i> -CH ₃ C ₆ H ₄ -)-5-CH ₃ NH- · HCl	65	164-165				59a
5-(<i>m</i> -CH ₃ C ₆ H ₄ -)-5-CH ₃ NH- · HCl	65	148-149				59a
5-(ϕ -CH ₃ C ₆ H ₄ -)-5-CH ₃ NH- · HCl	65	156-157				59a
5-(ϕ -CH ₃ OC ₆ H ₄ -)-5-CH ₃ NH- · HCl	73	167-168				59a
4, 4, 6-(CH ₃ -) ₃			71-73	3. 5	n_D^{25} 1.4528	49
			95. 5-97	13		37a
4-[(CH ₃) ₂ CH-]-5, 5-(CH ₃ -) ₂	90		100	15	n_D^{25} 1.4554	62
4, 6-(C ₆ H ₅ -) ₂ -5-CH ₃ CONH-		190-191				60
4, 6-(C ₆ H ₅ -) ₂ -5-C ₆ H ₅ CONH-		203-204				60
4, 6-(C ₆ H ₅ -) ₂ -5-Cl ₂ CHCONH-		210-211				60
4, 6-(ϕ -O ₂ NC ₆ H ₄ -) ₂ -5-CH ₃ CONH-		195				60

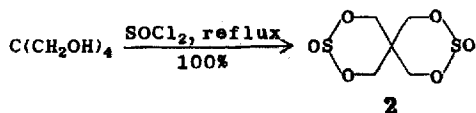
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quantity of cyclic sulfite, whereas under similar conditions the cyclic sulfite is the major product from ethylene glycol. The highest reported yield (42%) of trimethylene sulfite was obtained by reacting the glycol with thionyl chloride at 0° under vacuum to remove the hydrogen chloride as it formed.^{22a} According to Bunton, de la Mare, and co-workers,¹² not only is the yield lower with 1,3-diols but the cyclic sulfite is more difficult to purify. Myles and Prichard⁴⁹ claimed that 1,3-butanediol gives a mixture of cyclic and polymeric sulfites; no polymeric sulfite has been reported from the reaction of a 1,2-glycol with thionyl chloride.

Pyridine has little, if any, effect on the synthesis of cyclic sulfites from 1,2-glycols. With 1,3-diols the situation is more confused. According to Myles and Prichard⁴⁹ the presence of pyridine favors the formation of polymeric sulfites over that of cyclic sulfites. Lingo³⁸ reported a quantitative yield of 5-methyl-5-nitro-1,3,2-dioxathiane 2-oxide (**1a**, R = CH₃) from the corresponding diol and thionyl chloride in carbon tetrachloride. Although this may be a substitution effect (*gem*-disubstituted compounds appear to give higher than normal yields), it is more likely that the high yield resulted from the use of carbon tetrachloride, a poor solvent for the evolved hydrogen chloride. By comparison, Urbański and Koliński^{62b} reported only a 5% yield of 5-ethyl-5-nitro-1,3,2-dioxathiane 2-oxide (**1a**, R = C₂H₅) using thionyl chloride and pyridine, the major product being 2-ethyl-2-nitro-1,3-dichloropropane.



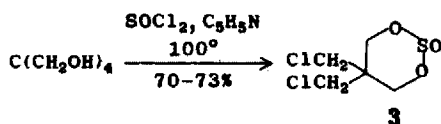
With tri- and tetrahydroxy compounds, however, the products seem to depend on the quantities of reagents used and on the reaction conditions. Govaert and Hansens²³ claimed that treatment of pentaerythritol with an excess of refluxing thionyl chloride gives a quantitative yield of the bis(cyclic sulfite) (**2**) (see section I A-1c).



Pyridine or diethylaniline was reported to have no effect, but unfortunately the conditions were not stated. Mooradian and Cloke⁴⁶ reacted pentaerythritol with thionyl chloride and pyridine in ratios of 1:2:2 to 1:4:4 and, by heating the reactions to about 150-160°, obtained mixtures of pentaerythrityl chlorides, the amounts of products depending on the ratios used. Pietsch^{52,53,55} repeated the work of Mooradian and Cloke and isolated as a by-product the bis(chloromethyl) cyclic sulfite, 5,5-bis(chloromethyl)-1,3,2-dioxathiane 2-oxide (**3**). By using

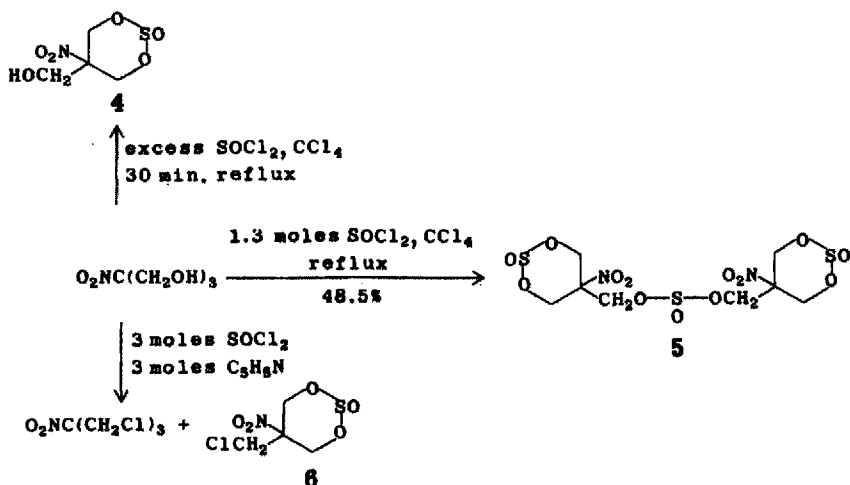
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less than one mole of pyridine per mole of pentaerythritol, a large excess of thionyl chloride, and by carrying out the reaction below 100°, he was able to obtain **3** as the major product.



Since this reaction has been confirmed,^{42,33a} it is all the more surprising that, according to Govaert and co-workers,²⁴ thionyl chloride and a catalytic quantity of pyridine hydrochloride at 90-95° give a 93% yield of pentaerythritol tetrachloride.

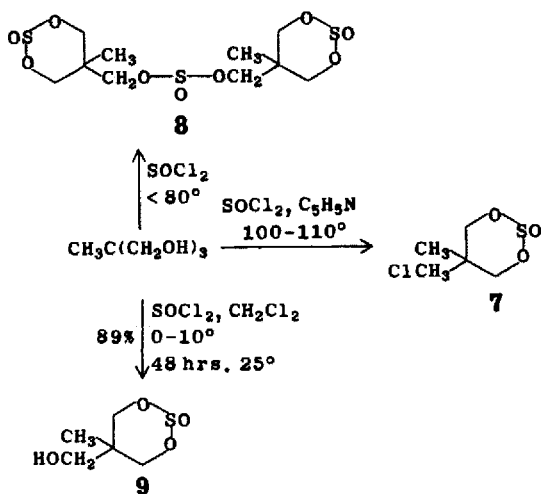
According to Kleinfeller³¹ treatment of trimethylolnitromethane with excess thionyl chloride yields a cyclic sulfite, 5-nitro-5-hydroxymethyl-1,3,2-dioxathiane 2-oxide (**4**). Lingo³⁸ reported that under essentially the same conditions an insufficiency of thionyl chloride gives a fair yield of the sulfite of this product (**5**), but no properties were described. Fort and McLean²¹ treated the triol with 3 moles of thionyl chloride and of pyridine overnight at 40-50° and then for one hour at 95-100° to eliminate sulfur dioxide and obtained tris(chloromethyl)nitromethane in 72.5% yield with the chloromethyl cyclic sulfite (**6**) as a by-product. For some unknown reason, however, **6** was sometimes the major product. Using 2 moles of thionyl chloride and of pyridine they obtained **4** in 28% yield. Both compounds were incorrectly called sulfates.



Étienne and Soulas¹⁸ investigated this general question. According to these authors a polyhydroxy compound containing n hydroxyl groups ($n = 3$ or 4), when treated with $n - 1$ moles of thionyl chloride and $(n - 1)/10$ moles of pyridine and heated to 100-110°, gives a chlorome-

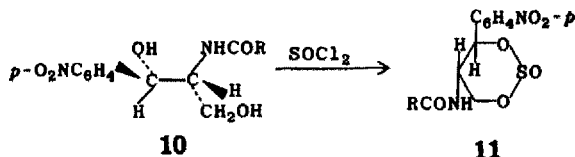
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thyl sulfite. Thus, trimethylolethane under these conditions yields 5-methyl-5-chloromethyl-1, 3, 2-dioxathiane 2-oxide (7). With stoichiometric amounts of pyridine the major product is the polychloro derivative, whereas in the absence of tertiary amine the major product is a cyclic sulfite; trimethylolethane yields the sulfite of 5-methyl-5-hydroxymethyl-1, 3, 2-dioxathiane 2-oxide (8). In contrast to this, Wawzonek and Loft⁶³ reported an excellent yield of 5-methyl-5-hydroxymethyl-1, 3, 2-dioxathiane 2-oxide (9) from trimethylolethane and thionyl chloride at room temperature. Unfortunately, experimental details of the work of Étienne and Soulas are not available, so the reason for this discrepancy is not apparent.

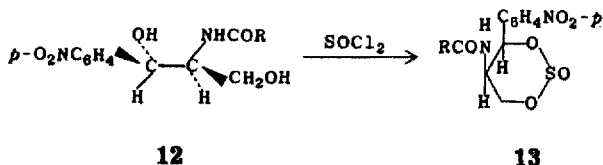


It would appear that the best method for synthesizing 1, 3, 2-dioxathiane 2-oxides is to react a 1, 3-diol with an excess of thionyl chloride at moderate temperatures, perhaps preferably in the presence of a poor solvent for hydrogen chloride. If it is necessary to tie up the liberated hydrogen chloride, a tertiary amine may be added, but the temperature should be lowered to room temperature or below.

Several cyclic sulfites related to chloramphenicol, D-(-)-*threo*-1-*p*-nitrophenyl-2-dichloroacetamido-1, 3-propanediol (10, R = Cl₂CH), have been prepared in which substituents on the phenyl group and on the amide nitrogen have been varied.^{3, 4, 43-45, 47} The *threo* isomers (10), when treated with thionyl chloride at about room temperature, yield the *trans* sulfites (11), while the *erythro* isomers (12) yield the *cis* sulfites (13).

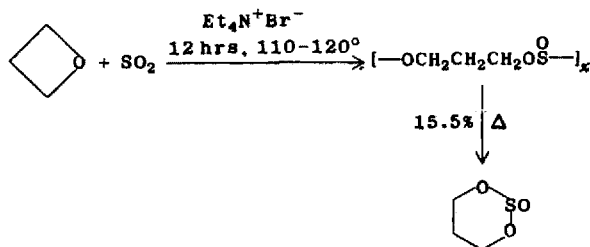


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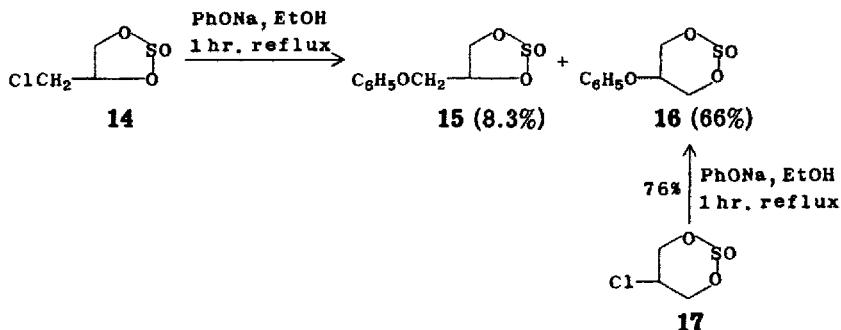
Some confusion exists as to the conditions required for forming the cyclic sulfites. Although in most examples the dihydroxyamides were treated with thionyl chloride in an inert solvent at room temperature or below, Miyamoto⁴³ reported that under these conditions DL-*threo*-1-*p*-nitrophenyl-2-acetamido-1,3-propanediol (**10**, R = CH₃) forms a chlorosulfite which yields the cyclic sulfite (**11**, R = CH₃) only after heating in methanol at 50°. Similarly, Moersch and Moore⁴⁴ claimed that the *erythro*-dichloroacetamide (**12**, R = Cl₂CH), when reacted with thionyl chloride at room temperature and the product hydrolyzed, yields the *threo* isomer (**10**, R = Cl₂CH); the cyclic sulfites have been shown to hydrolyze without inversion (see section I A-1a-(3)). In other patents, however, these authors^{45, 47} claimed that under identical conditions the *threo* amide (**10**) forms the *cis* sulfite (**11**) with thionyl chloride.

Two unusual syntheses of 1,3,2-dioxathiane 2-oxides have been reported. Razuvaev, Etlis, and Grobov^{57b} reported that the reaction of oxetane with sulfur dioxide, catalyzed by a quaternary ammonium salt, yielded a polymer. Heating this polymer with a free flame gave a low yield of trimethylene sulfite.



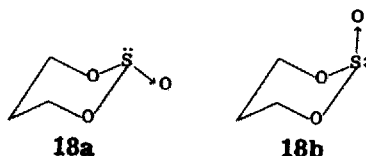
Ben-Ishay⁸ found that treatment of 4-chloromethyl-1,3,2-dioxathiolane 2-oxide (**14**) with sodium phenoxide gives only a small amount of the expected 4-phenoxyethyl-1,3,2-dioxathiolane 2-oxide (**15**); the major product is 5-phenoxy-1,3,2-dioxathiane 2-oxide (**16**), which was also prepared from 5-chloro-1,3,2-dioxathiane 2-oxide (**17**). Potassium theophylline reacted similarly.^{8a} A reasonable mechanism for this ring enlargement reaction has already been given (see Chapter 1, section I A-3).

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(2) Structure and Physical Properties

Although the structure of 1, 3, 2-dioxathiane 2-oxide has not been determined, it appears reasonable that it exists in the staggered chair form. Arbuzov and co-workers^{5,6} found the molecule to have a dipole moment of 3.60 D and a parachor of 231.3. Arbuzov^{6a} found, making reasonable assumptions as to bond angles and distances, that the calculated dipole moment for a planar molecule came closest to the experimental value. Nevertheless, he concluded that the molecule exists in the chair form, predominantly with an equatorial sulfoxide oxygen (**18a**, $\mu = 4.92$ D) but with some contribution from a structure with axial oxygen (**18b**, $\mu = 1.78$ D).



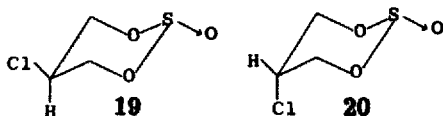
This structure has recently been questioned by Hellier, Tillet, and co-workers.^{26a} They have concluded that the molecule exists in a single conformation, probably a rigid chair with an axial oxygen.

Inasmuch as the three oxygens on the sulfur are not in the same plane, monosubstituted derivatives should exist in two isomeric forms, *cis* and *trans*. Two such examples have been reported, one by Herzog and Ehrenstein²⁷ (see section I F) and one by de la Mare, Klyne, and co-workers.¹⁶ The latter authors isolated two isomers from the reaction of 2-chloro-1, 3-propanediol with thionyl chloride; **19**, m.p. 42°, was the major product, while only a small amount of **20**, m.p. 62°, was obtained. That both compounds are cyclic sulfites was indicated by the fact that neither chloride nor sulfur dioxide were formed readily on neutral or acid hydrolysis, while sulfite ion was quantitatively liberated at room temperature with base. A comparison with 4-chloromethyl-1, 3, 2-dioxathiolane 2-oxide (**14**), prepared from 3-chloro-1, 2-propanediol, showed that neither compound had undergone ring contraction. Further evidence on this point was obtained from infrared spectra. Cyclic sulfites of 1, 2-glycols have no band in the 600-640 cm⁻¹ region, while cyclic sulfites of 1, 3-glycols have a weak band at 610-620 cm⁻¹ and a

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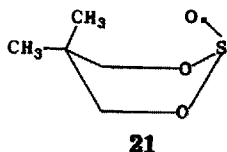
medium intensity band at $620\text{--}635\text{ cm}^{-1}$ attributed to vibrations of the six-membered ring. Szmant and Emerson⁶² reported that both types of cyclic sulfite have a band at 1220 cm^{-1} , whereas de la Mare, Klyne, and co-workers found the sulfoxide stretching band at 1214 cm^{-1} in 1, 2-sulfites and at 1190 cm^{-1} in 1, 3-sulfites. Both **19** and **20** showed absorption in the $600\text{--}640\text{ cm}^{-1}$ region and had strong bands at $1188\text{--}1189\text{ cm}^{-1}$.

Only tentative assignments of configuration have been made. Molecular models indicate that 5 β -cholestane-3 β , 5-diol cyclic sulfite must have an equatorial sulfoxide oxygen (see section I F). This compound absorbs at 1190 cm^{-1} . Comparison of the infrared spectra of **19** and **20** with chlorocyclohexanes of known configuration indicated that the low-melting isomer (**19**) has an equatorial chlorine and the high-melting isomer (**20**) an axial chlorine. Assuming that all sulfites which absorb at 1190 cm^{-1} have an equatorial oxygen, **19** was tentatively assigned the diequatorial *trans* configuration and **20** the *cis*. This assignment is based on both rings being in the chair form. Although there is no "flagpole" hydrogen interaction, the authors felt that electrostatic repulsion of the strongly dipolar carbon-chlorine and sulfur-oxygen bonds would tend to keep the rings in the chair form. Recently, Hellier, Tillett,



and co-workers^{26a} concluded that the 1190 cm^{-1} band should be assigned to the axial sulfur-oxygen bond, in which case both **19** and **20** should have the sulfoxide oxygen axial.

There is another point of difference between the spectroscopic assignments of de la Mare, Klyne, and co-workers,¹⁶ and Szmant and Emerson.⁶² The latter authors claimed that substitution in the 4-position of 1, 3, 2-dioxathiane 2-oxide has no effect on the 1220 cm^{-1} band, whereas substitution in the 5-position, as exemplified by 5, 5-dimethyl- and 4-isopropyl-5, 5-dimethyl-1, 3, 2-dioxathiane 2-oxides, shifts this band to 1203 cm^{-1} . Szmant and Emerson attributed this shift to an interaction, analogous to hydrogen bonding, between the methyl group and the sulfoxide oxygen. These groups could interact, however, only when the molecule is in the boat form with an axial sulfur-oxygen bond (**21**), a rather unlikely conformation.

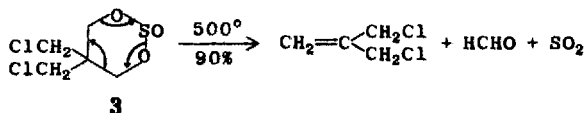


The cyclic sulfites of the lower molecular weight 1, 3-diols are high-boiling liquids only slightly soluble in water.

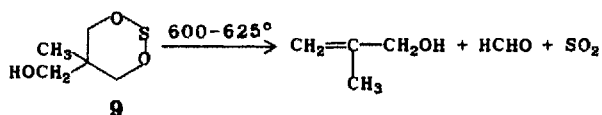
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(3) Reactions

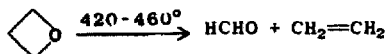
Cyclic sulfites of 1, 3-glycols are quite stable thermally. Their stability and the products obtained on pyrolysis are dependent on the substituents present. Thus, Matlack and Breslow⁴² found that the pyrolysis of 5, 5-bis(chloromethyl)-1, 3, 2-dioxathiane 2-oxide (**3**) at 500° yields formaldehyde and dichloroisobutylene in 90% yield. The reaction appears to be analogous to the pyrolysis of the cyclic sulfites of 1, 2-glycols (see Chapter 1, sections IA-3 and VIII A).



According to Wawzonek and Loft⁶³ the pyrolysis of the unsubstituted compound, trimethylene sulfite, follows the same course at 300°, yielding formaldehyde and, presumably, ethylene, but the reaction was not clean. 5, 5-Dimethyl-1, 3, 2-dioxathiane 2-oxide, on the other hand, is stable at 500°, as is 5-methyl-5-hydroxymethyl-1, 3, 2-dioxathiane 2-oxide (**9**). The latter compound decomposes slightly at 600-625°, presumably to methallyl alcohol and formaldehyde, although this was not proved.

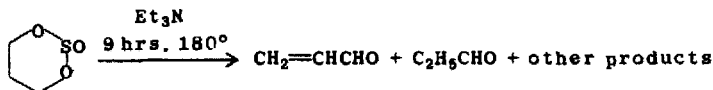


Wawzonek and Loft suggested that oxetanes might be the intermediates in all these reactions, since Bittker and Walters^{9b} reported that oxetane pyrolyzes to formaldehyde and ethylene.



However, Matlack and Breslow^{42a} found that 3, 3-bis(chloromethyl)-oxetane is stable under the conditions of pyrolysis of **3**. The pyrolysis of the spiro compound, pentaerythritol disulfite, follows still another course (see section IA-1c). No explanation for the differences has been forthcoming.

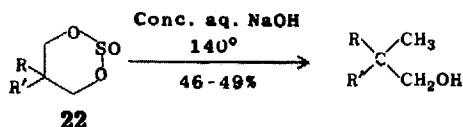
In the presence of basic reagents a different reaction takes place. Gillis^{22a} attempted to rearrange trimethylene sulfite to a sultone by heating it with triethylamine under the same conditions which yielded methyl methanesulfonate from dimethyl sulfite.^{9a} A variety of products were formed, among which only acrolein and propionaldehyde were identified.



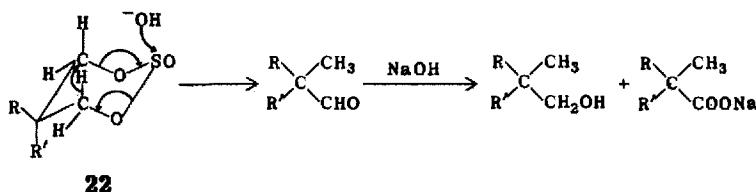
The course of this reaction can be explained from the work of Crowdle, Knipper, and co-workers.^{15a} These authors found that 5, 5-disubstituted

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1, 3, 2-dioxathiane 2-oxides (**22**, R and R' = CH₃, C₂H₅ or *n*-C₄H₉) yield neopentyl-type alcohols on heating with aqueous sodium hydroxide.

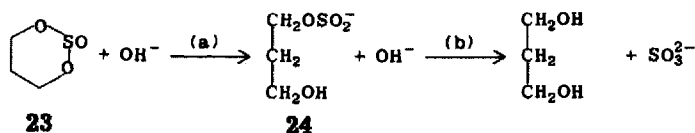


The authors explained this reaction as involving a hydride shift to yield aldehyde, followed by a Cannizzaro reaction.



1, 3, 2-Dioxathiane 2-oxides are hydrolyzed readily by acids and bases. The hydrolysis has been studied in detail by Bunton, de la Mare, and coworkers.^{11-14, 14a, 62a} No fundamental differences between the hydrolysis of 1, 3, 2-dioxathiane 2-oxides and 1, 3, 2-dioxathiolane 2-oxides were found (see Chapter 1, section IA-3). Thus, hydrolysis in the presence of H₂O¹⁸^{11, 12} showed no isotopic enrichment in the glycol, indicating that hydrolysis involves exclusively sulfur-oxygen cleavage. As with the 1, 2-glycol sulfites there was also very little exchange of water with the sulfoxide oxygen. These results agree with the reported hydrolysis of chloramphenicol sulfites.^{4, 43, 47} Both *trans*-4-*p*-nitrophenyl-5-acylamido-1, 3, 2-dioxathiane 2-oxide (**11**), prepared from *threo*-1-*p*-nitrophenyl-2-acylamido-1, 3-propanediol (**10**), and the *cis*-sulfite (**13**), prepared from the *erythro* glycol (**12**), underwent alkaline hydrolysis to regenerate the parent glycol. Under acidic conditions the results were the same; however, here the amide group was also hydrolyzed. Further proof that no carbon-oxygen cleavage is involved in hydrolysis is the fact that optically active *trans* sulfite yields optically active *threo*-glycol.⁴⁷

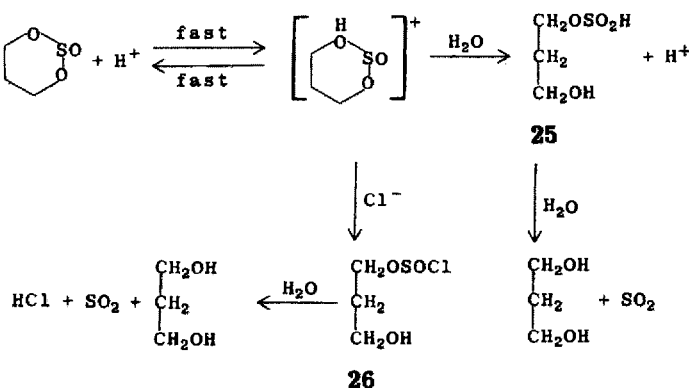
Bunton, de la Mare, and co-workers,^{11, 13, 14} studied the kinetics of the hydrolysis of several simple 1, 3-glycol sulfites. Both 1, 2- and 1, 3-glycol sulfites hydrolyzed more rapidly under alkaline conditions than under acidic. The alkaline hydrolysis of 1, 3, 2-dioxathiane 2-oxide (**23**) was second order, following the kinetic equation $d[\text{SO}_2]/dt = k[\text{sulfite}][\text{OH}^-]$. The reaction presumably proceeds in two steps.



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Titration with different indicators and with iodine showed that reaction (b) is much faster than (a) and therefore there is no build-up in concentration of intermediate **24**. Since the O¹⁸ experiments showed that there is little or no introduction of O¹⁸ into the cyclic sulfite, there is no equilibrium between **23** and **24**, and **24** must decompose as fast as it forms. The alkaline hydrolysis of 4-methyl-1, 3, 2-dioxathiane 2-oxide proceeded at one-fourth the rate of trimethylene sulfite. This small effect is not surprising, since the structural change is far removed from the reaction center.

The kinetics of acid hydrolysis were more complicated. It followed the rate equation $d[\text{SO}_2]/dt = k[\text{sulfite}][\text{H}_3\text{O}^+]$ at constant electrolyte concentration, but the hydrolysis was catalyzed by anions in the order $\text{Br}^- > \text{Cl}^- \gg \text{HSO}_4^-$. Since this is the order of decreasing nucleophilic power, the conclusion was drawn that hydrolysis could follow two paths, one involving nucleophilic attack by the anion on the sulfur atom. The fact that hydrolysis in 90% D₂O was faster than in water by a factor of 1.5 or more was taken to mean that the initial step in hydrolysis involves a reversible proton transfer. The following mechanism was written (the position of the proton was not specified):



The same reasoning as used in alkaline hydrolysis showed that intermediate **25** decomposes to glycol more rapidly than it reverts to sulfite. **26** is the intermediate in the reaction of 1,3-glycols with thionyl chloride. In that reaction some chlorohydrin is always formed. Since no chlorohydrin was formed in the hydrolysis, it follows that the intermediate is hydrolyzed as fast as it forms. Here, too, structural changes had little effect on the rate of hydrolysis, 4-methyl-1, 3, 2-dioxathiane 2-oxide hydrolyzing at 0.6 the rate of the unsubstituted cyclic sulfite.

De la Mare and co-workers^{14a, 16b, 62a} compared the relative hydrolysis rates of cyclic and open-chain sulfites under acidic and basic conditions; Davis^{15c} studied ethylene sulfite. The results are shown in Table 2.

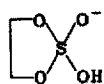
[For references, see pp. 671-674.]

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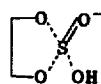
TABLE 2. Relative Rates of Hydrolysis of Sulfite Esters

		Sulfite			
Temp.	Condi- tions	Ethylene	Trimethylene	Dimethyl	Diethyl
0°	Acidic	1	4	20 22 ^{15c}	48
0°	Basic	ca. 1000	4.8	1.4	0.35
25°	Basic	8000 3600 ^{15c}	30	10	2.6

Thus, under acidic conditions the order is dialkyl > six-membered ring > five-membered ring, whereas under basic conditions the order is five-membered ring >> six-membered ring > dialkyl. De la Mare and co-workers suggested originally that, under neutral or alkaline conditions, ethylene sulfite is destabilized by electronic repulsions between the lone pairs of electrons on the oxygen atoms and is therefore highly reactive. The effect would be less in a puckered six-membered ring and still less in a dialkyl sulfite. However, Davis^{15c} and Pagdin, Pine, Tillett, and van Woerden^{50a} have shown that dimethyl sulfite and ethylene and trimethylene sulfites all have the same heats of hydrolysis. Thus, there is no ring strain in either ethylene or trimethylene sulfite to explain the rapid alkaline hydrolysis. Davis suggested, from molecular orbital calculations, that there might be sufficient strain in a tetracoordinated sulfur intermediate (**26a**) to account for the rapid alkaline hydrolysis of ethylene sulfite, although de la Mare and co-workers^{16b} apparently prefer to consider this a transition state (**26b**), in light of the very small amount of exchange between the sulfite and D₂O. Presumably the strain would be less in trimethylene sulfite and in a dialkyl sulfite.



26a



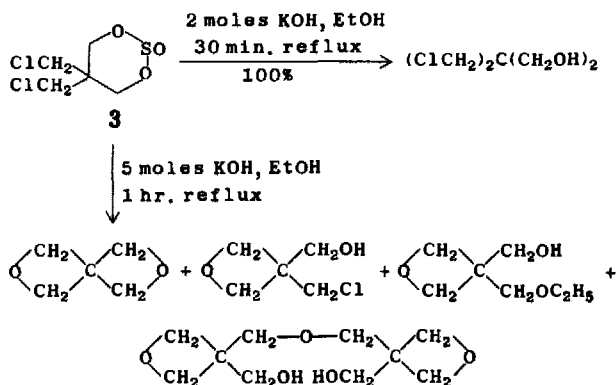
26b

This still leaves unexplained the order of hydrolysis found under acidic conditions. The differences under acidic conditions are so much smaller, however, that they could be attributed to more subtle changes in structure.

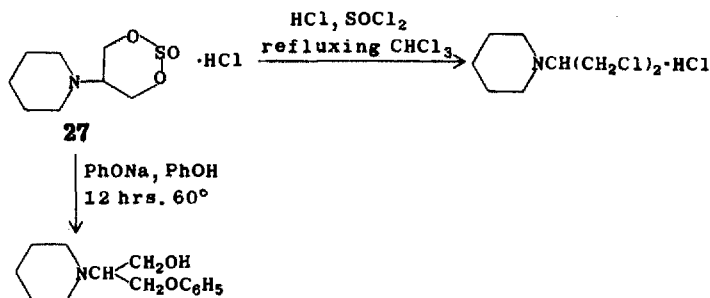
Although hydrolysis of the simple sulfites regenerates the parent glycol quantitatively, hydrolysis of 5, 5-bis(chloromethyl)-1, 3, 2-dioxathiane 2-oxide (**3**) is frequently complicated by further reaction of the diol. Dilute hydrochloric acid or the calculated quantity of alcoholic potassium hydroxide give the diol in almost quantitative yield,^{51,52,55}

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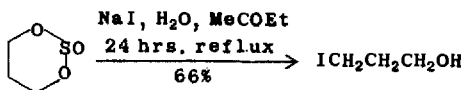
thus making 2, 2-bis(chloromethyl)-1, 3-propanediol readily available. However, excess base gives a mixture of products.



Cromwell and Hassner¹⁵ reported the conversion of 5-piperidino-1, 3, 2-dioxathiane 2-oxide hydrochloride (**27**) to the corresponding dichloride, although the reaction took place only slowly and in poor yield. That 1, 3, 2-dioxathiane 2-oxides can undergo carbon-oxygen cleavage in the same manner as 1, 3, 2-dioxathiolane 2-oxides was shown by Chapman, Isaacs, and Parker,^{14b} who isolated 3-phenoxy-2-piperidino-1-propanol from the reaction of **27** with sodium phenoxide.



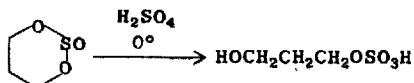
Similarly, Wawzonek and Loft^{63a} cleaved trimethylene sulfite with sodium iodide to form 3-iodo-1-propanol.



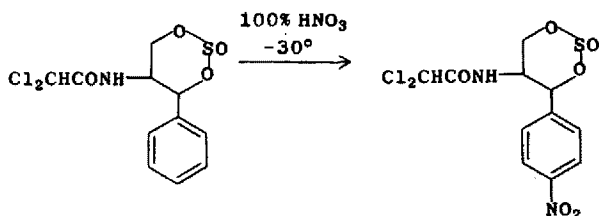
5-Methyl-5-hydroxymethyl-1, 3, 2-dioxathiane 2-oxide (**9**) reacted similarly, but the corresponding 5, 5-dimethyl derivative failed to react.

According to Brunken and Poppe^{10c} trimethylene sulfite reacts with sulfuric acid to form 3-hydroxypropylsulfuric acid.

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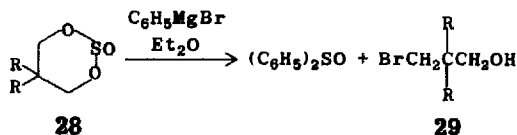


Cyclic sulfites have been reported to be sufficiently stable to nitric acid to allow nitration of a benzene ring.^{47, 60}



The reaction has been used to synthesize chloramphenicol; a variety of amides and substituted phenyl compounds were used.

Szmant and Emerson⁶² reacted 1, 3, 2-dioxathiane 2-oxide (**28**, R = H) and the corresponding 5, 5-dimethyl derivative (**28**, R = CH₃) with phenylmagnesium bromide and isolated 50-55% of diphenyl sulfoxide and 8-13% of bromohydrin (**29**). The reaction follows the same path as



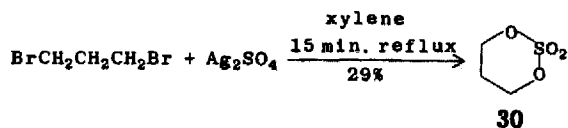
with 1, 2-glycol sulfites; the mechanism has already been discussed (see Chapter 1, section IA-3).

1, 3, 2-Dioxathiane 2-oxides have been patented⁴⁹ as stabilizers for cellulose esters and ethers. Their activity is presumably related to their ability to liberate sulfur dioxide on heating.

b. Sulfate Esters

(1) Preparation and Properties

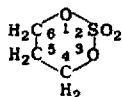
Very few cyclic sulfates of aliphatic 1, 3-diols are known (Table 3). Baker and Field⁷ prepared the parent compound, 1, 3, 2-dioxathiane 2, 2-dioxide (**30**), by the reaction of 1, 3-dibromopropane with silver sulfate.



Lichtenberger and Lichtenberger³⁴ found that treatment of a 1, 3-diol with sulfonyl chloride, chlorosulfonic acid, or oleum gives a mixture of

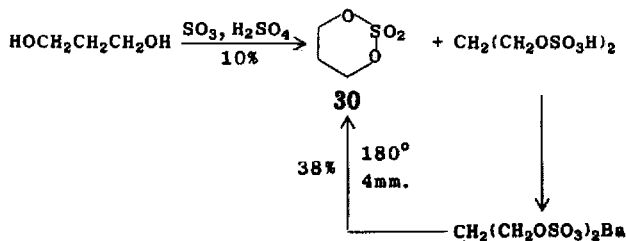
C₃O₂S Ring Systems

TABLE 3. 1, 3, 2-Dioxathiane 2, 2-Dioxides



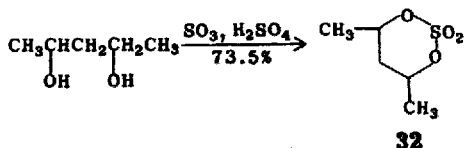
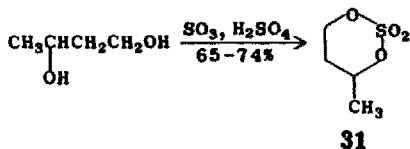
Substituents	Yield (%)	M. p. (°C)	B. p. (°C)	B. p. (mm)	Ref.
None	29	63			7
	33	61-62			10a
	71	57-59			10b
	72	57-58			10c
		63	153	14	34
	20				7a
4-CH ₃ -	65-74	44	150	15	34
	44				37a
	56	44-46			42b
4, 6-(CH ₃ -) ₂	73.5	40	153-154	14	34
5, 5-(CH ₃ -) ₂	30	79-80			10a
	71	81-82			37a
4, 4, 6-(CH ₃ -) ₃	86	60-62			37a

cyclic sulfate and bis(hydrogen sulfate). Best yields are obtained with oleum (47% SO₃) at 0-10° using chloroform as solvent. 1, 3-Propanediol gives a low yield of 30, although the yield is improved by pyrolyzing the barium salt of the by-product bis(sulfate).

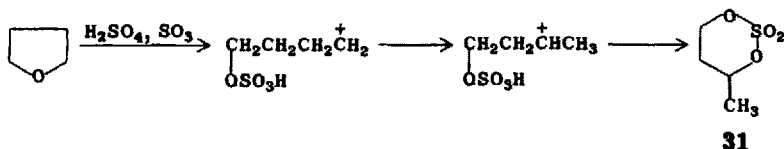


Excellent yields are obtained, however, if one hydroxyl group is secondary. Thus, 1, 3-butanediol gives 4-methyl-1, 3, 2-dioxathiane 2, 2-dioxide (31), and 2, 4-pentanediol gives the 4, 6-dimethyl derivative (32).

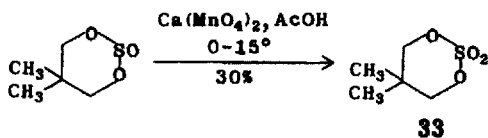
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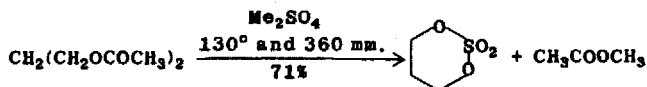
Miller^{42b} reported a 56% yield of **31** by this procedure. According to Lichtenberger the reaction is unsuccessful with ethylene glycol and with pentaerythritol. Lichtenberger and co-workers^{37,37a} reported a 9% yield of **31** from tetrahydrofuran and oleum. They considered this to be an example of ring contraction, the initial product being the cyclic sulfate of 1,4-butanediol. It would seem more reasonable to explain the formation of **31** as involving a hydride shift in the initially formed carbonium ion.



The most generally useful synthesis of cyclic sulfates involves oxidation of the corresponding sulfite with calcium permanganate (see Chapter 1, section IB-1). Thus, Brimacombe, Foster and co-workers,^{10a} prepared 5,5-dimethyl-1,3,2-dioxathiane 2,2-dioxide (**33**) by this procedure in 30% yield, while Lichtenberger and Hincky^{37a} reported a 44% yield of **31**, a 71% yield of **33**, and an 86% yield of 4,4,6-trimethyl-1,3,2-dioxathiane 2,2-dioxide. Baker and Burrows^{7a} reported a 20% yield of trimethylene sulfate.

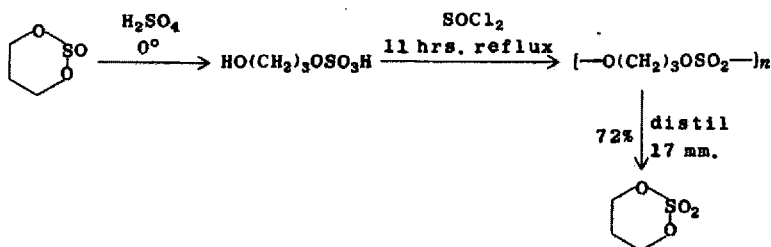


Two excellent synthesis of trimethylene sulfate were reported recently by Brunken and co-workers. One synthesis involves heating trimethylene diacetate with dimethyl sulfate and distilling out the methyl acetate formed; ^{10b} apparently the monoester can also be used.¹



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The second synthesis involves treatment of 3-hydroxypropylsulfuric acid with thionyl chloride.^{2, 10c} Apparently a polymer is formed initially, which is converted into the cyclic sulfate during distillation.

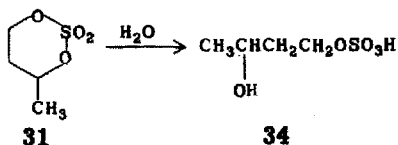


Unfortunately, both methods are successful only with diprimary glycols.

The cyclic sulfates which have been isolated are all white, crystalline solids, insoluble in water and soluble in organic solvents.

(2) Reactions

1, 3, 2-Dioxathiane 2, 2-dioxide is more stable than ethylene glycol sulfate (Chapter 1, section IB-2), since it does not hydrolyze in moist air and can be recrystallized from methanol.⁷ Lichtenberger and co-workers^{34, 35, 37} studied a number of reactions of the cyclic sulfates. Hot water hydrolyzes all the sulfates first to the hydroxy hydrogen sulfate and then to the diol. The unsymmetrical sulfate from 1, 3-butenediol (**31**) apparently yields the secondary alcohol (**34**).

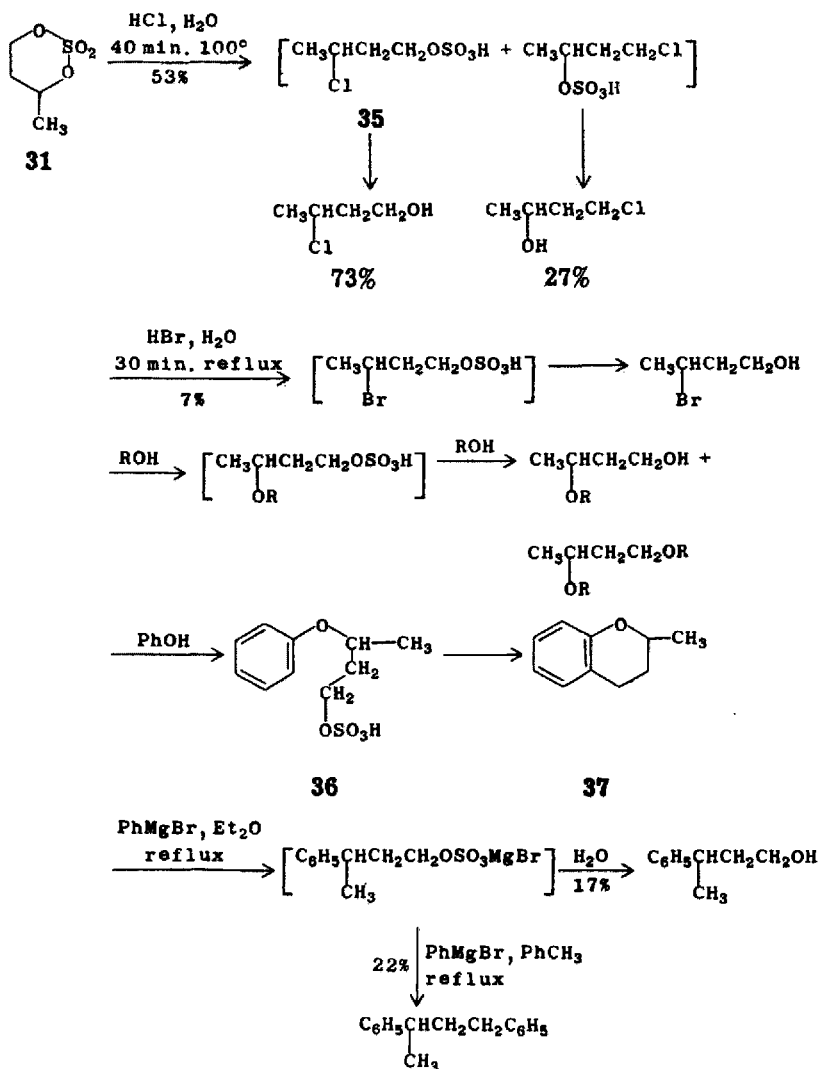


This was shown in two ways. Hydrogen sulfates of primary alcohols were found to hydrolyze more slowly than those of secondary alcohols; **34** was found to hydrolyze to 1, 3-butanediol at the same rate as 3-hydroxypropylsulfuric acid. Chromic acid oxidation of 1, 3-butanediol yielded crotonaldehyde, whereas oxidation of **34** yielded methyl vinyl ketone, thus indicating that the primary hydroxyl was blocked.

Concentrated hydrochloric acid accelerates hydrolysis. Although Lichtenberger reported only 3-chloro-1-butanol as the product, Miller^{42b} found that 1-chloro-3-butanol is formed as well, the ratio of the two being about 3:1. According to Lichtenberger the hydroxy sulfate is not an intermediate, at least in the case of the butane derivative, since no chlorohydrin is formed by treating **34** with hydrochloric acid under the same conditions. An attempt to isolate the postulated intermediate, 3-chlorobutylsulfuric acid (**35**), by carrying out the hydrolysis in the presence of potassium chloride was unsuccessful. Other acidic reagents react to cleave the sulfate ring of 4-methyl-1, 3, 2-dioxathiane

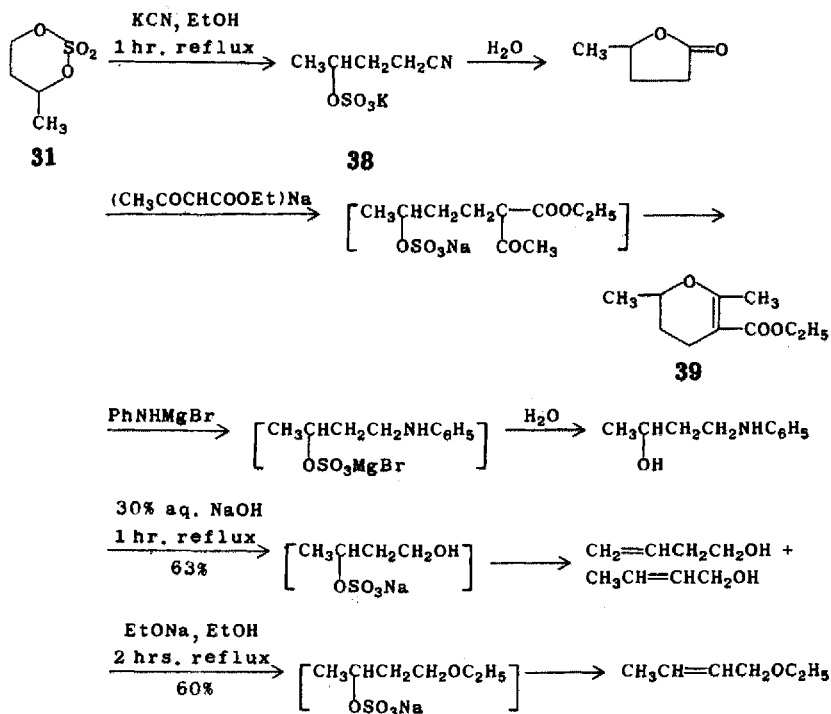
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2, 2-dioxide (31) predominantly at the secondary carbon atom. Hydrobromic acid yields 3-bromo-1-butanol, although in low yield. Alcohols react to form 3-alkoxy-1-butanol and 1, 3-dialkoxybutanes, the former product showing that cleavage takes place initially at the secondary carbon atom. Phenol yields a compound formulated as 2-methylchroman (37), presumably *via* the intermediate 3-phenoxybutylsulfuric acid (36). Grignard reagents also cleave the ring at the secondary carbon atom, phenylmagnesium bromide yielding either 3-phenyl-1-butanol or 1, 3-diphenylbutane, depending on the reaction conditions; other Grignard reagents react similarly.

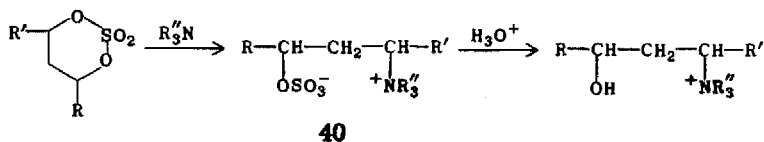


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Basic reagents lead to products resulting from cleavage at the primary carbon atom. Thus, potassium cyanide yields the sulfate of 4-hydroxyvaleronitrile (**38**), whose structure was proved by hydrolysis to γ -valerolactone. Sodiumacetoacetic ester gives the known 2, 6-dimethyl-3-carbethoxy-5, 6-dihdropyran (**39**) rather than the 4, 6-dimethyl derivative. Anilinemagnesium bromide gives, after hydrolysis, 1-anilino-3-butanol. Aqueous alkali yields a mixture of allylcarbinol and crotyl alcohol, while crotyl ethyl ether is isolated from the reaction with sodium ethoxide; these products are best explained by basic elimination of the 3-sulfate.



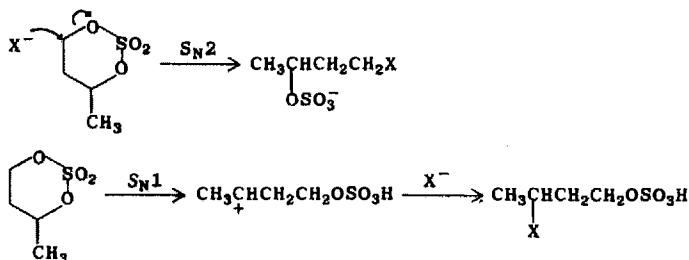
Primary, secondary, and tertiary amines, whether aliphatic, aromatic, or heterocyclic, as well as ammonia, react with all three cyclic sulfates, frequently in excellent yield, to form the zwitterion (**40**); acid hydrolysis gives the amino alcohol.



The sulfate of 1, 3-butanediol (**31**) reacts to put the amine group on the primary carbon, analogous to the reaction with other basic reagents.

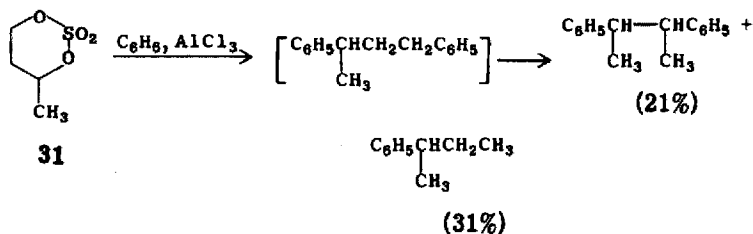
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Lichtenberger compared these reactions to similar ring opening reactions on unsymmetrical epoxides. It seems reasonable to postulate that in alkaline media an S_N2 reaction takes place on the primary carbon atom because of steric hindrance at the secondary carbon. Under acidic conditions the reaction is S_N1 , leading to the 3-substituted-1-alcohol because of the greater stability of the secondary carbonium ion; Lichtenberger considered the magnesium in a Grignard reagent to be a Lewis acid to account for the substitution in the 3-position.



If this explanation is correct, it follows that the reactions of 1, 3, 2-dioxathiane 2, 2-dioxides are probably different from those of 1, 3, 2-dioxathiolane 2, 2-dioxides (see Chapter 1, sections IB-2 and VIII B). It is unfortunate that there is no stereochemical evidence relating to the mode of hydrolysis of the six-membered cyclic sulfates so that an accurate comparison could be made with the five-membered compounds.

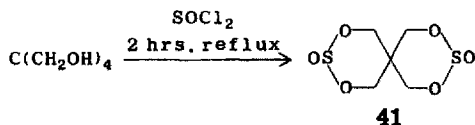
The cyclic sulfate of 1, 3-butanediol reacts with benzene in the presence of aluminum chloride to form presumably 1, 3-diphenylbutane, which reacts further.³⁵



c. Spiro Derivatives

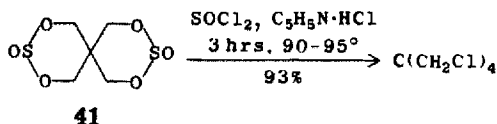
The only known 1, 3, 2-dioxathia spiro derivatives are derived from pentaerythritol. The disulfite (41), the 3, 9-dioxide of 2, 4, 8, 10-tetroxa-3, 9-dithiaspiro[5. 5]undecane (RRI 1529) was first prepared by Bougault¹⁰ in low yield by the reaction of pentaerythritol with sulfur monochloride. As pointed out by Orthner,⁵⁰ Bougault's monochloride probably was contaminated with thionyl chloride, since Orthner found that the compound could be prepared in good yield by treating pentaerythritol with thionyl chloride.

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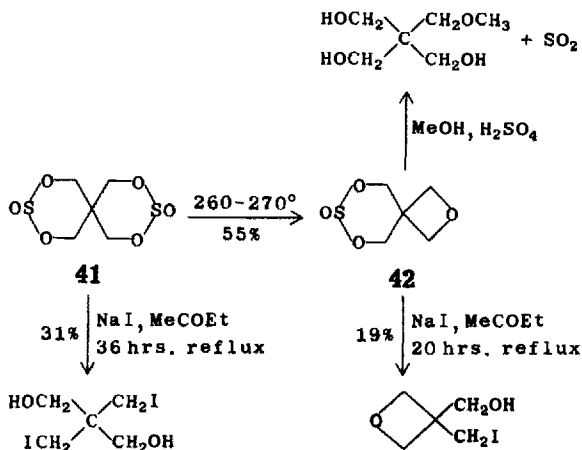


According to Govaert and co-workers^{23,24} both thionyl chloride and thionyl bromide give practically quantitative yields of **41**, essentially no halo derivatives being formed. There appears to be ample verification of the preparation.⁴⁶ However, Govaert's claim that the reaction takes the same course in the presence of *tert*-amines is open to question; this may be so at low temperatures, but is very probably incorrect at temperatures above about 30° (see section IA-1a-(1)). **41** forms rhombic crystals reported to melt at either 151°^{23,24} or at 153-154°.^{10,50} It is stable in hot water, in which it is insoluble, and sublimes without decomposition.

Hydrolysis with dilute acid takes place readily.¹⁰ Treatment with excess thionyl chloride in the presence of a catalytic quantity of pyridine hydrochloride is reported to yield a tetrachloride.²⁴



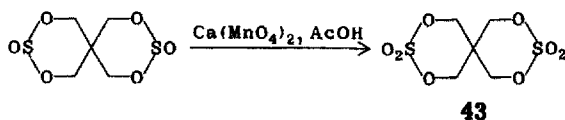
Wawzonek and Loft⁶³ investigated the pyrolysis of pentaerythritol disulfite. At 25% conversion they obtained a 55% yield of 2, 6, 8-trioxa-7-thiaspiro[3.5]nonane 7-oxide (**42**), m.p. 74-75°. The structure was proved by methanolysis to pentaerythritol monomethyl ether. Thus, the reaction takes a course different from that of other 1, 3, 2-dioxathiane 2-oxide derivatives (section IA-1a-(3)). Both **41** and **42** react with sodium iodide with carbon-oxygen cleavage to yield the corresponding iodohydrins.^{63a}



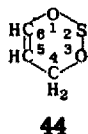
[For references, see pp. 671-674.]

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Lichtenberger and Hincky³⁶ reported that pentaerythritol disulfate, 2, 4, 8, 10-tetroxa-3, 9-dithiaspiro[5. 5]undecane 3, 3, 9, 9-tetroxide (**43**), melts at 202° with decomposition. Although they gave no details of its preparation, it may be assumed that it was made by permanganate oxidation of the disulfite.

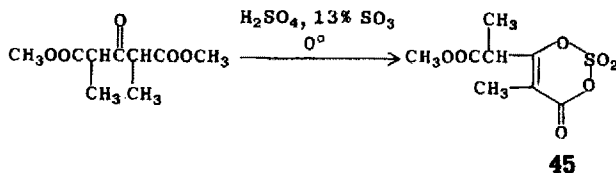


2. 4*H*-1, 3, 2-Dioxathiin (**44**)



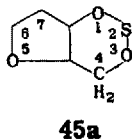
(RRI 219)

In 1916 Schroeter⁵⁹ reported that the reaction of the dimethyl ester of dimethylacetonedicarboxylic acid with cold fuming sulfuric acid gives a product melting at 67-68°, which he formulated as a cyclic sulfate, 4-oxo-5-methyl-6-(1-carbomethoxy-1-ethyl)-4*H*-1, 3, 2-dioxathiin 2, 2-dioxide (**45**).



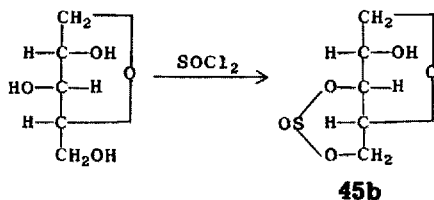
The compound decomposed to an oil on standing at room temperature and gave a strong test for sulfuric acid after decomposition with nitric acid. The only analysis reported was a cryoscopic molecular weight in benzene. The structure of this compound is therefore in doubt.

B. $C_4O-C_3O_2S$ 4*H*-FURO[3, 2-*d*]-1, 3, 2-DIOXATHIIN (**45a**)



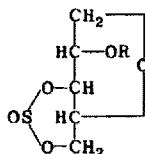
Danilov, Anikeeva, and co-workers,^{15b} reacted 1, 4-anhydroxylitol with thionyl chloride and formulated the product as 7-hydroxytetrahydro-4*H*-furo[3, 2-*d*]-1, 3, 2-dioxathiin 2-oxide (**45b**), rather than as a dioxathiolane derivative, because the compound would not form a trityl derivative, indicating the absence of a primary hydroxyl group.

C₃O₂S Ring Systems



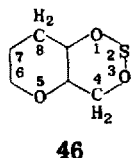
Several derivatives were prepared (Table 4). Inasmuch as five-membered cyclic sulfites are formed more readily than six-membered cyclic sulfites, more definitive proof that these compounds are actually 1, 3, 2-dioxathianes would be desirable.

TABLE 4. 1, 4-Anhydroxylitol Cyclic Sulfites



R	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
H	37	83-84	140	0.5		15b
CH ₃ CO-			105-107	0.15	n_D^{20} 1.4810 d_4^{20} 1.4261	15b
C ₆ H ₅ CO-		96-98				15b
<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ -		60-61				15b
C. C ₃ O ₂ S-C ₅ O						

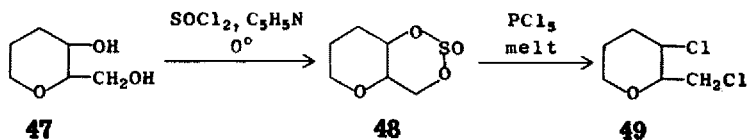
1. 4*H*,8*H*-Pyrano[3, 2-*d*]-1, 3, 2-dioxathiin (46)



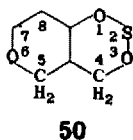
Bergmann and Breuers⁹ reported that optically active 2-hydroxymethyl-3-hydroxytetrahydropyran (**47**) reacts with thionyl chloride to form a cyclic sulfite, tetrahydro-4*H*,8*H*-pyrano[3, 2-*d*]-1, 3, 2-dioxathiin 2-oxide (**48**), m.p. 99°, $[\alpha]_D^{25} + 8.6^\circ$. Treatment with phosphorus pentachloro-

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ride yielded a compound presumed to be 2-chloromethyl-3-chlorotetrahydropyran (**49**). The ring fusion in **48** is probably *cis*.

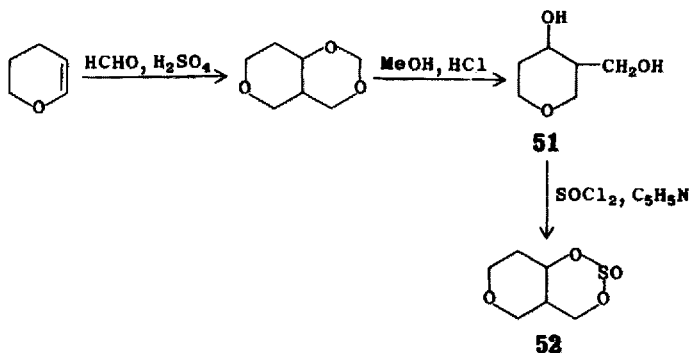


2. 4*H*,5*H*-Pyrano[4,3-*d*]-1,3,2-dioxathiin (**50**)

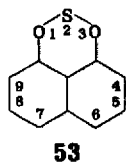


(RRI 1530)

Hanschke²⁶ reacted 3-hydroxymethyl-4-hydroxytetrahydropyran (**51**) with thionyl chloride and isolated a cyclic sulfite, tetrahydro-4*H*,5*H*-pyrano[4,3-*d*]-1,3,2-dioxathiin 2-oxide (**52**), as a colorless liquid, b.p. 80-82° at 0.2 mm, n_D^{20} 1.4905, d_4^{20} 1.356. The starting material (**51**) was prepared by a Prins reaction on dihydropyran, and the stereochemistry of the ring fusion in **52** is therefore unknown.



D. $\text{C}_3\text{O}_2\text{S}-\text{C}_6-\text{C}_6$ NAPHTHO[1,8-*de*]-1,3,2-DIOXATHIIN (**53**)

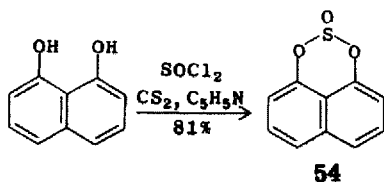


(RRI 3253)

The only representative of this ring system is the 2-oxide (**54**), pre-

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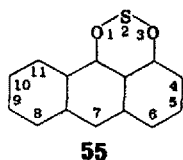
pared by Green²⁵ by the action of thionyl chloride on 1, 8-dihydroxynaphthalene in the presence of pyridine.



Green reported a melting point of 97°, while de la Mare, Tillett, and van Woerden,^{16b} who repeated the preparation, reported a melting point of 102-103°. Although Green reported the cyclic sulfite to be stable to moisture and to cold aqueous alkali, de la Mare and co-workers^{16a, 16b} found the resistance to hydrolysis to be the result of insolubility. **54** is saponified in aqueous dioxane at 25° at 12 times the rate of its acyclic analog, diphenyl sulfite, and at about 10⁶ times the rate of trimethylene sulfite. Its hydrolysis is much slower than that of catechol sulfite, however. Thus, the generalization that aromatic cyclic sulfites hydrolyze under alkaline conditions more rapidly than their aliphatic analogs, while six-membered cyclic sulfites hydrolyze much more slowly than five-membered, holds here as well (see section I A-1a-(3)).

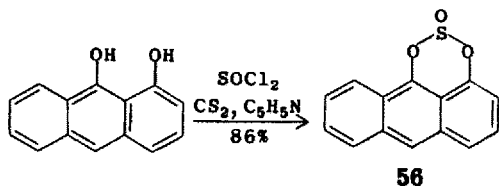
E. C₃O₂S-C₆-C₆-C₆

1. Anthra[1, 9-*de*]-1, 3, 2-dioxathiin (**55**)

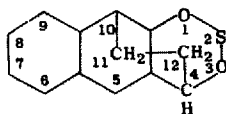


(RRI 4898)

These cyclic sulfites of 1, 9-dihydroxyanthracenes are prepared by reaction of the diol with thionyl chloride in the presence of pyridine.²⁵ The parent compound (**56**) is isolated as pale greenish-yellow plates, m.p. 115° (dec.). The 6-chloro derivative is prepared similarly in 85% yield; it has the same color, m.p. 123-124° (dec.). The compounds are insoluble in cold aqueous sodium hydroxide, but dissolve on warming.

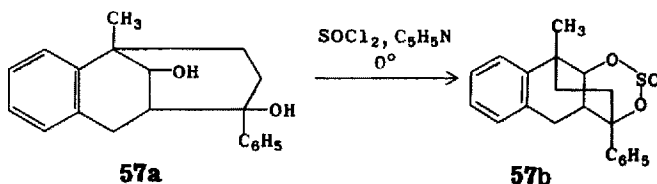


[For references, see pp. 671-674.]

2. 4, 10-Ethano-4*H*-naphtho[2, 3-*d*]-1, 3, 2-dioxathiin (57)

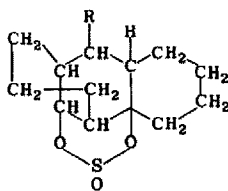
57

Zwahlen, Horton, and Fujimoto⁶⁵ prepared 4a, 5, 10, 10a-tetrahydro-10-methyl-4-phenyl-4, 10-ethano-4*H*-naphtho[2, 3-*d*]-1, 3, 2-dioxathiin 2-oxide (57b), m.p. 142-143° with decomposition, from 8, 11-dihydroxy-5-methyl-8-phenyl-5, 6, 7, 8, 9, 10-hexahydro-5, 9-methanocyclooctabenzene (57a) and thionyl chloride.



57a

57b

3. Decahydro-5, 9-methanobenzocyclooctene-4a, 11(2*H*)-diol Cyclic Sulfite (57c, R = H)

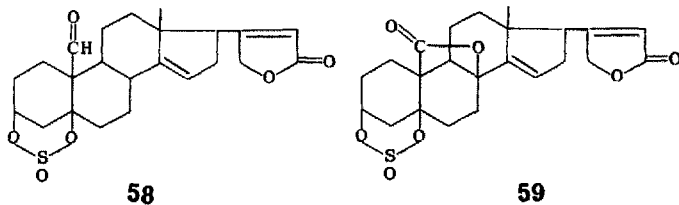
57c

Julia and Varech^{30a, 30b} prepared this cyclic sulfite (R = H), m.p. 95-97°, from the corresponding glycol and thionyl chloride in the presence of pyridine. The formation of a sulfite proved that the two hydroxyl groups are *cis* to each other and presumably axial. The corresponding 10-methyl derivative (57c, R = CH₃) melts at 93-95°.

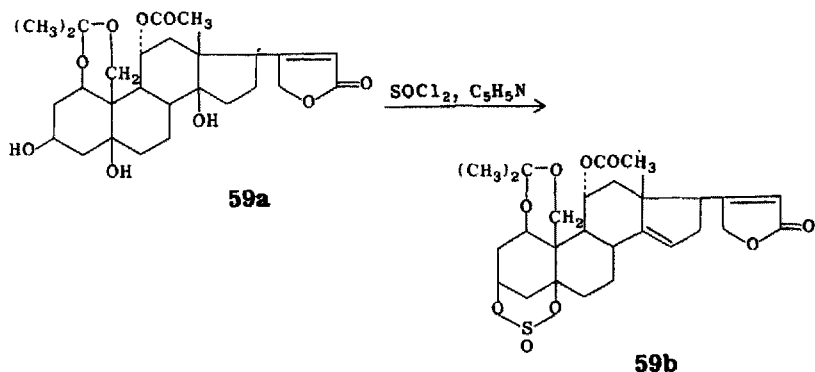
F. CYCLIC SULFITES OF STEROIDS AND RELATED COMPOUNDS

Plattner, Segre, and Ernst⁵⁷ prepared anhydrostrophanthidin cyclic sulfite (58), m.p. 220-222°, by treating the diol with thionyl chloride and pyridine. This was taken as evidence for the *cis* arrangement of the two hydroxyls. Previously, Jacobs and Elderfield²⁹ had reacted an anhydrolactone in the strophanthidin series with thionyl chloride and had isolated a cyclic sulfite, m.p. 242-243°, to which Shoppee⁶¹ assigned structure 59.

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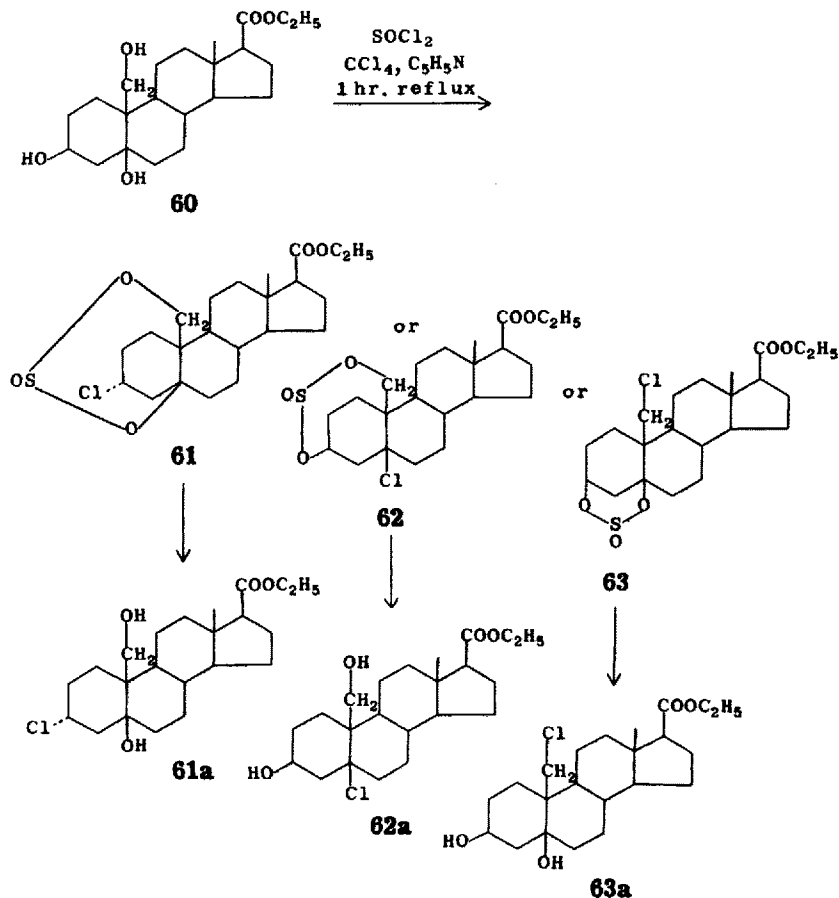


Volpp and Tamm^{62c} reacted 1, 19-isopropylidene-11-*O*-acetyloubaen-9-in (59a) with thionyl chloride and isolated the 14-anhydro-3, 5-cyclic sulfite (59b), m. p. 205-208° (dec.), $[\alpha]_D^{22} - 24^\circ$, proving the *cis* arrangement of the two hydroxyls.

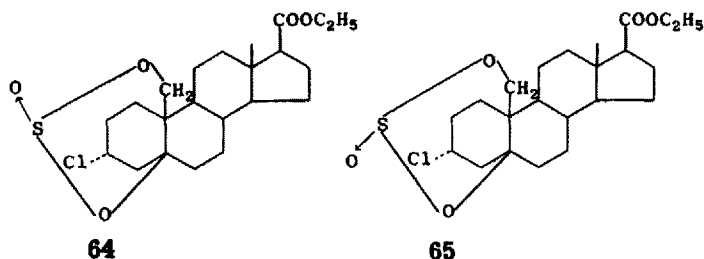


Herzig and Ehrenstein²⁷ investigated the action of thionyl chloride and pyridine on steroid triols. Ethyl 3 β , 5, 19-trihydroxyetiocholanate (60) yields two crystalline compounds, one melting at 222-224° with decomposition, $[\alpha]_D^{28} + 69^\circ$, and the other at 203-205° with decomposition, $[\alpha]_D^{28} + 67^\circ$. Analysis showed both compounds to be monochloro-sulfites. Three possibilities exist, a 3-chloro-5, 19-sulfite (61), a 5-chloro-3, 19-sulfite (62), and a 19-chloro-3, 5-sulfite (63). However, hydrolysis of the two compounds yields the same chlorodiols. Chemical reactions showed that both compounds are 61. Acetylation of the hydrolyzed product with acetic anhydride in pyridine gives a monoacetate, ruling out 62a which should yield a diacetate; furthermore, the hydrolyzate is not readily dehydrochlorinated, arguing against a tertiary chlorine. Oxidation with *N*-bromoacetamide has no effect on the hydrolyzate, ruling out 62a and 63a, which should form 3-keto derivatives. Finally, oxidation with chromic acid yields an acid, indicating that the hydrolyzate is 61a and the sulfite 61; the assignment of the α -configuration to the chlorine is tentative. Inasmuch as both acid and basic hydrolysis of the two compounds yield 61a, the authors ruled out the possibility of the two compounds differing by the stereochemistry of

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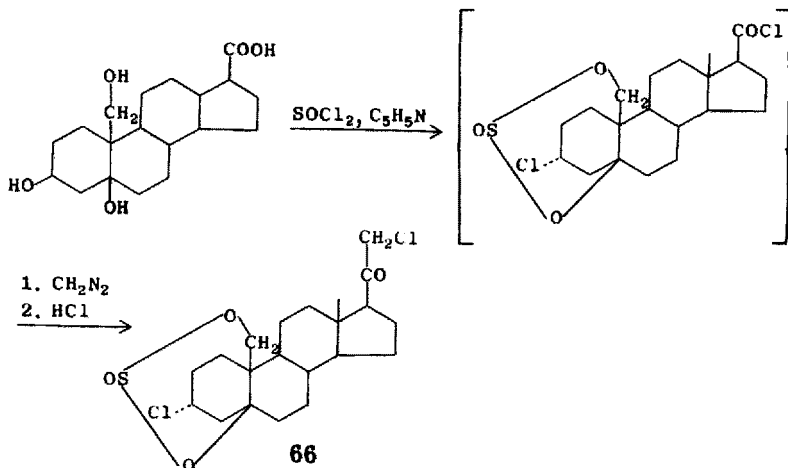
the chloro group, and concluded that they differ only in the sulfite, the sulfoxide oxygen being up or down in the molecule (**64** and **65**).



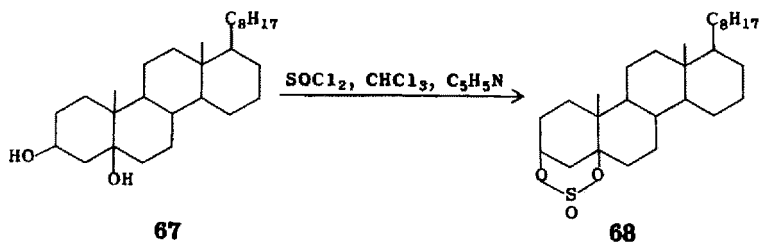
This was apparently the first example of stereoisomerism in a cyclic sulfite, and it has since been confirmed in a simpler compound by de la Mare, Klyne, and co-workers¹⁶ (see section I A-1a-(2)). Herzig and Ehrenstein²⁷ also prepared a cyclic sulfite from 3β , 5, 19-trihydroxy-

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etiocholanolic acid. The intermediate acid chloride was not isolated, but successive treatments with diazomethane and hydrogen chloride converted it into the cyclic sulfite of 3 α , 21-dichloropregnane-5, 19-diol-20-one (**66**), melting at 197-199° with decomposition, $[\alpha]_D^{28} + 105^\circ$; only one isomer was isolated.

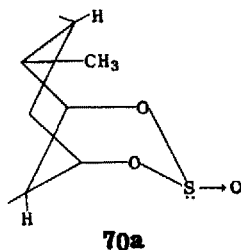
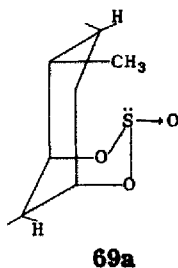
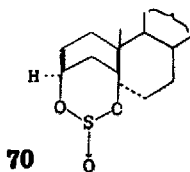
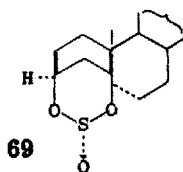


De la Mare, Klyne, and co-workers,¹⁶ investigated a simpler steroid, 5 β -cholestane-3 β , 5-diol (**67**). The sulfite (**68**) exists in polymorphic forms, melting at 160-162° or 135-137°, $[\alpha]_D + 4.5^\circ$.



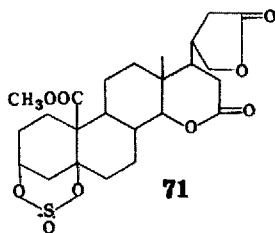
Considering the geometry of **68**, it can exist as **69**, in which the S→O bond is *trans* to the bridge formed by the rest of the steroid A ring, or as **70**, in which it is *cis*. For each isomer two conformations are possible, the sulfite ring being chair or boat. According to the authors the preferred conformations are the chair form for **69** and the boat form for **70**, the sulfur-oxygen bond being equatorial in both **69a** and **70a**. In the opposite conformations the axial oxygen would undergo steric repulsion by the 4 β -hydrogen in **69a** or by the 1 β -hydrogen in **70a**. Thus, whichever isomer had been isolated, the S→O bond must be equatorial. Inasmuch as **68** has an absorption band at 1192 cm⁻¹, this was taken as evidence that all 1, 3, 2-dioxathiane 2-oxides which absorb in the 1190 cm⁻¹ region have the S→O bond equatorial, and this in turn was

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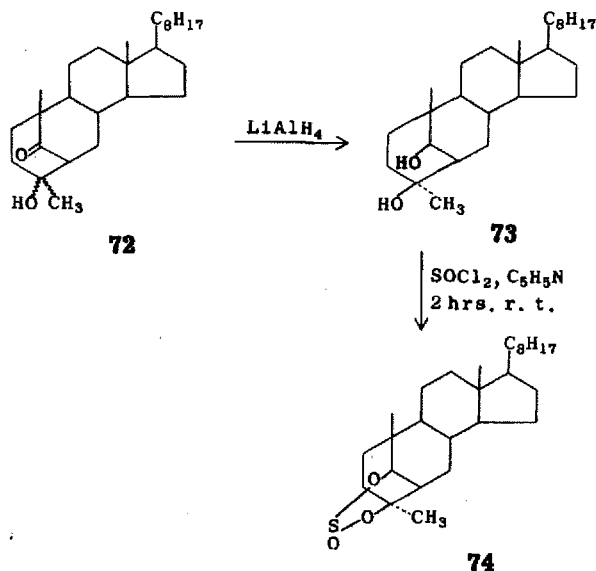
used to assign structures to the two isomeric 5-chloro-1, 3, 2-dioxathiane 2-oxides. Their conclusions have recently been questioned by Hellier, Tillett and co-workers.^{26a}

Jacobs and Elderfield²⁸ prepared a cyclic sulfite, m.p. 229° with decomposition, from an ester in the strophanthidin series. Shoppee⁶¹ assigned structure **71** to it.

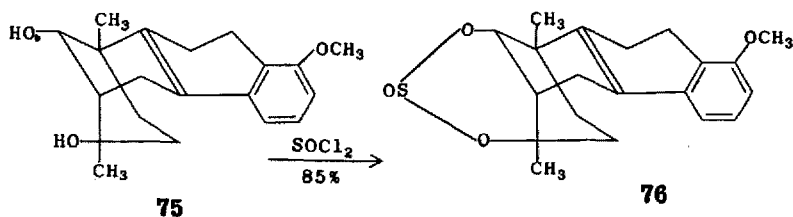


Fujimoto and Zwahlen^{21a} reduced 3-hydroxy-4, 5-seco-3, 6-cyclocholestan-5-one (**72**) with lithium aluminum hydride and obtained an isomeric mixture of diols. One of these (**73**) forms a cyclic sulfite (**74**), m.p. 139-141. 5°. From the results of Johnson and co-workers,^{29a} **73** is probably the 3-*exo*, 5 α -glycol.

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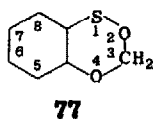


Johnson and co-workers^{29a} found that 1 β , 6-*endo*-dimethyl-6-*exo*, 9 α -dihydroxy-2, 3-(1'-methoxy-7', 8'-dihydro-6', 5'-naphtho)- Δ^2 -bicyclo-[3. 3. 1]nonene (**75**) forms a cyclic sulfite (**76**), m.p. 137-139°, whereas the corresponding 1 β , 6-*exo*-dimethyl-6-*endo*, 9 α -dihydroxy compound does not.



Romo de Vivar, Ruelas, and Romo^{58a} prepared a cyclic sulfite, m.p. 193-194°, $[\alpha]_D -74^\circ$, from 5-hydroxysmilagenin.

II. 1, 3, 4-DIOXATHIA COMPOUNDS. C₃O₂S-C₆ 2, 4, 1-BENZO-DIOXATHIIN (**77**)



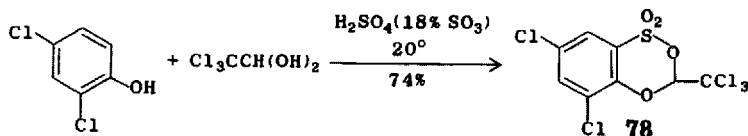
(RRI 1531)

Ettel and Weichet¹⁹ reported that 2, 4-dichlorophenol reacts with chloral hydrate in the presence of fuming sulfuric acid to give 3-

[For references, see pp. 671-674.]

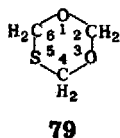
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trichloromethyl-5, 7-dichloro-2, 4, 1-benzodioxathiin 1, 1-dioxide (**78**), m.p. 118-120°, presumably *via* the *o*-phenolsulfonic acid. Riemschneider reported a melting point of 116°.



Similarly, *p*-bromophenol yields the 7-bromo derivative, m.p. 108-110°, in 71% yield. The compounds are insoluble in cold alkali and are surprisingly stable in hot, concentrated hydrochloric acid or ethanol. The structures were indicated by hydrolysis with alcoholic potassium hydroxide to the corresponding *o*-phenolsulfonic acids. According to Riemschneider **78** is inactive as a contact insecticide.

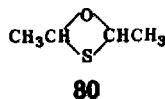
III. 1, 3, 5-DIOXATHIA COMPOUNDS. C₃O₂S 1, 3, 5-DIOXATHIANE (**79**)



(RRI 220)

This ring system is indexed in Chemical Abstracts as 1, 3, 5-dioxathiane. Alternative names are 1, 3-dioxo-5-thiacyclohexane, and for the 2, 4, 6-trimethyl derivative, monothioparaldehyde and monothiotriacetaldehyde.

In 1878 Klinger³² reacted a solution of acetaldehyde in concentrated hydrochloric acid with hydrogen sulfide. A variety of products were formed, from which he isolated an impure material, melting at about 35°, which he formulated as **80**.

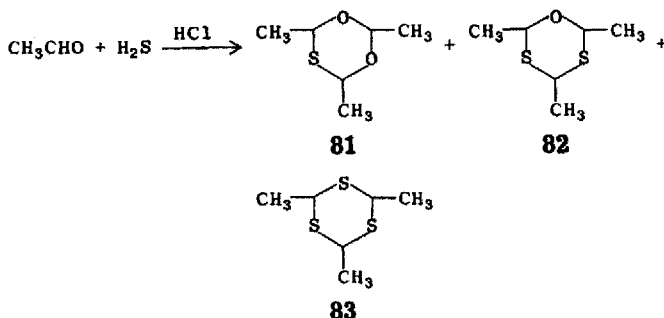


This work was repeated by Marckwald,⁴⁰ who assigned the same structure to a purified product, melting at 60-61°, on the basis of a vapor density molecular weight determination, sulfur analysis, and the lack of reaction with mercuric oxide. Drugman and Stockings¹⁷ confirmed Marckwald's findings.

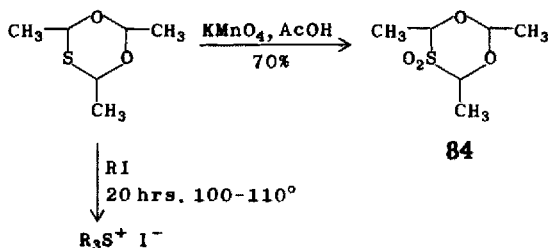
The correct structure of this compound was elucidated almost simultaneously by Lebedev and Platonov³³ and by Müller and Schiller.⁴⁸ Passage of hydrogen sulfide into a dilute hydrochloric acid solution of acetaldehyde at room temperature gave three products, 2, 4, 6-trimethyl-1, 3, 5-dioxathiane (**81**), 2, 4, 6-trimethyl-1, 3, 5-oxadithiane (**82**), and

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2, 4, 6-trimethyl-*s*-trithiane (**83**). Marckwald probably had a mixture of **81** and **82** to account for his sulfur analysis and melting point. His molecular weight determination was incorrect because 2, 4, 6-trimethyl-1, 3, 5-dioxathiane boils above 160° with decomposition. Cryoscopic and ebulliometric molecular weight determinations corresponded with the above formula.



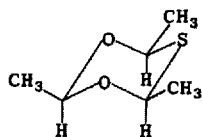
2, 4, 6-Trimethyl-1, 3, 5-dioxathiane (**81**) melts at 55°. It is a volatile solid, subliming *in vacuo* at 30°. It is soluble in common organic solvents, insoluble in water and is steam distillable. Its lack of reactivity with lead acetate and with mercuric oxide in hot ethanol showed the absence of a labile sulfur function. It forms an insoluble yellow adduct with mercuric chloride, and treatment with silver nitrate slowly precipitates silver sulfide. The compound is stable in hot alkali. It reacts with aqueous hydrochloric acid to form the α -isomer of 2, 4, 6-trimethyl-*s*-trithiane (**83**) and with acetyl chloride or phosphorous pentachloride to form the β -isomer. Nitric acid, hydrogen peroxide, and sodium hypochlorite oxidize it to acetic acid and sulfur. Oxidation with acid potassium permanganate yields a monosulfone (**84**), m.p. 152°, indicating that the assigned structure is correct. The sulfone is split readily by acid or base, the former yielding a mixture of sulfur dioxide and sulfur. Alkylation with methyl or ethyl iodide yields the corresponding trialkylsulfonium iodide.^{5 6}



[For references, see pp. 671-674.]

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Only one of the numerous possible stereoisomers has been isolated. Lebedev and Platonov³³ believed this to be a racemic form of one of the two possible *trans* isomers, but no evidence for this assignment has been forthcoming. An investigation of the Raman spectrum of this compound shed no light on the problem, since a solution in carbon tetrachloride decomposed to liberate sulfur upon irradiation with a mercury arc.²² Modern conformational theory would make it seem more likely that this is the all *cis* isomer (**85**), inasmuch as the structure with the three methyl groups equatorial should be the most stable one.



85

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C₃O₂S Ring Systems

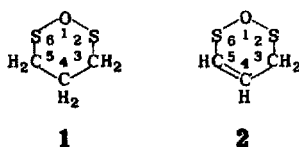
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C₃OS₂ RING SYSTEMS

Several types of compounds containing a C₃OS₂ ring are known. 1, 2, 6-Oxadithiin and oxadithiane are represented by cyclic anhydrides of 1, 3-disulfonic acids, 1, 2, 4-oxadithianes are cyclic esters of compounds of the type HOCH₂CH₂SO₂CH₂SO₂H(SO₃H), 1, 3, 5-oxadithianes are reaction products of aldehydes with hydrogen sulfide, while 1, 3, 4-oxadithiins are cyclic 1, 2-sulfides.

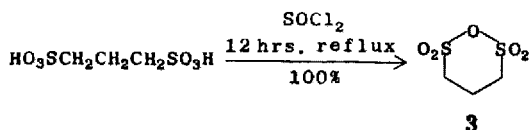
I. 1, 2, 6-OXADITHIA COMPOUNDS**A. C₃OS₂ 1, 2, 6-OXADITHIANE (1) and 3H-1, 2, 6-OXADITHIIN (2)**

(RRI 216)

Since **1** and **2** are known only as their 2, 2, 6, 6-tetroxides, i.e. as cyclic anhydrides of 1, 3-disulfonic acids, they are listed in Chemical Abstracts under the parent acids.

1. 1, 2, 6-Oxadithiane

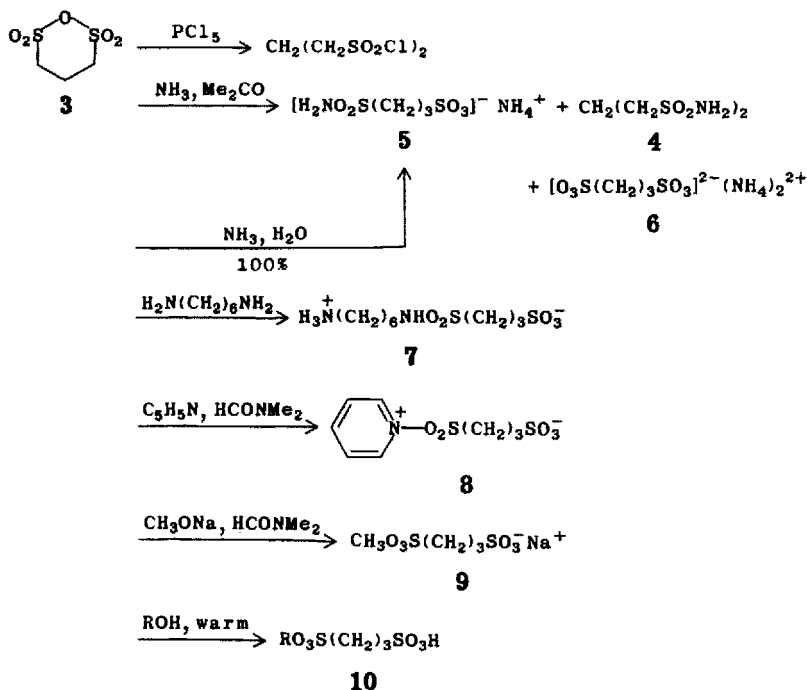
1, 3-Propanedisulfonic anhydride, or 1, 2, 6-oxadithiane 2, 2, 6, 6-tetroxide (**3**), was prepared by McElvain, Jelinek, and Rorig¹⁴ by treatment of the acid with thionyl chloride.



It was also formed in 60-69% yield by heating the acid *in vacuo* at 150-170°. Geiseler and Kuschniers⁹ reported an 80% yield of **3** with thionyl chloride and claimed that heating the acid with phosphorus oxychloride for one hour at 80° is a better procedure, a 92% yield of **3** being obtained. They also prepared **3** in 61% yield by heating 1, 3-propanedisulfonyl chloride with mercuric oxide; lower yields are obtained with lead oxide, zinc oxide, and magnesium oxide.

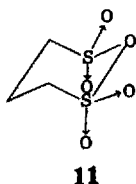
Chapter 9

McElvain, Jelinek, and Rorig reported a melting point of 194–196° with decomposition for the cyclic anhydride, while Geiseler and Kuschmiers reported a melting point of 198°. According to the latter authors the anhydride can be sublimed at 160–170° at 0.2 mm with only slight decomposition. The compound is soluble only in solvents possessing a carbonyl group — acetic anhydride, ethyl acetate, acetone, and dimethylformamide; that solubility is not merely a function of polarity of the solvent was shown by its limited solubility in acetonitrile. McElvain, Jelinek, and Rorig found that the cyclic anhydride is insoluble in cold water and hydrolyzes slowly in hot water. Thus, it is much more stable to hydrolysis than either acyclic sulfonic anhydrides or 1,2-ethanedithionyl anhydride (see Chapter 2, section I); Geiseler and Kuschmiers attributed this resistance toward hydrolysis to the stability of the six-membered ring. Geiseler and Kuschmiers studied a few reactions of the cyclic anhydride (3). Phosphorus pentachloride gave 1,3-propanedisulfonyl chloride. Anhydrous ammonia gave a 19% yield of the diamide (4), a 57% yield of the half-amide ammonium salt (5), and a 6% yield of the diammonium salt (6); aqueous ammonia gave a quantitative yield of 5. Hexamethylenediamine gave only the amide zwitterion (7) and no polymer, while pyridine gave presumably the trimethylenesulfonylpyridinium sulfonate (8). With sodium methoxide the half-ester sodium salt (9) was formed, while alcohol gave the half-ester acid (10); the latter could not be obtained pure, since it readily decomposed to the ether.

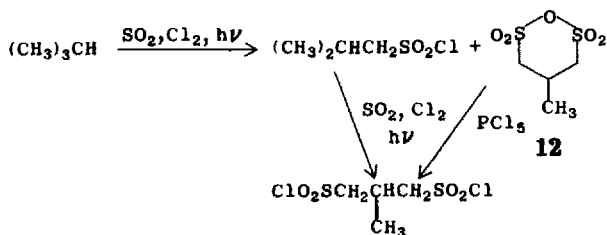


C₃OS₂ Ring Systems

Geiseler and Kuschmiers¹⁰ determined the infrared absorption spectrum of **3** and concluded that the molecule probably exists in the chair form (**11**).

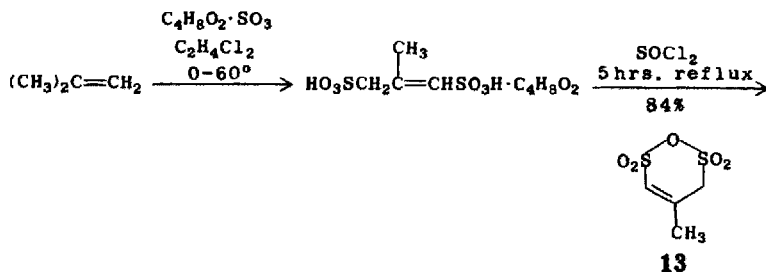


Asinger and Ebeneder² isolated a 1% yield of 4-methyl-1, 2, 6-oxadithiane 2, 2, 6, 6-tetroxide (**12**) as white crystals, m.p. 188°, from the chlorosulfonation of isobutane. The structural assignment was based on the facts that isobutane showed no tendency to react on the tertiary carbon atom, in other chlorosulfonations no 1, 1- or 1, 2-substitution was ever found, and the chlorosulfonation of isobutanesulfonyl chloride yielded a disulfonyl chloride identical with that prepared from **12** and phosphorus pentachloride.



2. 3H-1, 2, 6-Oxadithiin

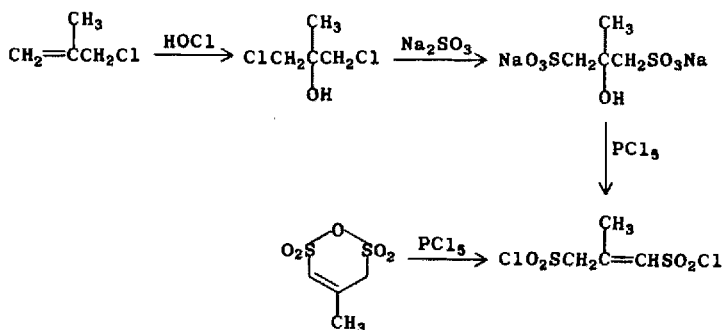
In 1941 Suter and Malkemus¹⁷ reported that the sulfonation of isobutylene with the dioxane-sulfur trioxide complex yields a disulfonic acid in the form of a dioxane complex. Treatment of the complex with thionyl chloride yields a cyclic anhydride, m.p. 167-170°, which they formulated as 4-methyl-3H-1, 2, 6-oxadithiin 2, 2, 6, 6-tetroxide (**13**).



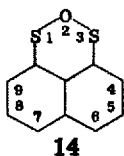
The anhydride is quite stable. It dissolves slowly in hot water or alkali, and is hydrolyzed slowly by moist air. It is insoluble in organic solvents other than acetone and ethyl acetate. Hydrolysis with barium hydroxide yields the same barium salt as obtained from the dioxane

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complex, indicating that no unexpected reaction takes place with thionyl chloride. Its structure was shown by the following synthesis, the identical sulfonyl chloride being obtained by both routes.

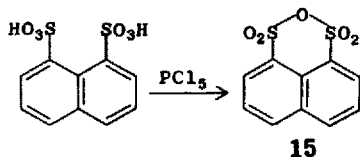


B. $\text{C}_3\text{O}_2\text{S}-\text{C}_6-\text{C}_6$ NAPHTH[1, 8-*cd*][1, 2, 6]OXADITHIIN (14)



(RRI 3251)

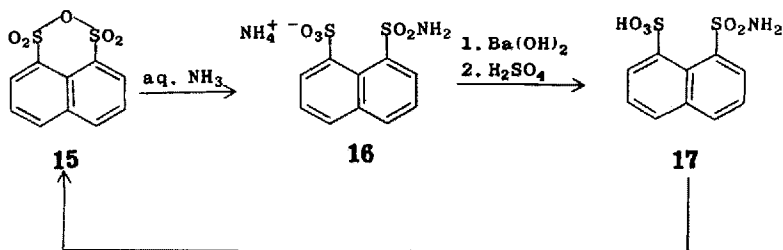
The sole representative of this ring system is the cyclic anhydride of 1, 8-naphthalenedisulfonic acid (15), first prepared by Armstrong and Wynne¹ from the acid and phosphorus pentachloride.



According to Karavaev and Spyrskov¹² heating the acid with phosphorus pentachloride or phosphorus pentoxide gave 35-55% yields of 15; the best procedure, giving 15 in 85% yield, is to heat the acid with chlorosulfonic acid for 2.5 hours at 55-60°.

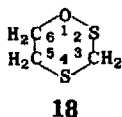
Armstrong and Wynne reported a melting point of 227°, Cumming and Muir⁷ found 225°, while Karavaev and Spyrskov claimed the correct melting point to be 232°. The last authors used the insolubility of the anhydride in water to prove that no 1, 8-naphthalenedisulfonic acid is formed in the sulfonation of 1-naphthalenesulfonic acid. The anhydride reacts with aqueous ammonia to give the half-amide ammonium salt (16); however, even removal of the water at room temperature from the half-amide acid (17) results in loss of ammonia and reformation of the anhydride.

C₃OS₂ Ring Systems



II 1, 2, 4-OXADITHIA COMPOUNDS

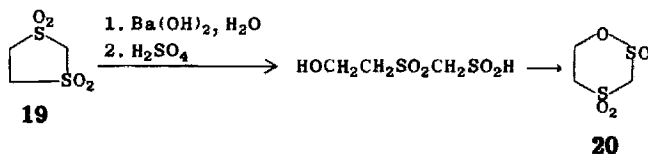
C₃OS₂ 1, 2, 4-Oxadithiane (18)



(RRI 214)

An alternative name for this ring system is 1-oxa-2, 4-dithiacyclohexane.

According to Baumann and Walter³ hydrolysis of 1, 3-dithiolane 1, 1, 3, 3-tetroxide (19) with aqueous barium hydroxide gives a hydroxy-sulfonic acid which, when its aqueous solution is concentrated, cyclizes to a sulfinate ester, 1, 2, 4-oxadithiane 2, 2, 4-trioxide (20).



20, m.p. 164°, is soluble in cold water, giving a neutral solution which becomes acid on long heating. Alkaline solutions hydrolyze it in the cold to the original hydroxy acid. It is less soluble in ethanol than in water and insoluble in ether. Acid permanganate oxidizes it to the cyclic sulfonate ester, 1, 2, 4-oxadithiane 2, 2, 4-tetroxide, obtained as prisms, m.p. 206-207°. This compound is readily soluble in hot water, less soluble in cold, soluble in ethanol, and sparingly soluble in ether, benzene, and chloroform. It, too, is readily hydrolyzed by base.

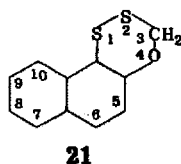
The solubilities reported for these compounds are rather surprising. Although sulfonic acids can be esterified with alcohols by azeotropeing the water formed,¹¹ the ease of ring closure in this case, taking place as it reportedly does in aqueous solution, is somewhat unusual. Apparently no other compounds of this type have been reported.

III 1, 3, 4-OXADITHIA COMPOUNDS

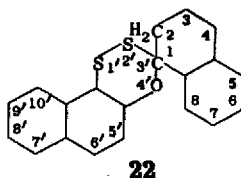
C₃OS₂-C₆-C₆ Naphth[1, 2-*e*][1, 3, 4]oxadithiin (21) and Spiro[naphtha-

Chapter 9

lene-1(2*H*), 3'-naphth[1, 2-*e*][1, 3, 4]oxadithiin] (**22**)

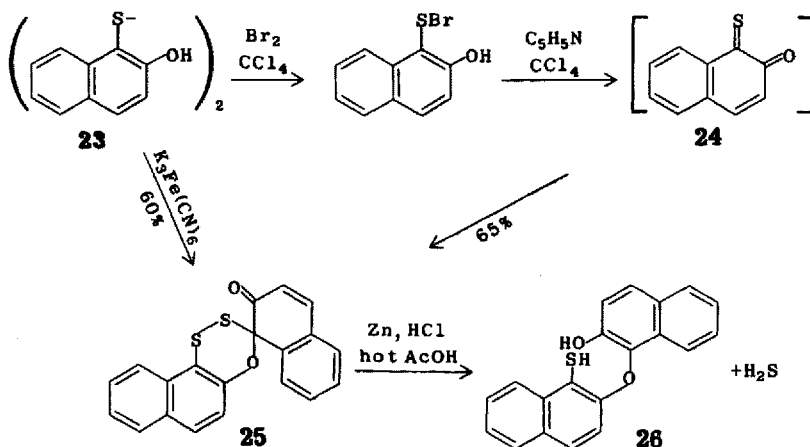


(RRI 3250)



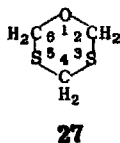
(RRI 6130)

The spiro compound is listed in Chemical Abstracts under the parent ring system, naphth[1, 2-*e*][1, 3, 4]oxadithiin, which has not yet been reported. According to Stevenson and Smiles¹⁶ β -naphtha-1-thioquinone (**24**) dimerizes spontaneously to a spiro compound (**25**), isolated as orange prisms melting at 171°. The compound was called dehydro-2-naphthol-1-disulfide. It was also formed in 60% yield by alkaline oxidation of 2-naphthol-1-disulfide (**23**) with potassium ferricyanide. The structure of the compound was based on the fact that reduction liberates half the sulfur as hydrogen sulfide, indicating a different character for the two sulfurs, and forms the known dinaphthyl ether (**26**).



IV. 1, 3, 5-OXADITHIA COMPOUNDS

C_3OS_2 1, 3, 5-Oxadithiane (**27**)

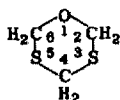


(RRI 215)

A variety of names have been used for this ring system. Although

C₃OS₂ Ring Systems

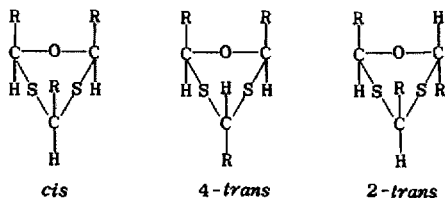
TABLE 1. 1, 3, 5-Oxadithianes



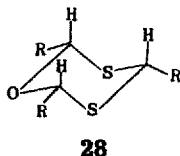
Isomer	Substituents	Yield (%)	M. p. (°C)	Ref.
	2, 4, 6-(CH ₃ -) ₃		70-72	13
	2, 4, 6-(CH ₃ -) ₃ 3, 3, 5, 5-tetroxide		215 dec.	13
α	2, 4, 6-(Cl ₃ C-) ₃		236	5
β	2, 4, 6-(Cl ₃ C-) ₃		108	5
α	2, 6-(Cl ₃ C-) ₂ -4-(Cl ₂ C=)		97	5
β	2, 6-(Cl ₃ C-) ₂ -4-(Cl ₂ C=)		92	5
	2, 4, 6-(Cl ₂ C=) ₃		89	5
α	2, 4, 6-(Cl ₃ C-) ₃ -2, 4, 6-Cl ₃ }	70	175 dec.	5
β	2, 4, 6-(Cl ₃ C-) ₃ -2, 4, 6-Cl ₃ }		157 dec.	5
α	2, 4, 6-(Cl ₃ C-) ₃ -4-Cl		136	5
β	2, 4, 6-(Cl ₃ C-) ₃ -4-Cl		98-99	5
	2, 4, 6-(Cl ₃ C-) ₃ -4-C ₂ H ₅ O-		137	5
	2, 6-(Cl ₂ C=) ₂ -4-Cl ₃ C-4-C ₂ H ₅ O-		94	5
	2, 6-(Cl ₂ C=) ₂ -4-Cl ₃ C-4-Cl		88	5
	2, 6-(Cl ₃ C-) ₂ -4-(Cl ₂ C=) 3, 3-dioxide	82	166-167	6
	2, 4-(Cl ₂ C=) ₂ -6-Cl ₃ C- 3, 3-dioxide		148	6
	2, 6-(Cl ₂ C=) ₂ -4-CO ₂ C ₂ H ₅ 3, 3-dioxide	61	112. 5	6
	2, 6-(Cl ₂ C=) ₂ -4-CO ₂ CH ₃ 3, 3-dioxide		126	6
	2-(Cl ₂ C=)-4-CO ₂ C ₂ H ₅ -6-Cl-6-Cl ₃ C- 3, 3-dioxide		151-152	6
	2-(Cl ₂ C=)-4, 6-Cl ₂ -4-CO ₂ C ₂ H ₅ -6-Cl ₃ C- 3, 3-dioxide		161. 5	6
	2, 6-(Cl ₂ C=) ₂ 3, 3, 5, 5-tetroxide	11-22	185	6
	2, 6-(Cl ₂ C=) ₂ -4-Cl ₂ 3, 3, 5, 5-tetroxide		143	6
	2, 4, 6-(C ₆ H ₅ -) ₃ 3, 3- or 3, 5-dioxide		195	8

Chemical Abstracts prefers 1, 3, 5-oxadithiane, it has listed the compounds as cyclo-1, 3, 5-oxadithia-2, 4, 6-trimethylene in the past. An alternative name is 1-oxa-3, 5-dithiacyclohexane. Older literature related the name to the parent aldehyde from which it was derived, such as dithiopaldehyde or dithiotriacetaldehyde. The compounds which have been prepared are listed in Table 1.

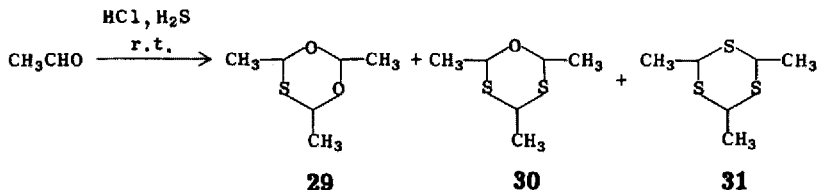
Three geometrical isomers are possible for 2, 4, 6-trisubstituted derivatives of this ring system.



The *cis*- and *4-trans*-isomers are symmetrical, but the *2-trans*-isomer should exist in two distereoisomeric forms. There is very little evidence available for assigning structures to these compounds. By analogy with the *s*-trithianes, however (see Chapter 10, section II A-2), it is reasonable to assume that the most stable, least soluble, highest melting isomer is the *cis*-isomer existing in the chair form with the substituents equatorial (28), while the more soluble, lower melting isomer is one of the two possible *trans* isomers.



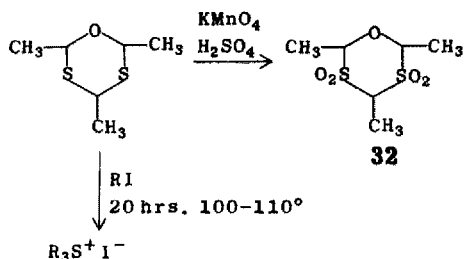
The reaction of aldehydes or ketones with hydrogen sulfide under acidic conditions is known to give *s*-trithianes as the major product (see Chapter 10, section II). Lebedev and Platonov¹³ were apparently the first to show that under mild conditions acetaldehyde gives a mixture of 2, 4, 6-trimethyl-1, 3, 5-dioxathiane (29) (Chapter 8, section III), 2, 4, 6-trimethyl-1, 3, 5-oxadithiane (30), and 2, 4, 6-trimethyl-*s*-trithiane (31).



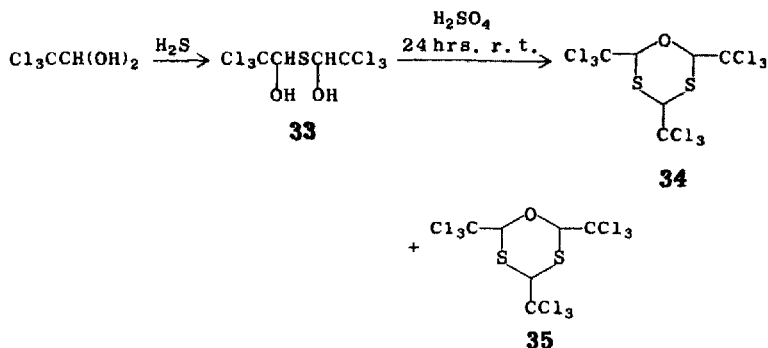
The 1, 3, 5-oxadithiane was separated from the two other products by a combination of distillation and sublimation. The compound is soluble in most organic solvents and insoluble in water. Only one compound has been isolated, and this was believed to be a racemic *trans* configuration,

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although no evidence for this assignment has been forthcoming. Acid permanganate oxidizes the product to a disulfone (**32**), indicating the correctness of the assigned structure. The disulfone is very soluble in hot water. Methyl and ethyl iodide give the corresponding trialkylsulfonium iodide; ethyl bromide does not react.¹⁵



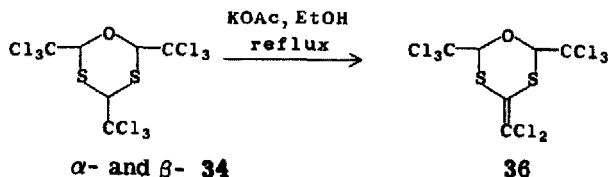
2, 4, 6-Tris(trichloromethyl)-1, 3, 5-oxadithiane (**34**), derived from chloral, is the most thoroughly studied derivative of this ring system.^{5, 6} Chloral hydrate reacts with hydrogen sulfide to form chloral sulfhydrate (**33**). Chattaway and Kellett⁵ found that the reaction of **33** with concentrated sulfuric acid gives a mixture of the 1, 3, 5-oxadithiane (**34**) and the *s*-trithiane (**35**).



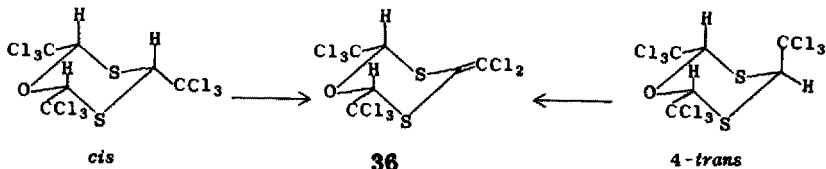
Even in the presence of a large excess of chloral there was no indication of the formation of a 1, 3, 5-dioxathiane; the excess chloral merely repressed the formation of the *s*-trithiane. Only two of the possible three geometrical isomers were isolated, a less soluble α -form, m.p. 236° (needles), and a more soluble β -form, m.p. 108° (prisms). The yields were poor; 200 g. of sulfhydrate yielded 11-12 g of α -isomer, 23-24 g of β -isomer, and 2-3 g of *s*-trithiane.

The oxadithianes (**34**) undergo a number of interesting reactions. Alcoholic potassium acetate eliminates one hydrogen chloride from each isomer, and two different compounds are formed. Since β -chlorosulfides are known to lose hydrogen chloride readily,⁴ it is reasonable to assume that the elimination involves the trichloromethyl group on C-4 to form 2, 6-bis(trichloromethyl)-4-dichloromethylene-1, 3, 5-oxadithiane (**36**).

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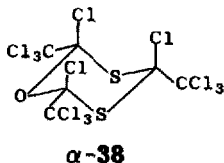
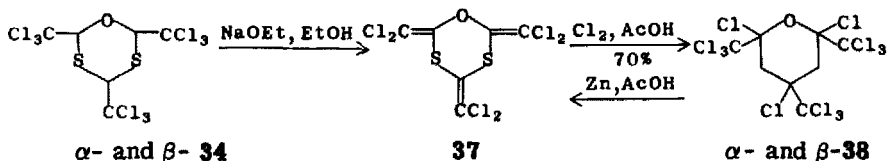


It follows that one of the two isomers of **34** must be the racemic 2-*trans*-derivative, since the *cis* and 4-*trans* isomers would give the same dichloromethylene derivative.



By analogy with the *s*-trithianes the tentative assignments can be made of the *cis* structure to the α -isomers and the 2-*trans* to the β -isomers of both **34** and **36**.

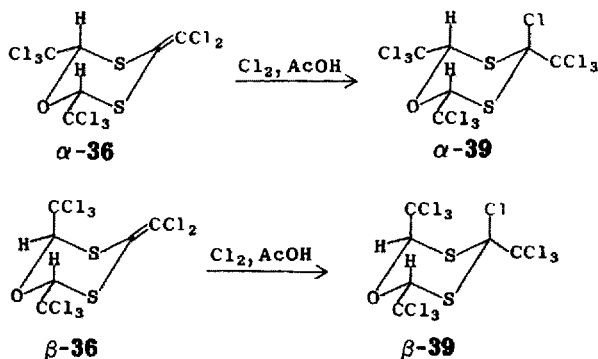
Stronger bases, such as sodium ethoxide or potassium cyanide eliminate three moles of hydrogen chloride from both isomers of **34** to form 2, 4, 6-tris(dichloromethylene)-1, 3, 5-oxadithiane (**37**); as expected, only one isomer is formed. **37** readily adds chlorine to give 2, 4, 6-tris(trichloromethyl)-2, 4, 6-trichloro-1, 3, 5-oxadithiane (**38**); although three stereoisomers are possible, only two were isolated. Refluxing either isomer with zinc in acetic acid regenerates **37**. It would be reasonable to guess that the α -isomer of **38** would be the *cis* isomer with the bulky trichloromethyl groups equatorial, while the β -isomer would be the *trans* isomer with either the 2- or 4-trichloromethyl group axial.



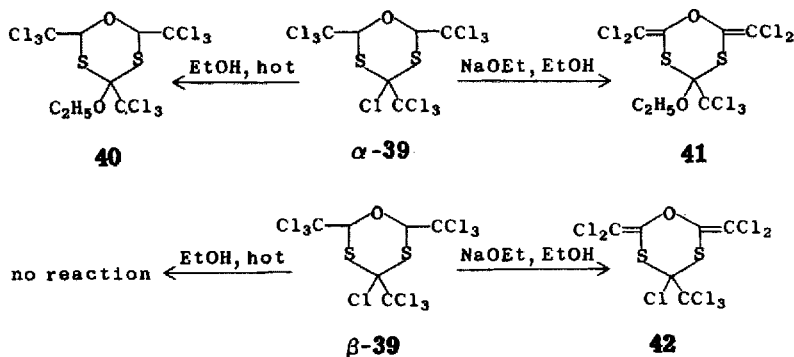
Both isomers of the 4-dichloromethylene derivative (**36**) react with chlorine similarly to form 4-chloro-2, 4, 6-tris(trichloromethyl)-1, 3, 5-oxadithiane (**39**). Only one isomer was isolated in each case, α -**36** giving α -**39** and β -**36** giving β -**39**. If our previous assignments are correct, α -**39** probably has the three bulky trichloromethyl groups *cis*-

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equatorial with an axial chlorine, while β -**39** has two equatorial trichloromethyl groups with one trichloromethyl group and the chlorine axial.



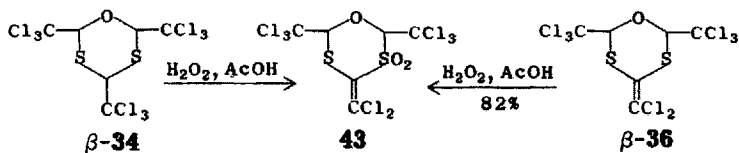
The α - and β -forms of **39** showed considerable difference in reactivity of the chlorine. The α -isomer reacts with hot ethanol to give 4-ethoxy-2, 4, 6-tris(trichloromethyl)-1, 3, 5-oxadithiane (**40**), while the β -isomer does not react. With sodium ethoxide the α -isomer gives 4-ethoxy-4-trichloromethyl-2, 6-bis(dichloromethylene)-1, 3, 5-oxadithiane (**41**), while the β -isomer gives 4-chloro-4-trichloromethyl-2, 6-bis(dichloromethylene)-1, 3, 5-oxadithiane (**42**).



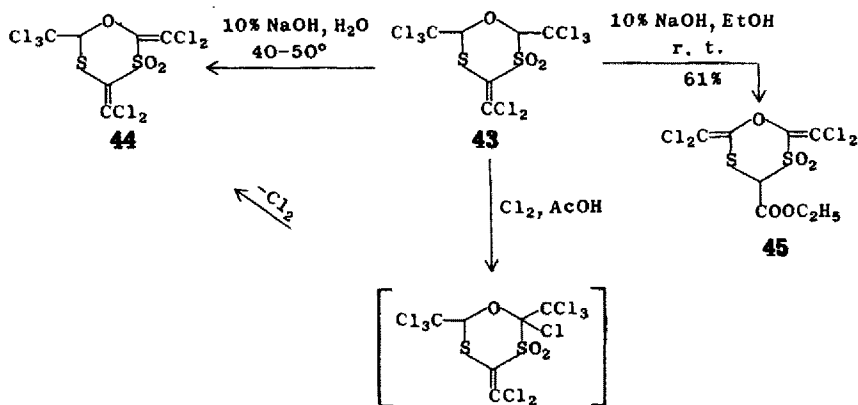
This is rather difficult to explain. Although it appears reasonable to assume that a bulky axial trichloromethyl group lowers the activity of the chlorine in the β -isomer, this steric factor is lost in the bis(dichloromethylene) derivative (**42**) and one would expect an axial chlorine to be displaced to give **41**. These results would be more understandable if the β -isomer had the chlorine equatorial; it is apparent that these conformational assignments require confirmation.

Oxidation of β -2, 4, 6-tris(trichloromethyl)-1, 3, 5-oxadithiane (**34**) with hydrogen peroxide leads to extensive disruption of the molecule. A small yield of monosulfone (**43**), however, can be isolated. The same compound is obtained in much better yield by oxidation of β -2, 6-bis(trichloromethyl)-4-dichloromethylene-1, 3, 5-oxadithiane (**36**).

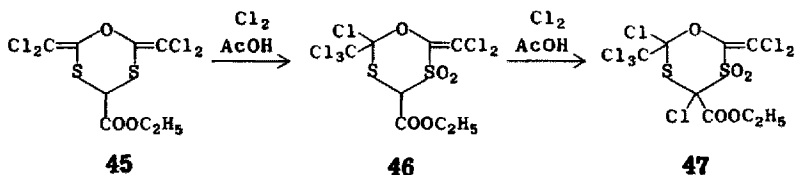
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The sulfone can be recovered unchanged from concentrated sulfuric acid. It is inert to chlorine and bromine in the cold, and it is not reduced by tin and acid. Alcoholic potassium acetate, aqueous sodium hydroxide, and chlorine in warm acetic acid all give the same product, presumably 2, 4-bis(dichloromethylene)-6-trichloromethyl-1, 3, 5-oxadithiane 3, 3-dioxide (**44**), since it is probably reasonable to postulate that the reactions take place on the carbon adjacent to the sulfone group rather than on the carbon next to the sulfide group. Alcoholic sodium hydroxide, however, causes a more deep-seated hydrolysis and yields a compound formulated as 2, 6-bis(dichloromethylene)-4-carbethoxy-1, 3, 5-oxadithiane 3, 3-dioxide (**45**).

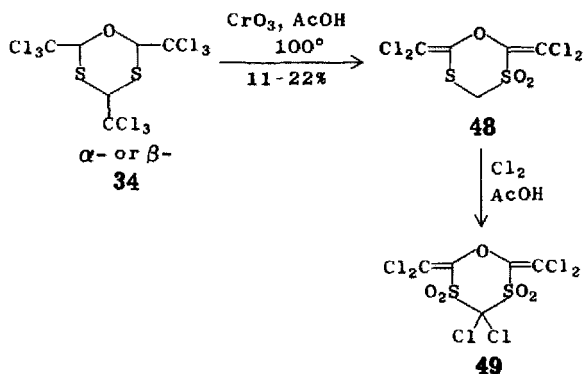


The methyl ester is prepared similarly. The esters decompose on long exposure to air and cannot be hydrolyzed to the free acid. Since the hydrogen in the 4-position is acidic, the esters are soluble in dilute sodium hydroxide. The ethyl ester can be chlorinated stepwise, first to a product (**46**) soluble in dilute alkali and therefore presumably still containing a hydrogen in the 4-position, and then to an alkali-insoluble product (**47**). Double bonds adjacent to a sulfone group have been found to be inert to chlorine, and it is reasonable, therefore, to expect chlorination to take place in the 6-position rather than in the 2-position.



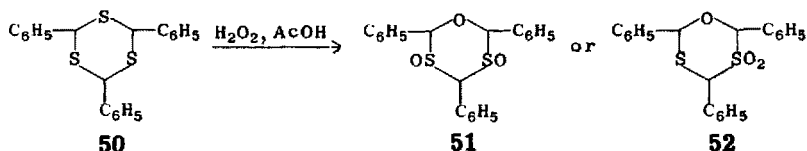
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Oxidation of either α - or β -2, 4, 6-tris(trichloromethyl)-1, 3, 5-oxadithiane (**34**) with chromic anhydride gives a small yield of an unsaturated disulfone (**48**), carbon dioxide being eliminated in the process. Chlorination of this yields a hexachloride, presumably 2, 6-bis(dichloromethylene)-4, 4-dichloro-1, 3, 5-oxadithiane 3, 3, 5, 5-tetroxide (**49**).



In accord with prediction the oxidation product (**48**) is soluble in aqueous sodium carbonate, from which it can be recovered unchanged, while the chlorination product (**49**) is insoluble in aqueous alkali.

Fromm and Schultis⁸ treated a hot acetic acid solution of α - or β -2, 4, 6-triphenyl-*s*-trithiane (**50**) with excess hydrogen peroxide and obtained a mixture of products from which 2, 4, 6-triphenyl-1, 3, 5-oxadithiane 3, 5-dioxide (**51**) or 3, 3-dioxide (**52**) could be isolated by treatment with alkali, the product being insoluble.



The reported stability of the compound towards strong sulfuric and nitric acids, as well as reducing and oxidizing agents, is quite unexpected.

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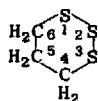
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CHAPTER 10

C_3S_3 Ring Systems

Two types of C_3S_3 rings are known, the 1, 2, 3-trithianes and the *s*-trithianes. The 1, 2, 3-trithianes consist of several compounds prepared by the reaction of 1, 3-dihalides with polysulfides. The *s*-trithianes are the reaction products of aldehydes and ketones with hydrogen sulfide; many examples are known. The latter category also includes an interesting series of compounds related to adamantane in structure.

I 1, 2, 3-TRITHIA COMPOUNDS. 1, 2, 3-TRITHIANE (1) AND RELATED SPIRO DERIVATIVES



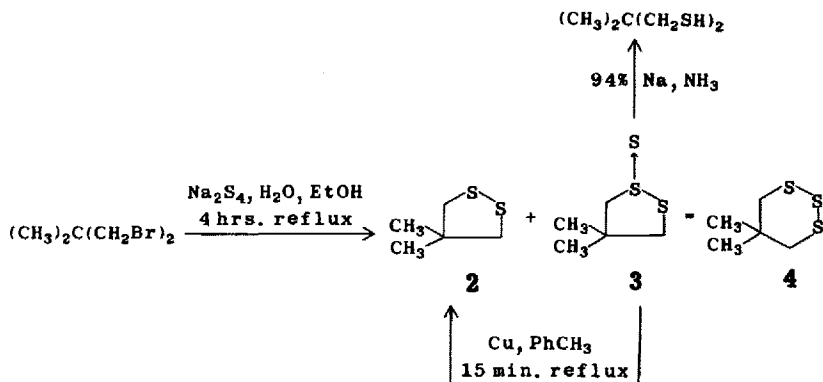
1

(RRI 225)

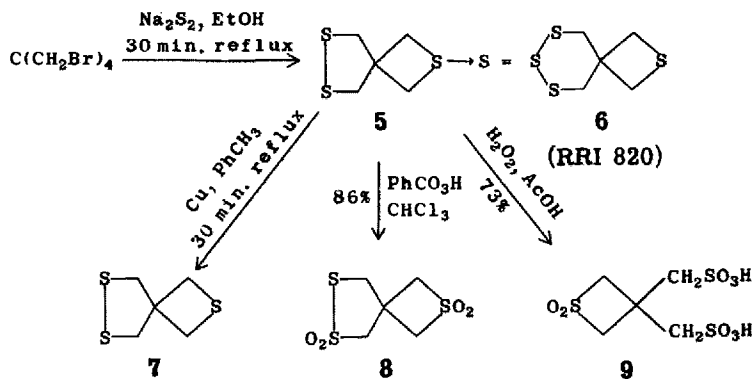
This ring system is indexed in Chemical Abstracts as *ν*-trithiane. However, the alternative, 1, 2, 3-trithiane, is used more frequently in the literature, while 1, 2, 3-trithiacyclohexane is apparently not used at all. The unsaturated derivative, 4*H*-1, 2, 3-trithiin, has not been reported.

Backer and Tamsma⁸ reacted 2, 2-dimethyl-1, 3-dibromopropane with sodium tetrasulfide and isolated two compounds, 4, 4-dimethyl-1, 2-dithiolane (2) and a compound to which they assigned the structure 1-thio-4, 4-dimethyl-1, 2-dithiolane (3), b.p. 114-116° at 12 mm.²⁰⁸ The structure was based on the observation that heating with copper converted 3 into 2, while sodium in liquid ammonia gave 2, 2-dimethyl-1, 3-dimercaptopropane (see Chapter 5, section I A-1a). Foss⁸⁶ was apparently the first to suggest that this and related compounds have the 1, 2, 3-trithiane structure instead. Thus, 3 would be 5, 5-dimethyl-1, 2, 3-trithiane (4).

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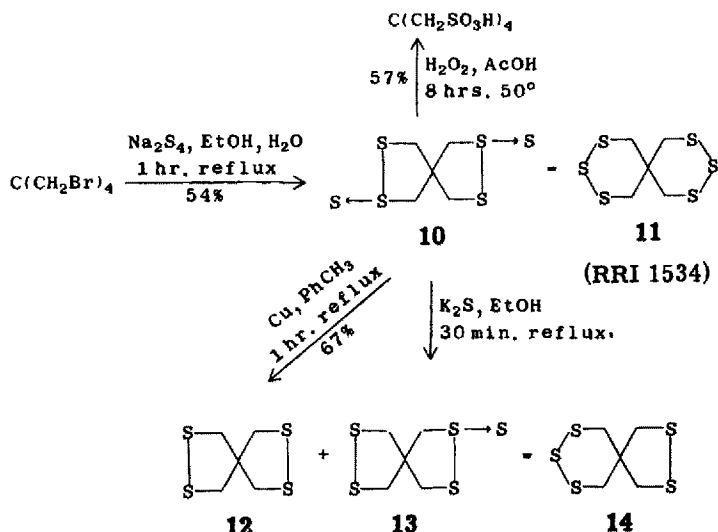


Similarly, Backer and Evenhuis⁶ reacted 2,2-bis(bromomethyl)-1,3-dibromopropane with sodium disulfide and isolated a compound, m.p. 78.5°, which they considered to be 2-thio-2,6,7-trithiaspiro[3.4]octane (5), and which Foss considered to be 2,6,7,8-tetrathiaspiro[3.5]nonane (6). Here, too, copper removed sulfur and yielded 2,6,7-trithiaspiro[3.4]octane (7). Oxidation with perbenzoic acid gave 2,6,7-trithia-spiro[3.4]octane 2,2,6,6-tetroxide (8), while hydrogen peroxide cleaved the 1,2-dithiolane ring to yield a disulfonic acid (9).



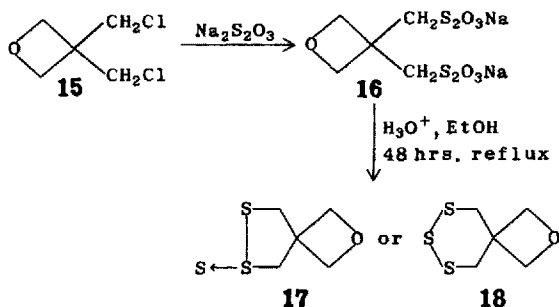
Backer and Evenhuis⁷ reported that the same tetrabromide with sodium tetrasulfide yields 2,7-dithio-2,3,7,8-tetrathiaspiro[4.4]nonane (10), m.p. 182-184°, more probably 2,3,4,8,9,10-hexathiaspiro[5.5]undecane (11). Treatment with potassium sulfide yields a mixture of 2,3,7,8-tetrathiaspiro[4.4]nonane (12) and the corresponding 2-thio derivative (13), m.p. 117.5-118°, more probably 2,3,7,8,9-pentathiaspiro[4.5]decane (14). Both 10 or 11 and 13 or 14 yield 12 with copper, and neopentane tetrasulfonic acid with hydrogen peroxide.

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It is interesting that the reaction is not a general one; thus, Backer and Tamsma⁸ found that 2, 2-bis(bromomethyl)-1, 3-propanediol with sodium tetrasulfide yields only the 1, 2-dithiolane derivative (see Chapter 5, section I A-1a).

Campbell⁵² prepared a compound in this series by a different procedure. The bis-Bunte salt (**16**) from 3, 3-bis(chloromethyl) oxetane (**15**), on acid hydrolysis in the presence of excess sodium thiosulfate, yielded a colorless compound, m.p. 90-91°, which Campbell formulated as either 6-thio-2, 6, 7-oxadithiaspiro[3. 4]octane (**17**) or 2, 6, 7, 8-oxatrithia[3. 5]nonane (**18**).

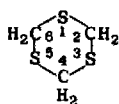


Schotte^{207, 208} repeated some of Backer's work and confirmed the physical properties of the compounds; molecular weight determinations showed all the compounds to be monomeric, as assumed by Backer. Schotte obtained spectroscopic evidence that these compounds are actually 1, 2, 3-trithianes. For example, the reaction product from pentaerythrityl tetrabromide and sodium disulfide cannot be 5, because

its ultraviolet absorption spectrum lacks the maximum at $350\text{ m}\mu$ present in 1,2-dithiolanes. Infrared spectra also are in accord with the 1,2,3-trithiane structure. Schotte's evidence is not unequivocal, since he had no authentic compounds with coordinate sulfur atoms with which to compare these. However, the overwhelming evidence that almost all polysulfides are linear^{82,86,229} leaves little doubt that these compounds have the 1,2,3-trithiane structure.

II 1,3,5-TRITHIA COMPOUNDS

A. s-TRITHIANE (19)



19

(RRI 226)

This class of compounds is indexed in Chemical Abstracts as *s*-trithiane. Alternatively, it might be called 1,3,5-trithiane or 1,3,5-trithiacyclohexane. Various other names have been used in the past — trimethylene 1,3,5-trisulfide, trithioformaldehyde, trimeric thioformaldehyde, and thialdehyde. Other trithianes have been named accordingly, based on the aldehyde or ketone from which they are derived.

s-Trithianes prepared from aldehydes other than formaldehyde or from unsymmetrical ketones can exist in two isomeric forms. There has been general agreement in the literature to call the more soluble, lower melting, less stable isomer the α -form, and the less soluble, higher melting, stable isomer the β -form.

This subject was reviewed in 1946 by Campaigne.⁴⁷

1. Preparation

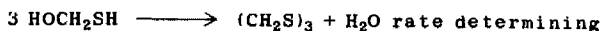
The reactions of aldehydes and ketones with hydrogen sulfide was a subject of interest to organic chemists as far back as the middle of the nineteenth century. Thus, in 1848 Weidenbusch²²⁸ reacted an aqueous solution of acetaldehyde with hydrogen sulfide and obtained a water-insoluble oil. This gave a crystalline precipitate of white needles immediately on treatment with sulfuric acid or hydrogen chloride, hydrogen sulfide being liberated. The crystals had an unpleasant odor and sublimed at 45° ; the compound was probably highly impure 2,4,6-trimethyl-*s*-trithiane.

Hofmann^{132,133} carried out essentially the same preparation with formaldehyde. Treatment of the initial oil with concentrated hydrochloric acid gave a crystalline solid, m.p. 216° , which analyzed as CH_2S . Molecular weight determinations showed that the compound was tri-

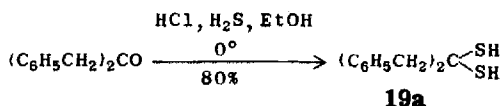
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meric.¹³⁴ Baumann¹³ was apparently the first to demonstrate that almost quantitative yields of *s*-trithiane could be obtained by treating a solution of formaldehyde in concentrated hydrochloric acid with hydrogen sulfide. The synthesis is reported in *Organic Syntheses* in 92-94% yield,³⁸ and is the most frequently used method of preparation for a wide variety of *s*-trithianes. Hinsberg^{122, 125, 127-129} claimed the existence of a second isomer of *s*-trithiane, m.p. 247°, formed by the treatment of *s*-trithiane or its trisulfoxide with hydrogen iodide, but this has been generally discounted.^{27, 60, 95, 96}

Very little attention has been paid to the mechanism of this ring closure. Bogdanski and Chrzasczewski^{35a} studied the kinetics of the reaction between formaldehyde and hydrogen sulfide in the presence of sulfuric acid. They interpreted their results by assuming an initial rapid, reversible reaction to form a hydroxymercaptan, followed by elimination of water to give *s*-trithiane in the rate determining step.

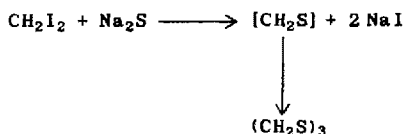


Berchtold, Edwards, Campaigne, and Carmack^{28a} were able to isolate a *gem*-dithiol (**19a**) from dibenzyl ketone, hydrogen sulfide, and hydrogen chloride.



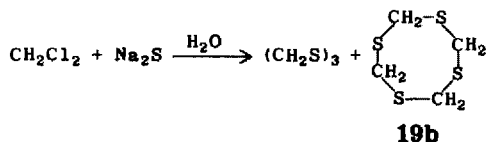
They believe that a *gem*-dithiol is first formed in every case, and that it is converted into an *s*-trithiane subsequently. Whether either is correct, or whether the initial product is a thioaldehyde or thioketone, which then undergoes an acid-catalyzed trimerization, just as formaldehyde trimerizes to *s*-trioxane, is not known.

Several other syntheses of *s*-trithiane have been reported. Heating lead formate with hydrogen sulfide at 200-300° gave what was probably impure *s*-trithiane in very low yields.^{4, 137, 160, 231} Girard^{105, 106} prepared impure *s*-trithiane by the reduction of carbon disulfide with zinc and hydrochloric acid. Hofmann¹³¹ showed that the same reagents reduce potassium thiocyanate, and ethyl or allyl isothiocyanate, to *s*-trithiane. Husemann¹³⁸ reacted methylene iodide with sodium sulfide and obtained an insoluble powder which was converted into *s*-trithiane by heating at 150°. Mansfeld¹⁶⁵ showed, however, that *s*-trithiane is the direct product of the reaction, according to the expected equation.

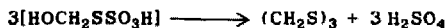


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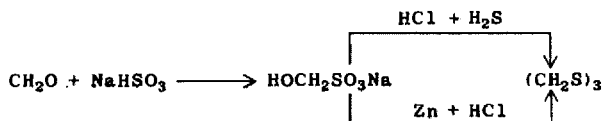
Recently, Schmidt and Blaettner^{201b} reported that the reaction of methylene chloride with aqueous sodium sulfide yields a mixture of *s*-trithiane and the tetramer of thioformaldehyde, 1, 3, 5, 7-tetrathiacyclooctane (**19b**), the latter in 6% yield.



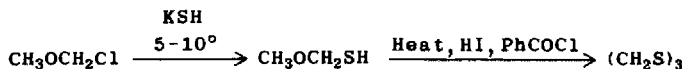
Vanino²²³⁻²²⁶ heated formaldehyde and sodium thiosulfate with concentrated hydrochloric acid and showed that the reaction takes place quantitatively according to the following equations:



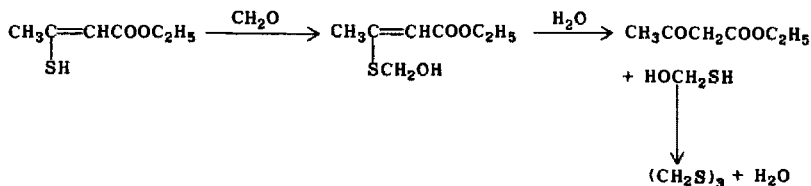
Concentrated hydrofluoric, hydrobromic, nitric, and sulfuric acids give the reaction, but phosphoric, hydriodic, trichloroacetic, and weak organic acids do not. Schmidt^{202,203} and Brintzinger and co-workers⁴² confirmed the synthesis, the former obtaining evidence for the existence of the intermediate (**20**) postulated by Vanino. Fromm and Gaup⁹⁴ used sodium formaldehydesulfoxylate, and showed that it could be converted into *s*-trithiane in two ways, by treatment with hydrochloric acid and hydrogen sulfide or by reduction with zinc and hydrochloric acid.



deLattre¹⁵³ prepared *s*-trithiane from chloromethyl ether by reacting it with potassium hydrosulfide.

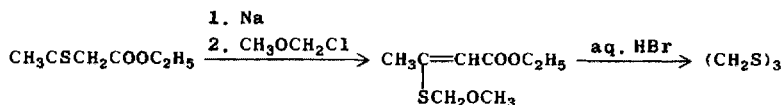


Mitra¹⁷⁵ prepared *s*-trithiane from thioacetoacetic ester and formaldehyde in the presence of hydrochloric acid. Although the thioketone may have been only a source of hydrogen sulfide, Mitra proposed the following course for the reaction:

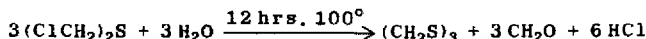


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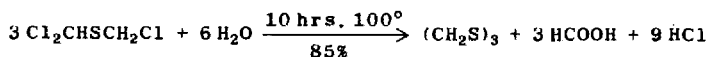
The plausibility of this mechanism was indicated by the following reactions:



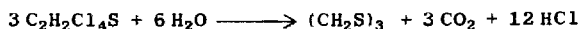
Bloch and Höhn³¹ and Richtzenhain and Alfredssohn¹⁹⁷ obtained *s*-trithiane by the hydrolysis of α, α' -dichlorodimethyl sulfide.



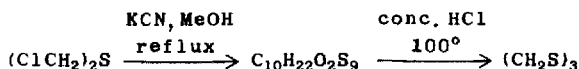
The latter authors also hydrolyzed α, α, α' -trichlorodimethyl sulfide.



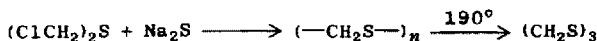
Feichtinger and Moos⁸³ hydrolyzed a tetrachlorodimethyl sulfide and isolated *s*-trithiane.



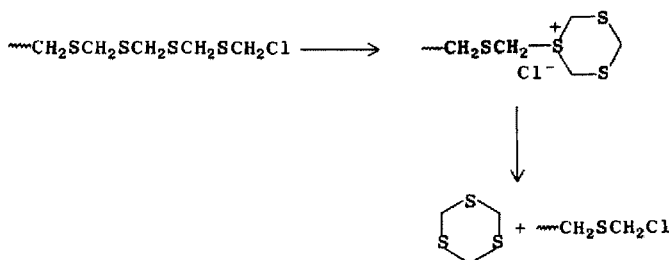
Davies and Hambly⁶³ treated α, α' -dichlorodimethyl sulfide with potassium cyanide. The resulting product, of unknown structure, yielded *s*-trithiane on treatment with concentrated hydrochloric acid.



Lal^{152a} prepared linear polythioformaldehyde from α, α' -dichlorodimethyl sulfide and sodium sulfide; pyrolysis of the polymer yielded *s*-trithiane.



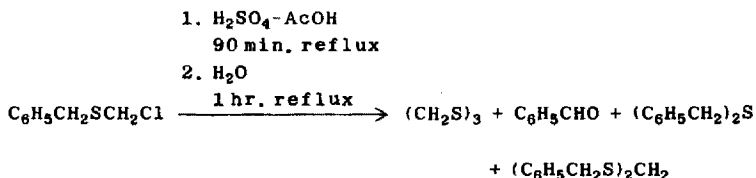
Lal postulated the presence of chloromethyl end groups in the polymer to account for the depolymerization, since a polymer prepared from hexamethylenetetramine and hydrogen sulfide did not give *s*-trithiane on pyrolysis. The mechanism is similar to that used to explain the formation of *p*-dithiane in many reactions (see Chapter 12, section III A-1a).



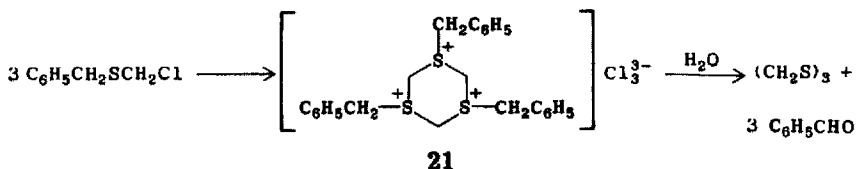
None of these reactions is of preparative value, since the chlorinated sulfides are generally prepared from *s*-trithiane.

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Horák and Gerovová¹³⁶ prepared *s*-trithiane from benzyl chloromethyl sulfide in an unusual reaction.



The reaction was postulated as taking place via an intermediate sulfonium ion (21).



Evidence for the mechanism was the fact that benzyl chloride with *s*-trithiane under the same conditions gave benzaldehyde. According to Reichert¹⁹⁰ treatment of benzylhexamethylenetetraminium chloride with aqueous hydrogen sulfide gives a colorless sirup, which yields *s*-trithiane on refluxing with concentrated hydrochloric acid.

The synthesis of 2, 4, 6-trimethyl-*s*-trithiane from acetaldehyde is not as simple as that of *s*-trithiane itself. As mentioned above, Weidenbusch,²²⁸ on reacting acetaldehyde with hydrogen sulfide and treating the resulting oil with acid, obtained a crystalline solid. Hofmann¹³⁴ showed by molecular weight determinations that this was trimeric CH_3CHS , but repetition of Weidenbusch's experiment by Pinner¹⁸³ did not lead to the isolation of a pure compound. Klinger^{144,146} carried out the reaction of acetaldehyde with hydrogen sulfide in the presence of dilute hydrochloric acid and isolated α -2, 4, 6-trimethyl-*s*-trithiane, m.p. 101°, from the reaction mixture. Treatment of this with acetyl or benzoyl chloride yielded a second isomer, β -2, 4, 6-trimethyl-*s*-trithiane, m.p. 125-126°. The same compound was formed on treating the oil obtained from acetaldehyde and hydrogen sulfide in the absence of acid with concentrated sulfuric acid. Both compounds boiled at 246-248°, and Klinger was the first to suggest that they were isomers of trithioacetaldehyde.

The preparation of the two isomers of 2, 4, 6-trimethyl-*s*-trithiane was investigated more thoroughly by Baumann and Fromm.^{12,16} They found that, as was the case with formaldehyde, the synthesis is best carried out by treating acetaldehyde with hydrogen sulfide in the presence of hydrogen chloride; yields are somewhat higher in ethanol than in water. Formation of the α -isomer is favored by low temperatures and low acid concentrations, while the β -isomer is favored at higher temperatures in the presence of large amounts of acid. Klinger's observation that strong mineral acids, as well as acetyl or benzoyl chlo-

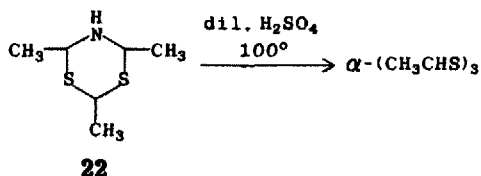
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ride, isomerize the α -isomer into the β -isomer was confirmed.

Suyver²²⁰ made a careful study of the preparation and isomerization of 2, 4, 6-trimethyl-*s*-trithiane. Saturation of a solution of acetaldehyde in 2 *N* hydrochloric acid with hydrogen sulfide at -15° and recrystallization of the resulting precipitate from acetone gave a 15% yield of the α -isomer. The β -isomer was prepared by passing hydrogen sulfide into a solution of acetaldehyde in saturated aqueous hydrochloric acid. The two isomers were isomerized by treatment under a variety of conditions with gaseous hydrogen chloride, concentrated hydrochloric acid, alcoholic hydrogen chloride, iodine, zinc chloride, dilute sulfuric acid, acetyl chloride, ethyl iodide, chlorosulfonic acid, and sulfur trioxide in chloroform. Isomerization was followed by determining the concentration of the two isomers from a melting point diagram, and Suyver reached the conclusion that the isomerization is an equilibrium reaction, the position of the equilibrium depending on the reagent and the conditions. The equilibrium mixture contained 0-11% of the α -isomer. Although in many cases the same mixture was obtained starting with the α - or the β -isomers, the possibility still exists that the melting points were lowered by impurities, and that the α -isomer is converted to the β -isomer irreversibly. Unfortunately, the problem has not been reinvestigated.

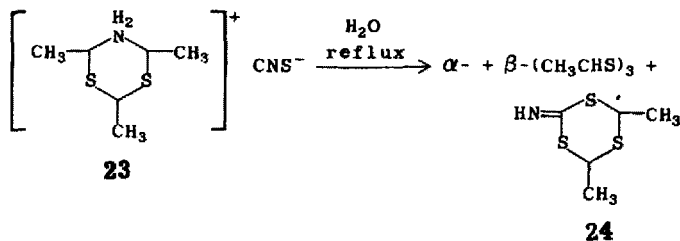
The synthesis of α -2, 4, 6-trimethyl-*s*-trithiane is complicated by the fact that, when the acid concentration is lowered, other compounds are formed. Thus, both 2, 4, 6-trimethyl-1, 3, 5-dioxathiane^{73, 102, 155, 177} (Chapter 8, section III) and 2, 4, 6-trimethyl-1, 3, 5-oxadithiane¹⁵⁵ (Chapter 9, section IV) have been isolated from reaction mixtures containing low concentrations of acid. Spiess and Waeser^{216b} claimed that treatment of equal parts of acetaldehyde, concentrated hydrochloric acid, and water with hydrogen sulfide yields α -2, 4, 6-trimethyl-*s*-trithiane, but unfortunately details of this work are not readily available.

Various other syntheses of 2, 4, 6-trimethyl-*s*-trithiane are known, but it is doubtful that they possess any advantage over the aldehyde-acid-hydrogen sulfide synthesis. Eriksson⁷⁵ prepared the α -isomer by heating thialdin (**22**) with dilute sulfuric acid.



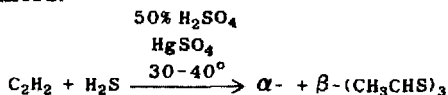
Marckwald¹⁶⁶ obtained a mixture of both isomers by heating a water solution of thialdin thiocyanate (**23**). Another product, m.p. 138° , was isolated, which he formulated as 6-imino-2, 4-dimethyl-*s*-trithiane (**24**).

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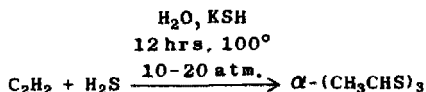


24 formed crystalline adducts, $\text{C}_5\text{H}_9\text{NS}_3 \cdot \text{AgNO}_3$ and $\text{C}_5\text{H}_9\text{NS}_3 \cdot \text{PtCl}_4$. Hot potassium hydroxide decomposed it to aldehyde resins, potassium sulfide, and potassium thiocyanate. It dissolved in concentrated sulfuric acid and precipitated unchanged on dilution, a surprising behavior for an imine. Its structure has not been confirmed.

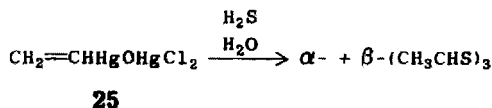
There are several reports on the use of acetylene instead of acetaldehyde as a starting material for the trithiane. Müller and Schiller¹⁷⁷ prepared acetaldehyde *in situ* and obtained a mixture of the α - and β -isomers.



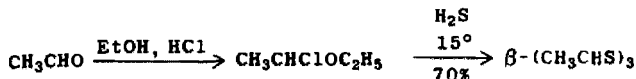
Reppe and Nicolai¹⁹¹⁻¹⁹³ used potassium hydrosulfide in the absence of mercuric salts and obtained only the α -isomer.



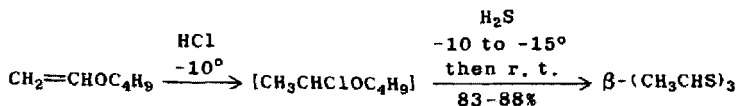
This, therefore, is a reaction of acetylene rather than of acetaldehyde. If the reaction were shown to go in reasonable yield, this might be a useful synthesis of the α -isomer. Poleck and Thümmel¹⁸⁴ obtained a mixture of isomers from "vinylmercuric oxychloride" (**25**).



deKok, Leendertse, and Waterman¹⁴⁹ prepared the β -isomer from ethyl α -chloroethyl ether.

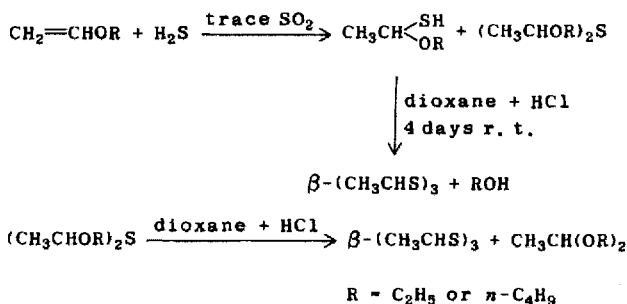


Shostakovskii and co-workers^{186,213} prepared the β -isomer from butyl vinyl ether, the corresponding chloroether being an intermediate in the reaction.

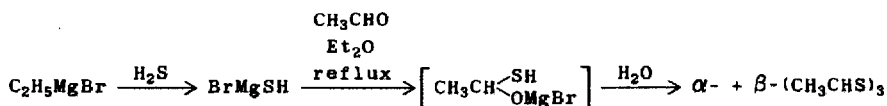


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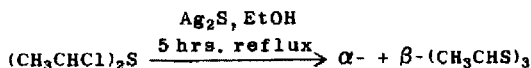
It is rather interesting that the order of addition can be reversed.²¹²



Mingoia¹⁷² obtained a mixture of isomers from acetaldehyde and magnesium bromide hydrosulfide.

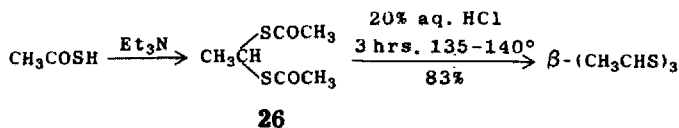


Mann and Pope¹⁶⁴ obtained a mixture of isomers by treating α, α' -dichlorodiethyl sulfide with a variety of reagents—hydrogen sulfide, silver sulfide, silver oxide, or sodium hydroxide.

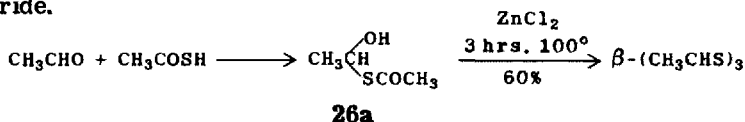


Bales and Nickelson⁹ isolated the β -isomer by treating the same compound with ethylene chlorohydrin, but apparently only in small yield. α, α' -Diethoxydiethyl sulfide gave a mixture of isomers on long standing.²⁸

Behringer and Grunwald²⁶ prepared β -2, 4, 6-trimethyl-s-trithiane by acid hydrolysis of ethylidene bis(thioacetate) (**26**); the starting material was prepared by treatment of thioacetic acid with a base. Presumably hydrolysis yields the thioaldehyde, which then trimerizes.



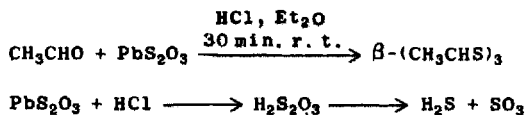
Böhme, Roehr, and Schlephack^{32a} prepared the β -isomer by heating the hemithioacetate, α -hydroxyethyl acetyl sulfide (**26a**), with zinc chloride.



Schmidt^{201a} prepared the β -isomer from lead thiosulfate and acetaldehyde in the presence of anhydrous hydrogen chloride; the thiosulfate was shown to be a source of hydrogen sulfide.

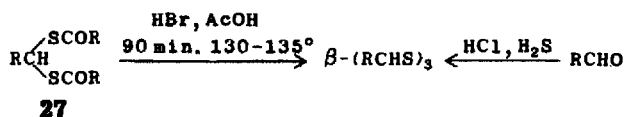
[For references, see pp. 765-773.]

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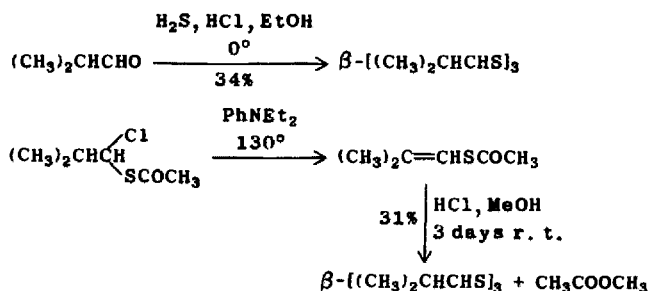


Surprisingly few trithianes have been prepared from aliphatic aldehydes other than formaldehyde and acetaldehyde. Douglass and Martin⁷⁰ prepared 2, 4, 6-triethyl-*s*-trithiane in low yield by the usual aldehyde-acid-hydrogen sulfide procedure and separated it into its two isomers. Douglass and Hydro⁷² made a simple but important modification of the synthesis of *s*-trithianes and applied it to phenylacetaldehyde. The usual procedure of saturating an alcoholic solution of the aldehyde with hydrogen chloride followed by the addition of hydrogen sulfide gave a very poor yield, presumably because of self-condensation of the aldehyde. By simultaneously adding the aldehyde and hydrogen sulfide to alcoholic hydrogen chloride they were able to raise the yield to 73%. This procedure should be applicable to any trithiane where the possibility of self-condensation exists. Quite surprisingly the mixture contained 78-86% of the α -isomer, one of the few examples in which an aliphatic aldehyde gave the α -isomer as the major product in high yield.

Behringer and Grunwald²⁶ prepared β -2, 4, 6-triethyl-*s*-trithiane, and presumably the β -isomer of 2, 4, 6-tri-*n*-propyl-*s*-trithiane, by acid hydrolysis of the corresponding alkylidene bis(thioacylates) (27); the structures were proved by comparison with compounds prepared according to Douglass and Martin.⁷⁰



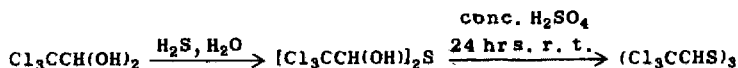
Böhme, Roehr, and Schlephack^{32a} prepared 2, 4, 6-triisopropyl-*s*-trithiane by two procedures, the normal condensation of aldehyde with hydrogen sulfide, and the acid-catalyzed alcoholysis of isobutenyl acetyl sulfide. The unsaturated sulfide was prepared by dehydrohalogenation of α -chloroisobutyl acetyl sulfide. Although this method is probably a general one, it is undoubtedly more convenient to use the corresponding α -hydroxy compound (*vide infra*).



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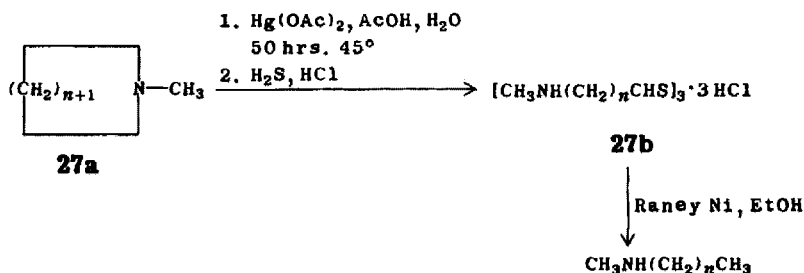
Considering the high melting point of the *s*-trithiane derivative, 175°, there can be little doubt that it is the β -isomer.

Chattaway and Kellett⁵⁸ prepared tris(trichloromethyl)-*s*-trithiane from chloral hydrate in very low yield.

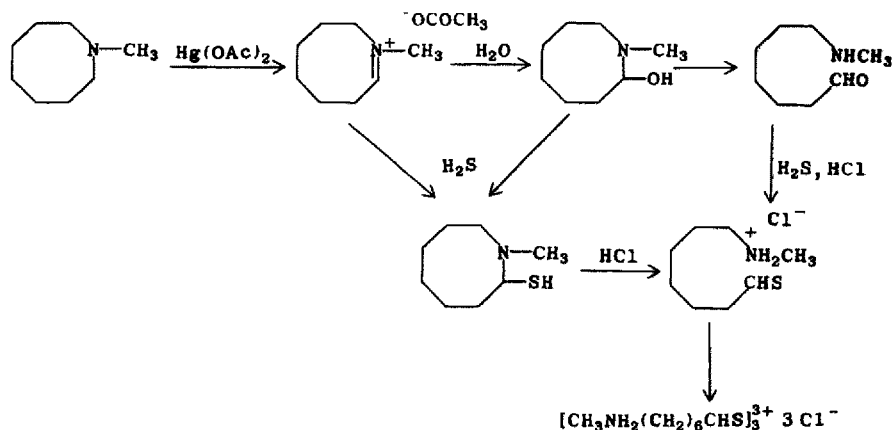


Only one isomer was found; the corresponding 1, 3, 5-oxadithiane was also formed (Chapter 9, section IV).

Leonard and Musker^{157b} prepared several 2, 4, 6-tris(methylaminoalkyl)-*s*-trithiane trihydrochlorides (**27b**, $n = 5-7$) by oxidizing cyclic *N*-methylamino compounds (**27a**, $n = 5-7$) with mercuric acetate and treating the reaction mixtures with hydrogen sulfide and hydrogen chloride. Only one isomer was isolated in each reaction. The structures were proved by Raney nickel desulfurization to the known amines. *N*-Methylpiperidine (**27a**, $n = 4$) did not undergo ring opening.



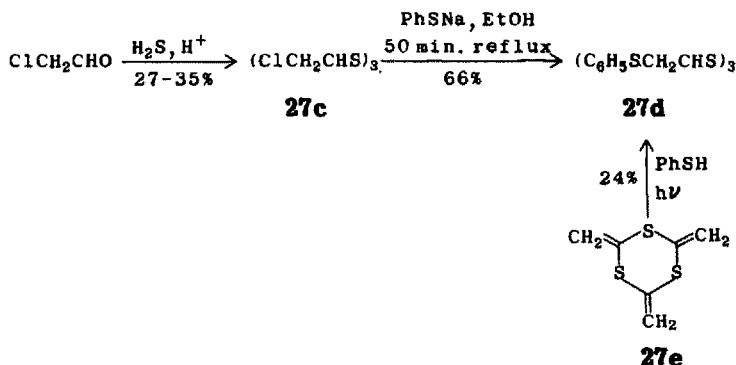
The authors postulated that the reaction follows one of the following paths:



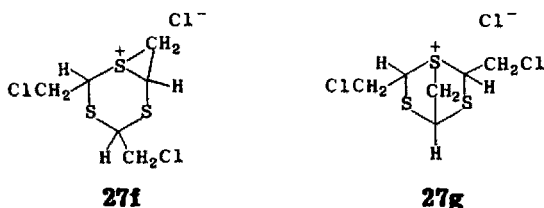
Matlack, Chien, and Breslow^{168a} prepared 2, 4, 6-tris(chloromethyl)-*s*-trithiane (**27c**) from chloroacetaldehyde, hydrogen sulfide, and an acid.

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Using hydrogen chloride as the catalyst gave a mixture of the two isomers, 84% β - and 16% α -. With 75% aqueous sulfuric acid, however, the ratio of α -isomer to β -isomer was 2:1. It is not readily apparent why the change in reaction conditions led to a change in the isomer distribution, but the β -isomer predominated when hydrogen chloride was used as the catalyst under all the conditions investigated. It is rather interesting that the usual acidic reagents would not isomerize **27c**. Treatment of **27c** with sodium thiophenoxide yielded 2, 4, 6-tris(phenylthiomethyl)-*s*-trithiane (**27d**) without rearrangement, α -**27c** yielding α -**27d** and β -**27c** yielding β -**27d**. β -**27d** was also obtained, although in poor yield, by the addition of thiophenol to 2, 4, 6-tris(methylene)-*s*-trithiane (**27e**) (see section II A-3f).

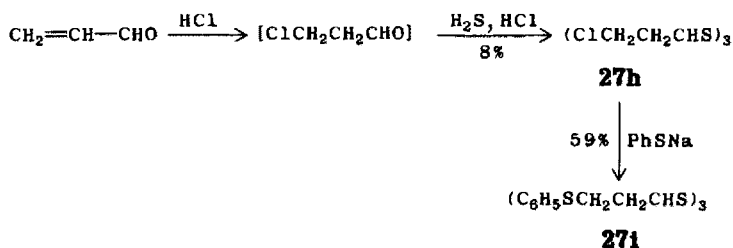


Inasmuch as both *cis*- and *trans*-**27c** reacted without rearrangement, there can be little doubt that the reaction involves a nucleophilic displacement and not an elimination reaction followed by addition. Although these reactions appear to be normal nucleophilic displacements, a comparison of the reactivity of **27c** with its oxygen analog, 2, 4, 6-tris(chloromethyl)-*s*-trioxane, casts some doubt on this conclusion. One would expect comparable rates for the trithiane and trioxane compounds in a straight nucleophilic displacement. However, both *cis*- and *trans*-**27c** reacted completely with sodium thiophenoxide in less than an hour in refluxing ethanol, as evidenced by sodium chloride formation, whereas the trioxane derivative precipitated only 13% of the calculated quantity of sodium chloride in 2 hours under the same conditions, and even after 5 days the reaction was incomplete. In an attempt to determine if there were any $\text{S}_\text{N}1$ character to the reaction of the trithiane with thiophenoxide, presumably involving sulfonium intermediates such as **27f** or **27g**, the reaction of *cis*-**27c** with ethanol was investigated. Although



chloride ion was liberated in refluxing ethanol, the reaction was considerably slower than in the presence of thiophenoxide, and the infrared spectrum of the residue indicated considerable decomposition of the molecule. It appears, therefore, that a detailed kinetic investigation would be required to determine the course of this substitution reaction.

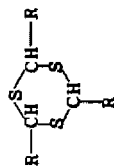
Matlack, Chien, and Breslow^{168a} also prepared 2, 4, 6-tris(2-chloroethyl)-s-trithiane (**27h**) in low yield from acrolein, hydrogen chloride, and hydrogen sulfide. Only one isomer, shown to be the β -isomer by proton magnetic resonance, was isolated. Reaction with sodium thiophenoxide yielded 2, 4, 6-tris(2-phenylthioethyl)-s-trithiane (**27i**).



The s-trithianes prepared from aliphatic aldehydes are listed in Table 1.

The history of the preparation of triaryl-s-trithianes closely parallels that of the trialkyl compounds. There were several early reports on ill-defined reaction products of benzaldehyde with ammonium sulfide or hydrogen sulfide,^{15,4} benzal chloride with potassium hydrosulfide,^{44,85} and the like. Klinger¹⁴⁴ reacted an alcoholic solution of benzaldehyde with hydrogen sulfide; the resulting amorphous solid, m.p. 83-85°, on treatment with a small amount of acetyl or benzoyl chloride, yielded a crystalline solid, m.p. 225-226°, the β -isomer of 2, 4, 6-triphenyl-s-trithiane. The same product was obtained by treating the amorphous solid with iodine or ethyl iodide¹⁴⁵ or with alcoholic hydrogen chloride.^{35,147} Baumann and Fromm¹² introduced the method which is now used generally to prepare s-trithianes, passage of hydrogen sulfide into an alcoholic solution of benzaldehyde containing hydrogen chloride or zinc chloride. By this procedure they were able to isolate the α -isomer, m.p. 166-167°, from a mixture of the two. Molecular weight determinations showed that only these two compounds were trithiobenzaldehydes.¹⁷ The β -isomer is the more stable of the two, since the α -isomer is isomerized to the β -isomer by the reagents mentioned above as well as by a variety of acidic materials. Suyver²²⁰ found no evidence for an equilibrium between the two forms as he did in the case of tri-thioacetaldehyde.

A large variety of triaryl-s-trithianes have been prepared. These are listed in Table 2. Baumann and Fromm¹⁸ showed that here, just as in the case of acetaldehyde, low temperatures and low acid concentrations favor the formation of the α -isomer. In more recent work Stanfield and Reynolds²¹⁷ claimed that ethyl acetate is the preferred solvent for pre-

TABLE 1. Trialkyl-*s*-trithianes

Isomer	Substituents, R=	Yield (%)	M.p. (°C)	Other properties	Ref.
α	H	92-94	214-215		38
		100	216		13, 73, 94, 133, 190
			216-217		31
			218		132, 165, 175, 224
			219		221b
	CH ₃ -	70	219-220		51a
			220		197
			100		59
			100.4		220
			100.5-101		51a
			101	b. p. 245-246°	91, 146
		15	101		102
			101		193
			101	d_4^{20} 1.178	5, 12
			102	b. p. 249°	75

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β	CH_3-	125			9
		125		b. p. 245-246°	91
		125			32a
	60	125-126			213
	83-88	125-126			12, 220
		125-126		b. p. 245-248°	144
		126		d_{4}^{20} 1. 150	5, 59, 102
		126-127			51a
	83				26
$\alpha + \beta$	CH_3-	65			214
α	C_2H_5-		36	b. p. 143° at 10 mm.	70
				n_D^{25} 1. 5472	
	30 (crude)			b. p. 155° at 15 mm.	26
			76	b. p. 143° at 10 mm.	70
				n_D^{25} 1. 5472	
β	C_2H_5-	42	77. 5		26
		28. 5	4. 5	b. p. 145° at 0. 01 mm.	26
β	$n-C_3H_7-$	34	175	n_D^{20} 1. 5370	32a
	$i-C_3H_7-$				

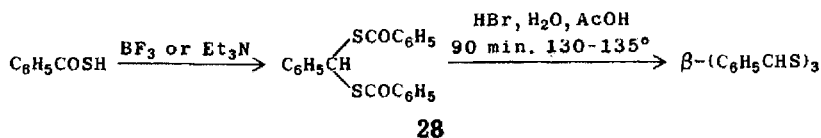
TABLE 1. Trialkyl-*s*-trithianes (contd)

Isomer	Substituents, R=	Yield (%)	M.p. (°C)	Other properties	Ref.
α	$\text{C}_6\text{H}_5\text{CH}_2^-$	73	122-123		72
β	$\text{C}_6\text{H}_5\text{CH}_2^-$		168-169		72
	$[\text{CH}_3\text{NH}_2(\text{CH}_2)_5^-]^+\text{Cl}^-$	23	223-225 (dec.)		157b
	$[\text{CH}_3\text{NH}_2(\text{CH}_2)_6^-]^+\text{Cl}^-$	40	236-239 (dec.)		157b
	$[\text{CH}_3\text{NH}_2(\text{CH}_2)_7^-]^+\text{Cl}^-$	37	234.5-236 (dec.)		157b
α	ClCH_2^-	35	100-100.5		168a
β	ClCH_2^-		160.5-161		168a
α	$\text{C}_6\text{H}_5\text{SCH}_2^-$		oil		168a
β	$\text{C}_6\text{H}_5\text{SCH}_2^-$	66	82-82.5		168a
β	$\text{ClCH}_2\text{CH}_2^-$	8	130-131.5		168a
β	$\text{C}_6\text{H}_5\text{SCH}_2\text{CH}_2^-$	59	82.5-83		168a
	Cl_3C^-		181		58

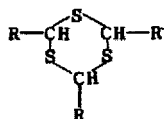
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paring the α -isomers. Although the two isomers are frequently obtained in close to quantitative yields, Suyver²²⁰ claimed that the β -isomer is prepared best by treating Klinger's amorphous solid¹⁴⁴ with a trace of iodine in benzene. Kopp¹⁵⁰ noted that in certain cases only one isomer could be isolated. This was confirmed and investigated more thoroughly by Wörner²³² and, more recently, by Campaigne and Budde.⁴⁹ A free or esterified phenolic hydroxyl prevents the formation of more than one of the two possible isomeric *s*-trithianes. *p*-Dialkylamino and *p*-acylamino substituents also yield only one isomer. Strongly electron-attracting substituents, such as nitro, cyano, carboxy, and carboethoxy groups, give only linear polymers, unless an electron-attracting group is also present, in which case one *s*-trithiane can be isolated. Two isomers are generally isolated from substituted benzaldehydes containing alkyl groups, alkoxy groups, or halogens. When only one isomer is formed, it is the β -isomer, as shown by its lack of isomerization with the usual isomerizing agents, as well as by direct interconversion in certain cases. Thus, benzylation of 2, 4, 6-tris(*p*-hydroxyphenyl)-*s*-trithiane gives a compound identical with the β -isomer formed directly from *p*-benzyloxybenzaldehyde. Furfural,²¹ 2-thenaldehyde²¹⁸ and 3-thenaldehyde⁴⁹ have been converted into the corresponding *s*-trithianes and both isomers have been isolated. The reasons for these unusual effects are discussed in section II A-2.

Other syntheses of triaryl-*s*-trithianes are relatively unimportant. Barbaglia and Marquardt¹⁰ isolated a small quantity of α -2, 4, 6-triphenyl-*s*-trithiane by heating benzaldehyde with sulfur at 180°; the major products were stilbene and benzoic acid. Cairns, Evans, Larcher, and McKusick⁴⁵ isolated a mixture of α - and β -2, 4, 6-triphenyl-*s*-trithiane in very low yield by heating benzaldehyde under pressure with hydrogen sulfide at 50°. Mitra¹⁷⁴ reacted thioacetoacetic ester with benzaldehyde in the presence of water and a trace of piperidine and isolated a polymer of thiobenzaldehyde. Treatment of this with acetyl or benzoyl chloride at 5° in the presence of a trace of piperidine gave a quantitative yield of the β -isomer of the *s*-trithiane. The reaction could be carried out in one step by treating a mixture of thioacetoacetic ester and benzaldehyde in alcohol with hydrogen chloride.¹⁷⁴ The latter reaction was applied to several substituted thioacetoacetic esters and substituted benzaldehydes.¹⁷⁵ The postulated course of the reaction has already been discussed. Böttcher and Bauer³³ reacted benzaldehyde and anisaldehyde with phosphorus pentasulfide in refluxing carbon disulfide; the β -isomer was formed in each case. Behringer and Grunwald²⁶ prepared β -2, 4, 6-triphenyl-*s*-trithiane from benzylidene bis(thiobenzoate) (**28**) by acid hydrolysis.



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TABLE 2. Triaryl-*s*-trithianes

Isomer	Substituents, R=	Yield (%)	M. p. (°C)	Ref.
α	C_6H_5-	3	164-166	45
		17-22	166-167	12, 51a, 95, 220
β	C_6H_5-	20	224	33
			224	35
		56	224	26
		50	225	12
		71	225	32a
			225-226	93, 145, 220
		87-96	225-226	144
			226	95, 174, 175
		4	227-228	45
		43	229-230	51a
α	$m\text{-CH}_3\text{C}_6\text{H}_4-$		144	232
β	$m\text{-CH}_3\text{C}_6\text{H}_4-$		225	232
α	$p\text{-CH}_3\text{C}_6\text{H}_4-$	50	149-150	232
β	$p\text{-CH}_3\text{C}_6\text{H}_4-$	50	180	232
β	$2, 4\text{-(CH}_3)_2\text{C}_6\text{H}_3-$		110	87, 111
β	$3, 4\text{-(CH}_3)_2\text{C}_6\text{H}_3-$		147	101
	$2, 4, 6\text{-(CH}_3)_3\text{C}_6\text{H}_2-$	33	186-187	100
α	$p\text{-(CH}_3)_2\text{CHC}_6\text{H}_4-$		165	232
β	$p\text{-(CH}_3)_2\text{CHC}_6\text{H}_4-$		205	232
α	$o\text{-ClC}_6\text{H}_4-$	98.7	162.7-163.5	217
β	$o\text{-ClC}_6\text{H}_4-$		223.9-224.6	217
α	$m\text{-ClC}_6\text{H}_4-$	91.2	115.8-116.4	217
β	$m\text{-ClC}_6\text{H}_4-$		163.0-163.2	217

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TABLE 2. Triaryl-s-trithianes (contd)

Isomer	Substituents, R=	Yield (%)	M.p. (°C)	Ref.
α	<i>p</i> -ClC ₆ H ₄ -	94.3	137.4-138.2	217
β	<i>p</i> -ClC ₆ H ₄ -		189.6-190.4	217
α	<i>p</i> -ClC ₆ H ₄ -		162	117
β	<i>p</i> -ClC ₆ H ₄ -		195.5	117
α	<i>o</i> -BrC ₆ H ₄ -	91.6	186.0-186.7	217, 232
β	<i>o</i> -BrC ₆ H ₄ -		220.6-221.0	217, 232
α	<i>m</i> -BrC ₆ H ₄ -	87.6	141.6-142.3	217
β	<i>m</i> -BrC ₆ H ₄ -		177.3-177.9	217
α	<i>p</i> -BrC ₆ H ₄ -	88.7	182.2-183.0	217
β	<i>p</i> -BrC ₆ H ₄ -		205.3-205.9	217
α	<i>p</i> -BrC ₆ H ₄ -		174	117
β	<i>p</i> -BrC ₆ H ₄ -		204	117
α	<i>o</i> -IC ₆ H ₄ -	91.4	188.7-189.6	217
β	<i>o</i> -IC ₆ H ₄ -		202.0-202.6	217
α	<i>m</i> -IC ₆ H ₄ -	84.6	196.2-197.4	217
β	<i>m</i> -IC ₆ H ₄ -		212.6-213.1	217
α	<i>p</i> -IC ₆ H ₄ -	78.7	113.6-114.8	217
β	<i>p</i> -IC ₆ H ₄ -		211.3-212.1	217
β	<i>o</i> -HOC ₆ H ₄ -	100	210.	150
α	<i>o</i> -CH ₃ OC ₆ H ₄ -		157	18
β	<i>o</i> -CH ₃ OC ₆ H ₄ -		224	18
α	<i>o</i> -(CH ₃) ₂ CHCH ₂ OC ₆ H ₄ -		142	18
β	<i>o</i> -(CH ₃) ₂ CHCH ₂ OC ₆ H ₄ -		162-163	18
β	<i>o</i> -C ₆ H ₅ CO ₂ C ₆ H ₄ -		218	150
β	<i>m</i> -HOC ₆ H ₄ -	100	212	150
β	<i>m</i> -CH ₃ OC ₆ H ₄ -	100	147	150
β	<i>m</i> -C ₆ H ₅ CO ₂ C ₆ H ₄ -		146	150
β	<i>p</i> -HOC ₆ H ₄ -	100	215	150, 232
α	<i>p</i> -CH ₃ OC ₆ H ₄ -		127	18

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TABLE 2. Triaryl-s-trithianes (contd)

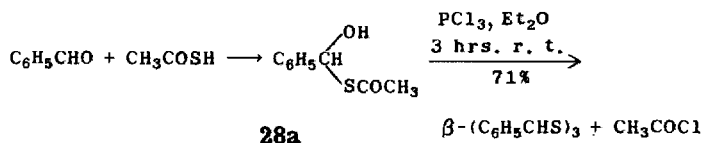
Isomer	Substituents, R=	Yield (%)	M.p. (°C)	Ref.
β	$p\text{-CH}_3\text{OC}_6\text{H}_4\text{-}$		183	18
		63	180	33
			186	175
α	$p\text{-C}_6\text{H}_5\text{CH}_2\text{OC}_6\text{H}_4\text{-}$	100	127	232
β	$p\text{-C}_6\text{H}_5\text{CH}_2\text{OC}_6\text{H}_4\text{-}$		198-199	232
β	$p\text{-CH}_3\text{CO}_2\text{C}_6\text{H}_4\text{-}$	25	186-187	49
β	$p\text{-C}_6\text{H}_5\text{CO}_2\text{C}_6\text{H}_4\text{-}$		225	150, 232
β	$p\text{-CH}_3\text{CONHC}_6\text{H}_4\text{-}$	70	174-176	49
β	$p\text{-(CH}_3)_2\text{NC}_6\text{H}_4\text{-}$	81	224-225	49
β	$p\text{-(C}_2\text{H}_5)_2\text{NC}_6\text{H}_4\text{-}$	82	196-198	49
β	2, 5-(HO) $_2\text{C}_6\text{H}_3\text{-}$		190	232
α	2, 5-(CH $_3\text{O}$) $_2\text{C}_6\text{H}_3\text{-}$		95-96	232
β	2, 5-(CH $_3\text{O}$) $_2\text{C}_6\text{H}_3\text{-}$		180	232
β	2-CH $_3\text{O}$ -4-HOC $_6\text{H}_3\text{-}$		220 (dec.)	175
β	3-CH $_3\text{O}$ -4-HOC $_6\text{H}_3\text{-}$	100	235-237	232
α	3, 4-(CH $_3\text{O}$) $_2\text{C}_6\text{H}_3\text{-}$		168	232
β	3, 4-(CH $_3\text{O}$) $_2\text{C}_6\text{H}_3\text{-}$		220	232
			223	235
β	3-CH $_3\text{O}$ -4-C $_6\text{H}_5\text{CO}_2\text{C}_6\text{H}_3\text{-}$		164	232
α	3, 4-Methylenedioxyphenyl-		183	232
β	3, 4-Methylenedioxyphenyl-		236	232
	3-O $_2\text{N}$ -4-(CH $_3$) $_2\text{CHC}_6\text{H}_3\text{-}$		118	232
β	3-O $_2\text{N}$ -4-CH $_3\text{OC}_6\text{H}_3\text{-}$		108	232
β	2-CH $_3$ -4-HO-5-(CH $_3$) $_2\text{CHC}_6\text{H}_2\text{-}$	76	245-246	49
β	3, 5-(O $_2\text{N}$) $_2$ -4-CH $_3\text{OC}_6\text{H}_2\text{-}$		188	232
α	C $_6\text{H}_5\text{CH=CH-}$		167	18
β	C $_6\text{H}_5\text{CH=CH-}$		213	18
	2-C $_2\text{H}_5\text{O}$ -1-naphthyl-	100	283	234
	9-Phenanthryl-	80	248	29

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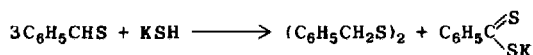
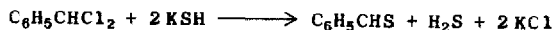
TABLE 2. Triaryl-*s*-trithianes (contd)

Isomer	Substituents, R=	Yield (%)	M.p. (°C)	Ref.
α	2-Furyl-	10	128	21
β	2-Furyl-		229	21
α	2-Thienyl-	100	179	218
β	2-Thienyl-		221	218
α	3-Thienyl-	30	179-180	49
β	3-Thienyl-	25	217-218	49

Böhme, Roehr, and Schlepack^{32a} prepared β -2, 4, 6-triphenyl-*s*-trithiane by treatment of α -hydroxybenzyl acetyl sulfide (**28a**) with phosphorus trichloride. The reaction is useful generally, because the hydroxythioacetate is prepared by simply mixing the aldehyde with thioacetic acid.



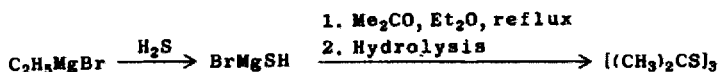
The reaction of benzal chloride with sulfides illustrates the confusion that frequently occurred in the field of sulfur derivatives of carbonyl compounds. In 1866 Fleischer⁸⁵ claimed that benzal chloride and potassium hydrosulfide gave a "thiobenzaldehyde". Klinger¹⁴⁷ investigated the reaction in 1882 and claimed that Fleischer's product was dibenzyl disulfide, formed by a Cannizzaro reaction on thiobenzaldehyde.



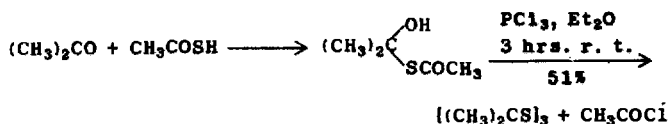
Potassium sulfide was reported to give the same reaction. In 1907 Fromm and Schmoldt⁹³ investigated the reaction of benzal chloride in alcohol with sodium sulfide and isolated a thiobenzaldehyde polymer plus β -2, 4, 6-triphenyl-*s*-trithiane. A more thorough investigation of this reaction by Wood and Bost²³³ in 1937 showed that practically all of the postulated products, as well as some others, were formed: β -2, 4, 6-triphenyl-*s*-trithiane; benzyl dithiobenzoate, benzyl mercaptan, and dithiobenzoic acid as a result of a Cannizzaro reaction; and benz-

aldehyde dibenzylmercaptan presumably by the reaction of benzyl mercaptan with thiobenzaldehyde.

Fromm and Baumann⁹¹ reported the first preparation of a trithiane from a ketone. Addition of hydrogen sulfide to a cold solution of acetone in concentrated hydrochloric acid gave an oil, which crystallized after being steam-distilled, m.p. 24°. 2, 2, 4, 4, 6, 6-Hexamethyl-*s*-trithiane was obtained as long, colorless needles in 39-55% yield. Only one isomer was found. A 66% yield has been reported using anhydrous zinc chloride.³² Mingoia¹⁷³ prepared the same compound from acetone and magnesium bromide hydrosulfide.

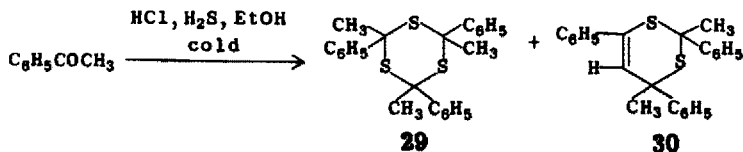


Böhme, Roehr, and Schlephack^{32a} prepared the *s*-trithiane from acetone and thioacetic acid by the procedure described above.

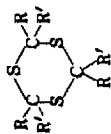


The only other aliphatic ketone which has been converted into a trithiane is 2-butanone. Leteur¹⁵⁸ prepared 2, 4, 6-trimethyl-2, 4, 6-triethyl-*s*-trithiane by passing hydrogen chloride and hydrogen sulfide into 2-butanone at -30°. The compound is a liquid. The preparation was repeated by Brintzinger and Ziegler.⁴⁰

Baumann and Fromm²³ were also the first to prepare 2, 4, 6-triphenyl-2, 4, 6-trimethyl-*s*-trithiane (**29**) by passing hydrogen chloride and hydrogen sulfide into a cold alcoholic solution of acetophenone. Only one isomer could be found, m.p. 122°. As a by-product there was obtained a compound formulated as 2, 4-dimethyl-2, 4, 6-triphenyl-*m*-dithiin (**30**) (see Chapter 12, section II A-3).



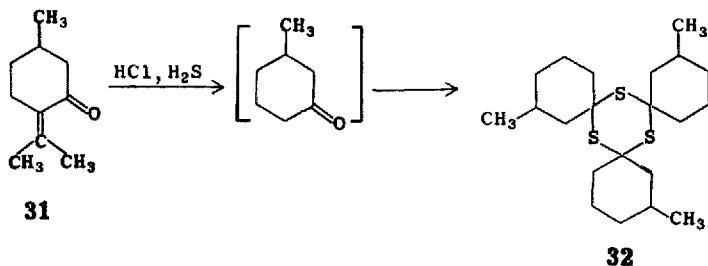
According to Campaigne, Reid, and Pera⁵¹ the yield of *m*-dithiin increases with increasing temperature with a variety of substituted acetophenones, the ratio of *s*-trithiane to *m*-dithiin depending on the nature of the *p*-substituent on the aromatic ring. Douglass and Hydro⁷² obtained an 80% yield of the *s*-trithiane (**29**) by adding acetophenone to a cold alcoholic hydrogen chloride solution containing hydrogen sulfide; this minimized self-condensation of acetophenone. Böttcher and Bauer³³ prepared **29** from acetophenone and phosphorous pentasulfide in refluxing carbon disulfide. The compounds reported are listed in Table 3.

TABLE 3. *s*-Trithianes Derived from Aliphatic and Aromatic Ketones

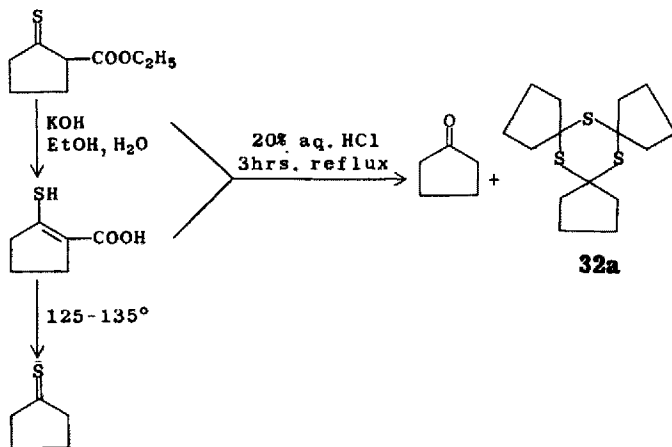
R	R'	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
CH ₃ -	CH ₃ -	39-55	24	130	13		91
		36		105-107	10	n_D^{24} 1.5400	70
			24				16, 173
		51	24	111-112	11		32a
		66	24	116-117	15		32
			22			n_{He}^{20} 1.542, d_4^{20} 1.068	5
		40					149
CH ₃ -	C ₂ H ₅ -			238	175	d_4^{20} 1.03	40, 158
C ₆ H ₅ -	CH ₃ -	37	121-122.1				61
		80	121-122				33, 72
			122				23
<i>p</i> -CH ₃ C ₆ H ₄ -	CH ₃ -	37	122-122.5				51
<i>p</i> -FC ₆ H ₄ -	CH ₃ -	44	151-152				51
<i>p</i> -ClC ₆ H ₄ -	CH ₃ -	56	165-166				51
<i>p</i> -BrC ₆ H ₄ -	CH ₃ -	54	193-193.5				51
<i>p</i> -IC ₆ H ₄ -	CH ₃ -	47	186.5-188				51

Chapter 10

A number of spiro-*s*-trithianes have been prepared from cyclic ketones, as shown in Table 4. Fromm⁹⁸ prepared the *s*-trithianes from cyclopentanone, cyclohexanone, and 4-methylcyclohexanone by the usual hydrogen chloride–hydrogen sulfide procedure. Pulegone (**31**) yielded the trithiane (**32**) derived from 3-methylcyclohexanone, not surprising in view of the fact that Wallach²²⁷ and Klages¹⁴³ have shown that acid cleaves pulegone to 3-methylcyclohexanone and acetone.



Sen²¹¹ showed that the monomeric thioketones of cyclopentanone and cyclohexanone could be isolated if they were removed from the reaction medium as soon as formed. Cyclopentanethione trimerized more readily than did cyclohexanethione. Mayer and Barthel^{169a} isolated a mixture of cyclopentanone and trithiocyclopentanone (**32a**) from the acid hydrolysis of 2-thiocyclopentanecarboxylic acid or its ethyl ester. Monomeric cyclopentanethione was obtained by pyrolysis of the acid.



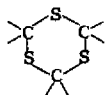
Campaigne and Moss⁵⁰ investigated the reactions of substituted 1-indanones and tetralones. The indanones gave higher yields of *s*-trithianes. Any 2-substituent prevented trithiane formation with both ring systems. A 3-methyl group in either system did not prevent trimerization. However, 3-phenyl-1-indanone and 4-methyl-1-tetralone gave monomeric thiones which would not trimerize. If this is an example of the effect of steric hindrance, it is a most unusual one.

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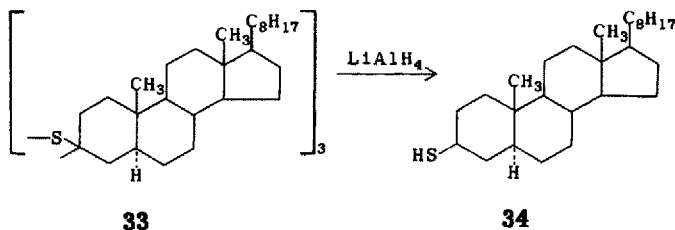
Reid and Klug^{197a} found that thiofluorene is trimerized by sodium phenylacetylde in liquid ammonia. This apparently base-catalyzed trimerization is rather unusual.

s-Trithianes prepared from keto-steroids are listed in Table 4. Their melting points indicate that they were generally either impure or a mixture of isomers. Bourdon³⁹ proved the structure of the trimer of 3-thiocholestanone (**33**) by lithium aluminum hydride reduction to 3 β -mercaptocholestanone (**34**).

TABLE 4. *s*-Trithianes from Cyclic Ketones



Ketone	Yield (%)	M.p. (°C)	Ref.
Cyclopentanone		99	98, 211, 169a
Cyclohexanone		101-102	98, 211
3-Methylcyclohexanone		182-183	98
4-Methylcyclohexanone		94. 5-95. 5	98
1-Indanone	46 (crude)	236-237 (dec.)	50
3-Methyl-1-indanone	70 (crude)	209. 5-210 (dec.)	50
1-Tetralone	7. 7	210-211. 5 (dec.)	50
3-Methyl-1-tetralone	16	226-227. 5 (dec.)	50
Fluorene	15	268-270 (dec.)	197a
4-Cholesten-3-one	65	116-120	140
Testosterone propionate		104-108	140
Coprostanone		146-152	140
Cholestanone	70	145 (dec.)	39

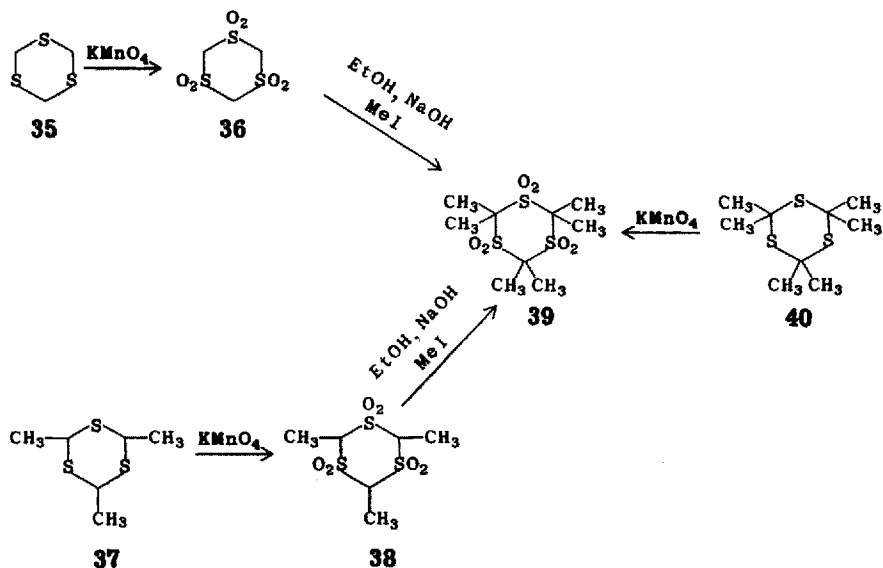


The methylene derivatives of *s*-trithiane constitute a different class of *s*-trithianes. Since they are prepared from other *s*-trithianes rather

than by ring closure, their chemistry is discussed under *s*-trithiane reactions (see section II A-3f).

2. Structure

The demonstration by Hofmann¹³⁴ that thioformaldehyde and thioacetaldehyde are trimeric, coupled with the fact that the compounds showed no mercaptan reactions, led Klinger¹⁴⁵ to postulate an *s*-trithiane structure for these compounds. Since α -trithioacetaldehyde could be converted into another compound having the same formula and the same boiling point, he reached the conclusion that the two are isomers of each other.¹⁴⁶ This was confirmed by Baumann and Fromm,^{12,22} who showed that both isomers are oxidized to the same trisulfone (**38**). The same authors^{11,12,14} proved that the trimers from formaldehyde (**35**), acetaldehyde (**37**), and acetone (**40**) have the same basic structure by showing that trithioformaldehyde trisulfone (**36**) and trithioacetaldehyde trisulfone (**38**), on alkylation with methyl iodide, yield the same trisulfone (**39**) as obtained by oxidation of trithioacetone (**40**).



Baumann and Fromm stated that the isomeric *s*-trithianes are stereoisomers⁹¹ and predicted correctly that trithioformaldehyde and trithioacetone should exist in only one form, while there should be two isomeric trithio derivatives of acetaldehyde and benzaldehyde.¹⁶ They were, however, faced with an embarrassment of riches; altogether too many isomers had been reported. The situation with regard to *s*-trithiane itself was satisfactory;¹³ only one isomer had been found from several different syntheses (see section II A-1). A number of thioaldehydes had been reported, however, from the reaction of acetaldehyde with hydrogen sulfide. Thus, Weidenbusch,²²⁸ and later Pinner,¹⁸³ ob-

tained an oil by reacting aqueous acetaldehyde with hydrogen sulfide. Klinger¹⁴⁴ indicated that the oil was a polymer of thioacetaldehyde, and Baumann^{13, 15, 19} did a considerable amount of work to show that *s*-trithianes are not formed from aldehydes and hydrogen sulfide in the absence of acids. It appeared, therefore, that the two isomers, melting at 101° and 125°, were the only authentic 2, 4, 6-trimethyl-*s*-trithianes known. However, a third γ -isomer, melting at 75-76° or at 80-81°, was reported as being the end product of several syntheses, Marckwald^{166, 167} obtaining it by heating thialdin thiocyanate, Poleck and Thümmel¹⁸⁴ by treating "vinylmercuric oxychloride" with hydrogen sulfide, and Mann and Pope¹⁶⁴ by reacting α , α' -dichlorodiethyl sulfide with a variety of reagents (see section II A-1). The isomer had the same boiling point as the α - and β -isomers, its properties were generally similar, and acid or ethyl iodide transformed it into the β -isomer.^{166, 167} Baumann and Fromm^{19, 22} claimed that the γ -isomer was impure, since recrystallization from acetone gave them some α -isomer. Suyver²²⁰ settled the controversy by showing that the γ -isomer is an eutectic mixture of α - and β -2, 4, 6-trimethyl-*s*-trithiane containing 60% of the α -isomer and melting at 75.3-76°. Bell, Bennett, and Mann²⁸ confirmed the eutectic composition but claimed a melting point of 80° for the eutectic, while Fromm and Engler⁹⁷ found an eutectic at 67% α -isomer melting at 78-80°. More recently, Campaigne, Chamberlain, and Edwards^{51a} determined the composition by proton magnetic resonance and concluded that the eutectic contains 56% of the α -isomer, in reasonable agreement with previous determinations.

The situation with benzaldehyde was even more confused than with acetaldehyde. Laurent¹⁵⁴ isolated a thiobenzaldehyde melting at 90-95° from the reaction of benzaldehyde with ammonium sulfide. Klinger¹⁴⁴ isolated a similar material melting at 83-85° from benzaldehyde and hydrogen sulfide, while Fleischer⁸⁵ isolated a material from benzal chloride and potassium hydrosulfide melting at 78-80°. Klinger^{144, 145, 147} showed that his compound, as well as Laurent's, gave a crystalline solid melting at 225° on treatment with iodine, acid chlorides, or hydrogen chloride. Fleischer's compound did not give this product and was identified as dibenzyl sulfide.^{145, 147} Baumann and Fromm^{16, 17} again brought order to the system by showing that Laurent's and Klinger's compounds are polymers and that *s*-trithianes are formed only in the presence of acids. It is of interest that only recently Cairns, Evans, Larcher, and McKusick⁴⁵ have shown that benzaldehyde gives a low yield of 2, 4, 6-triphenyl-*s*-trithiane on heating with hydrogen sulfide under pressure. α -2, 4, 6-Triphenyl-*s*-trithiane melts at 167° and the β -isomer at 225°. ¹²

A wide variety of aromatic aldehydes have been shown to give one or two, but never more, *s*-trithianes (see section II A-1).

This elegant fitting of fact to theory, a reversal of the usual procedure, was temporarily upset by the work of Hinsberg. In a series of articles^{122-125, 127, 129} Hinsberg described a product melting at 247° which was formed by the treatment of *s*-trithiane or its trisulfoxide with hy-

drogen iodide. Recrystallization of the product from any solvent transformed it back to the known *s*-trithiane melting at 216°. That a material melting at 247° can be isolated by treating *s*-trithiane with various reagents has not been denied, but the nature of the compound is still in doubt. Fromm and co-workers^{95,96} as well as others,^{27,60} insisted that it was not an isomer of *s*-trithiane, while Hinsberg maintained that it was. In addition, Hinsberg^{128,130} reported the existence of a third isomer stable only as its perchlorate; this claim has been ignored. Similarly, Hinsberg^{123,126} claimed the isolation of a third isomer of 2, 4, 6-triphenyl-*s*-trithiane, melting at 180°, from the reduction of an oxidation product with hydrogen iodide, but Fromm and Schultis⁹⁵ showed this was probably impure β -isomer. There is little doubt that Hinsberg's claims are incorrect.

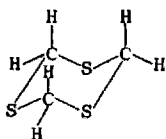
Before considering the conformation of *s*-trithiane and its derivatives, it would be well to discuss first the classical question of *cis-trans* isomerism in substituted *s*-trithianes. Baumann and Fromm¹⁶ argued, by analogy with the hexahydrophthalic acids, that the more stable, less soluble, higher melting β -isomer should be the *trans*-isomer. v. Auwers and Ottens⁵ arrived at the same conclusion by a consideration of density and refractive index; *cis* forms are reported to have higher densities and refractive indices, and α -2, 4, 6-trimethyl-*s*-trithiane has a higher density and refractive index than the β -isomer. The only direct evidence on the subject is the work of Chattaway and Kellett⁵⁹ on the oxidation of 2, 4, 6-trimethyl-*s*-trithiane. They found that the α -isomer gave two monosulfones while the β -isomer gave only one. The intermediate sulfoxides were isolated, and it was shown that no isomerization took place during their formation by reducing them to the parent trithianes. If no isomerization took place during the oxidation of the sulfoxides to the sulfones, this evidence would appear to be incontrovertible that the α -isomer is *trans* and the β -isomer *cis*.

These assignments have been confirmed by Matlack, Chien, and Breslow^{168a} by the use of proton magnetic resonance. Thus, β -2, 4, 6-tris-(chloromethyl)-*s*-trithiane showed two kinds of protons in the ratio of 2:1, a doublet representing the methylenic hydrogens and a triplet representing the ring hydrogens. It must therefore be the *cis* isomer. The α -isomer showed two sets each of doublets and triplets in the ratio of 4:2:1:2, in complete accord with expectations for a *trans* isomer. Similarly, β -2, 4, 6-tris(phenylthiomethyl)-*s*-trithiane showed only two kinds of hydrogen, in addition to the aromatic hydrogens, in the ratio of 2:1, while the α -isomer showed three kinds of hydrogen, in addition to the aromatics, in the ratio of 2:1:6; the two different kinds of methylene hydrogen were not resolved in this instance. More recently, Campaigne, Chamberlain, and Edwards^{51a} used the same method to determine the structures of α - and β -2, 4, 6-trimethyl- and triphenyl-*s*-trithianes, with the same results. It appears reasonable, therefore, to conclude that in all cases the less soluble, higher melting 2, 4, 6-tri-substituted-*s*-trithiane is the *cis* isomer, while the more soluble, lower melting isomer is the *trans*.

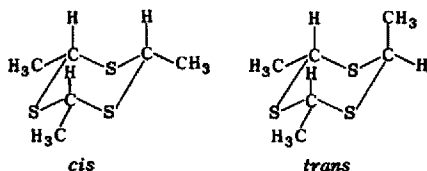
According to Desirant⁶⁴ and Purvis¹⁸⁸ *s*-trithiane shows no specific absorption in the ultraviolet region; the same is true for the α -trimethyl and β -triphenyl derivatives.¹⁸⁸ Fehnel and Carmack^{82a} however, found a strong maximum in the absorption spectrum of *s*-trithiane at 240 m μ and Leonard and Musker^{157b} found the same maximum in certain alkyl-substituted *s*-trithianes. More recently, Mecke and Spiesecke¹⁷¹ claimed that *s*-trithiane shows slight absorption at about 304 and 275 m μ . Leonard and Musker found bands in the infrared at 725, 1160, and 1375 cm⁻¹, which they attributed to the *s*-trithiane structure. Kohlrausch and Reitz¹⁴⁸ determined the Raman spectrum of *s*-trithiane, but drew no conclusions as to its structure. Gerding and co-workers^{102,103} concluded, from a determination of the Raman and infrared spectra of α - and β -2, 4, 6-trimethyl-*s*-trithiane, that the *s*-trithiane ring is puckered just as it is in paraldehyde, that the α -isomer is *trans* and the β -isomer *cis*, and that in the *cis* isomer the methyl groups lie almost in the plane of the sulfur atoms. However, the compounds decomposed to some extent during the Raman spectra determinations, and the authors admitted that the assignments of configuration were not unequivocal.

Moerman and Wiebenga¹⁷⁶ determined the crystal structure of *s*-trithiane; it belongs to the orthorhombic system and they reached the conclusion that the molecule is chair-shaped. Toussaint^{221b} claimed, however, that *s*-trithiane is dimorphous. One form has the structure found by Moerman and Wiebenga and melts at 219°, while a second form has a different crystal structure and melts at 205-218°. Calderbank and Le Fèvre⁴⁶ found a dipole moment of 2.38 D for *s*-trithiane. From this they concluded that the molecule exists either in the chair form or in a mobile equilibrium between chair and boat forms with the chair form predominating. Hayasaki¹¹⁶ found that α - and β -2, 4, 6-triphenyl-*s*-trithiane have essentially equal moments of 2.09 and 2.08 D in carbon tetrachloride and could not reconcile this with either a boat or a planar configuration. Hayasaki^{117,117a} reported, however, a dipole moment of 2.21 D for α -2, 4, 6-tri(*p*-chlorophenyl)-*s*-trithiane and 3.67 D for the β -isomer, while the corresponding *p*-bromophenyl derivatives had dipole moments of 2.17 D and 3.70 D, respectively. These values led to an assignment of a chair conformation for these *s*-trithianes, the β -isomers being *cis* with three equatorial substituents and the α -isomers *trans* with two equatorial substituents and one axial. 2, 2, 4, 4, 6, 6-Hexamethyl-*s*-trithiane is diamagnetic.^{237,238}

The electron diffraction investigation of Hassel and co-workers¹¹²⁻¹¹⁴ gives probably the most authoritative picture of the structure of the *s*-trithiane ring. The ring is in the staggered chair form, with the following assigned bond lengths and angles: S-C 1.81 Å, S-S 3.05 Å, C-S-C 106.5°, and S-C-S 114.5°.

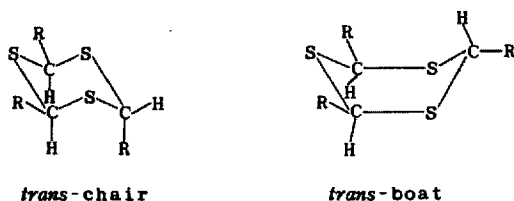


By analogy with cyclohexane it was postulated, with considerable justification, that steric hindrance would make the equatorial positions more favored for substituents than the axial, and *cis*- and *trans*-2, 4, 6-trimethyl-*s*-trithiane were assigned the following structures:



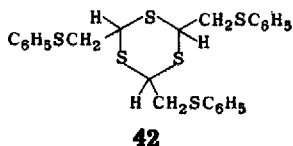
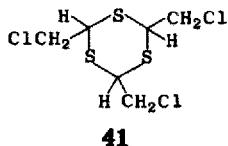
Unfortunately, electron diffraction was unable to differentiate between the α - and β -isomers, and Hassel fell back on Chattaway and Kellett's sulfone proof⁵⁹ to assign the *cis* configuration to the β -isomer and the *trans* configuration to the α -isomer.

The conformation of the *s*-trithiane ring is very interesting, as there is no possibility of hydrogen eclipsing, even in the boat form. There is little doubt, from the electron diffraction investigation of Hassel and Viervoll,¹¹⁴ that *s*-trithiane itself exists predominantly in the chair form. From the evidence in the literature it appears quite reasonable that *cis*-2, 4, 6-trialkyl-*s*-trithianes should exist in the chair form with three equatorial substituents. The situation with respect to the *trans* isomers is less clear, however. It has been calculated that in cyclohexane an equatorial group is favored over an axial by 1.8 kcal for a methyl group²⁵ and by 5.4-5.8 kcal for a *t*-butyl group.²³⁰ These estimates should be approximately correct for *s*-trithiane, inasmuch as the destabilizing axial alkyl group-axial hydrogen interactions exist here as well. Johnson, Margrave, and co-workers,^{141a} have shown that the chair form of cyclohexane is more stable than the boat form by 5.3 kilocalories, and in line with this, Allinger and Freiberg^{1a} have presented evidence that *trans*-1, 3-di-*t*-butylcyclohexane exists in the boat form, as in this form both *t*-butyl groups are essentially equatorial. As the energy difference between chair and boat forms has been attributed primarily to the eclipsed hydrogens on adjacent carbon atoms in the boat form,²⁵ the difference between the chair and boat forms of *s*-trithiane might be much less than 5.3 kcal. It would follow, therefore, that a *trans*-2, 4, 6-trialkyl-*s*-trithiane should exist in the boat form if the substituents are sufficiently bulky, inasmuch as the three groups could be essentially equatorial in this conformation; an inspection of Fisher-Hirschfelder-Taylor models shows the decreased steric hindrance in the boat form quite readily.



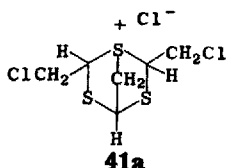
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Matlack, Chien, and Breslow^{168a} attempted to resolve this question by studying the proton magnetic resonance spectra of both isomers of 2, 4, 6-tris(chloromethyl)-*s*-trithiane (**41**) and 2, 4, 6-tris(phenylthiomethyl)-*s*-trithiane (**42**). In the *trans*-chloromethyl derivative one ring hydrogen was 13 c.p.s. to the high field side of the other two. Lemieux



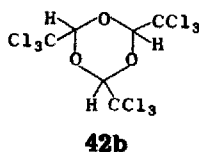
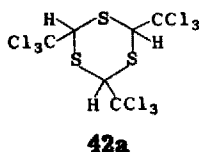
and co-workers^{157a} found that the signals for axial protons occur at higher field than those for equatorial protons in a number of substituted cyclohexanes. In particular, the axial proton shift was 17 c.p.s. higher than the equatorial shift in the closely related compound, *trans*-2, 4, 6-tris(trichloromethyl)-*s*-trioxane, which has been shown rather unequivocally by dipole moment studies to exist in the chair form (*vide infra*). In order for *trans*-**41** to agree with Lemieux's findings and to exist in the chair conformation, it would have to have two equatorial hydrogens and one axial, i.e. two axial chloromethyl groups and one equatorial. Inasmuch as this is highly unlikely, it would appear that the molecule might exist in the boat form. An inspection of molecular models shows that the one *trans*-axial hydrogen in this conformation would be expected to be shifted to the high field side of the two *cis*-axial hydrogens. The same reasoning applied to the phenylthiomethyl compound (**42**); here one ring hydrogen appeared at 18 c.p.s. to the high field side of the other two.

There was a fundamental difference, however, between the spectra of the chloromethyl and phenylthiomethyl derivatives. A comparison of the *cis*- and *trans*-chloromethyl derivative showed that the environment of the odd hydrogen in the *trans* isomer had changed, the two presumably axial hydrogens showing the same chemical shift as in the *cis* isomer. The reverse was true in the phenylthiomethyl derivative, however, since here the odd hydrogen in the *trans* isomer had the same chemical shift as the three axial hydrogens in the *cis* isomer, whereas the two presumably axial hydrogens in the *trans* isomer had shifted. No reason for this discrepancy is apparent, and Matlack, Chien, and Breslow were inclined to believe that an insufficient number of examples exist for proton magnetic resonance to be used to make unequivocal structural assignments in this area. This conclusion has been confirmed by Campaigne, Chamberlain, and Edwards,^{51a} who observed the same anomalous shift in the spectrum of α -2, 4, 6-trimethyl-*s*-trithiane. Since there is little doubt that it exists in the chair form, there appears to be no definitive evidence for the existence of an *s*-trithiane derivative in the boat form. Actually, 2, 4, 6-tris(chloromethyl)-*s*-trithiane (**41**) is a poor choice for studying trithiane conformation, as any contribution of structures such as **41a** would favor the boat form. Such structures would be



expected to be of negligible importance in the phenylthiomethyl derivative (42), however. It is unfortunate that the moment of a freely rotating chloromethyl group is so small that dipole moment measurements of the two chloromethyl isomers do not serve to distinguish between chair and boat forms.

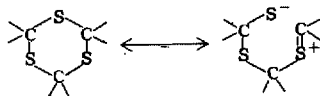
Evidence from other work indicates that *trans*-2, 4, 6-trialkyl-*s*-trithianes even with large alkyl substituents may exist only in the chair form. Although only one form of 2,4,6-tris(trichloromethyl)-*s*-trithiane (42a) is known,⁵⁸ two forms of parachloral, 2, 4, 6-tris(trichloromethyl)-*s*-trioxane (42b), have been isolated.⁵⁷ These have been examined by



Novak and Whalley.¹⁷⁹ The higher melting β -isomer showed only one peak in the proton magnetic resonance spectrum, while the lower melting α -isomer showed two peaks in a ratio of 2 : 1, thus, the α -isomer must be *trans* and β -isomer *cis*. The α -isomer has a dipole moment of 1.64 D. The calculated moment is 1.59 D for the *trans*-chair form and 0.6 D for the *trans*-boat form. Thus, there can be little doubt that the *trans* isomer is in the chair form with a bulky axial trichloromethyl group. It would appear, therefore, that the interaction between the ring hydrogens and the nonbonding p-electrons on the oxygen atoms is comparable in energy to the hydrogen-hydrogen interaction in the eclipsed form of ethane. In fact, from a study of piperidine, which appears to have the N-H bond axial, Aroney and LeFèvre^{2a} concluded that the lone pair of electrons on nitrogen is bulkier than a covalent bond to hydrogen. If one assumes that a trichloromethyl group is somewhat smaller than a *t*-butyl group, one might estimate that the chair form of *s*-trioxane (and probably of *s*-trithiane) is favored over the boat form by at least 3-4 kcal, and that therefore it would probably take a group at least as large as the *t*-butyl group to force the ring into a boat conformation.

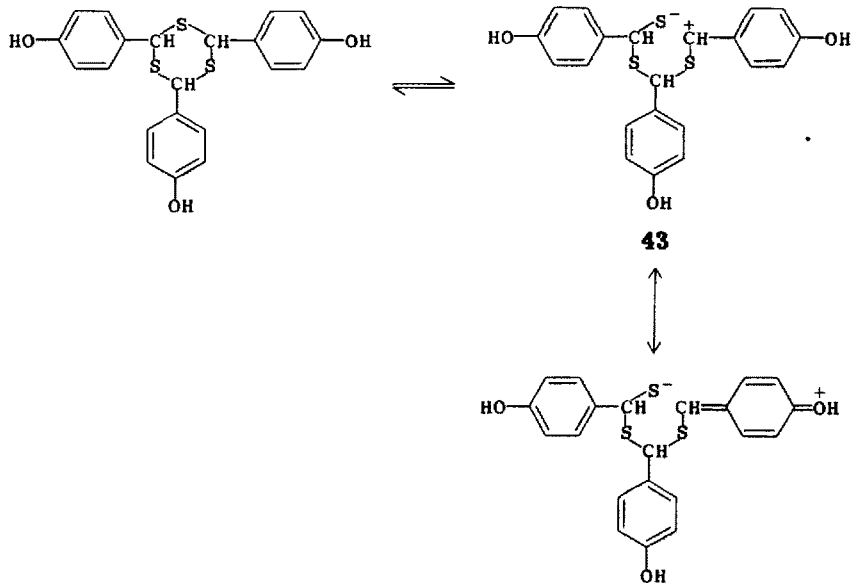
Schönberg^{205,206} took quite a different view. He postulated that the isomeric *s*-trithianes are either both *cis* or both *trans* isomers and that the isolable isomers are boat-chair isomers. The two forms are presumably stabilized by resonance, the partial double bond character of the bonds preventing ready interconversion.

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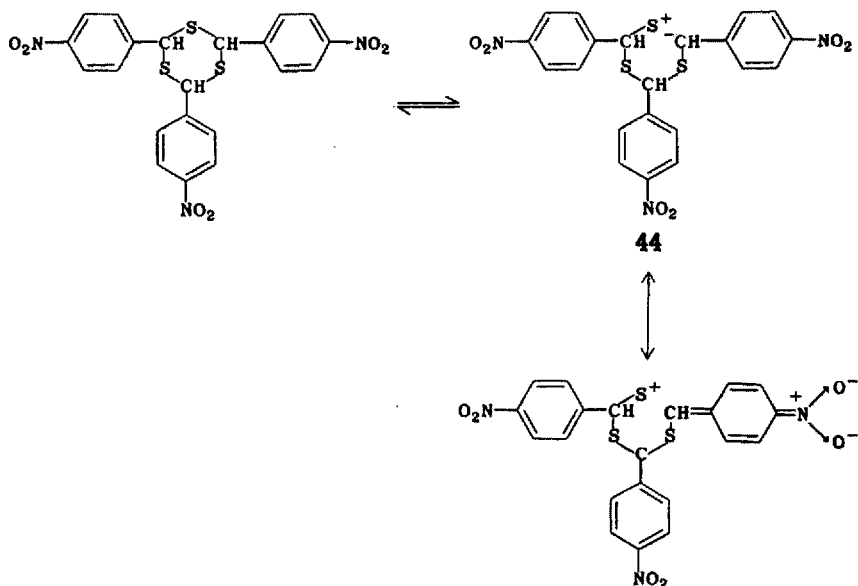


The basis for Schönberg's theory is that the *s*-trithianes are stable compounds, and he felt that isomerization took place under conditions too mild to be explained by the ring opening necessary for *cis-trans* isomerization.

Schönberg's viewpoint is objectionable on several grounds. It is somewhat questionable if isomers have ever been isolated from six-membered rings capable of existing in chair and boat forms. Secondly, this theory calls for more isomers than have been isolated. Furthermore, Suyver²²⁰ has shown that α -2, 4, 6-trimethyl-*s*-trithiane decomposes when heated at 125° with iodine. Thus, the *s*-trithiane ring is not as stable as Schönberg had assumed. Campaigne⁴⁹ made the assumption that resonance structures such as written by Schönberg are actually tautomeric forms and used this to explain very neatly both the isomerization of the *s*-trithianes and the reason for the existence of only one isomer in certain cases. Thus, he assumed that the ring could open to give either a carbonium ion (43) or a carbanion (44). Strong electron-releasing groups on a benzene ring would favor carbonium ion formation, while strong electron-attracting groups would favor carbanion formation.

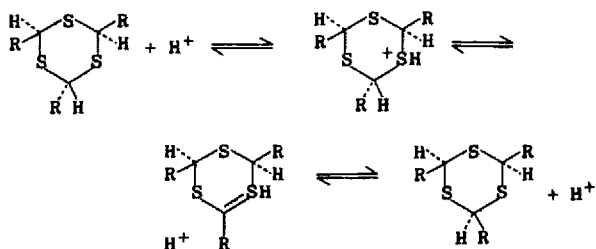


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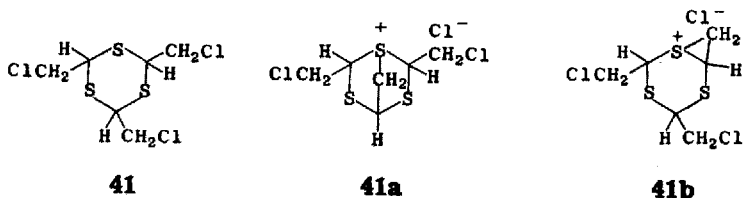
This scheme explains quite well why certain substituents give two isomers while others give only one. Thus, hydroxyl groups give only one isomer while methoxyl groups give two, presumably because the ethers have a greater tendency to form oxonium salts in the strongly acidic reaction medium, and are thus weaker electron-donating groups. In accord with this, anisaldehyde gives only the β -*s*-trithiane when zinc chloride is used as a catalyst. Similarly, the dimethylamino group is electron-attracting in an acid medium, while the strong electron-attracting groups, such as nitro and cyano, prevent the formation of an *s*-trithiane completely and only linear polymers can be isolated. The compound reported as being 2, 4, 6-tris(*o*-nitrophenyl)-*s*-trithiane²³⁵ is probably a polymer.

Campaigne's picture does not take into account the fact that the catalysts which isomerize *s*-trithianes—inorganic acids, acid chlorides, ethyl iodide, or iodine—would all tend to form sulfonium compounds. An alternative mechanism for isomerization could be as follows, using an acid as an example:



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Thus, it is not necessary to postulate a ring opening to account for the isomerization, as the returning proton could add to either side of the ring. The mechanism requires expanding the octet of sulfur, but this seems to be fairly well established.⁶⁶⁻⁶⁸ From this viewpoint it is understandable why Matlack, Chien, and Breslow^{168a} were unable to interconvert the two isomeric 2, 4, 6-tris(chloromethyl)-*s*-trithianes (**41**), as structures such as **41a** and **41b** would decrease the electron density on the sulfur atoms and prevent isomerization.



3. Reactions

a. General Properties

The *s*-trithianes are, with few exceptions, stable, white, crystalline solids. They are all insoluble in water and are soluble, to a greater or lesser extent, in organic solvents. By definition the α -isomers are lower melting and more soluble than the β -isomers. This appears to hold for a variety of solvents, as shown in Table 5 for α - and β -2, 4, 6-trimethyl-*s*-trithiane and the corresponding phenyl derivatives. The solubilities were determined by Suyver²²⁰ and are expressed as g per 100 g solvent at 25°.

TABLE 5. Solubilities of *s*-Trithianes

Solvent	<u>2, 4, 6-Trimethyl-<i>s</i>-trithiane</u>		<u>2, 4, 6-Triphenyl-<i>s</i>-trithiane</u>	
	α	β	α	β
Chloroform	57.59	51.22	11.1	0.2
Methanol	4.04	3.89	0.17	0.04
Ethanol	3.86	3.97	0.2	0.04
Ether	15.58	13.67	1.1	0.4
Acetone	20.96	18.31	2.5	1.1
Ethyl acetate	17.52	15.48	2.1	0.9
Carbon disulfide	25.50	20.75	5.8	0.2
Benzene	36.40	26.98	6.1	0.01

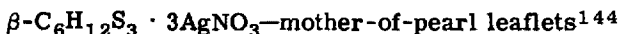
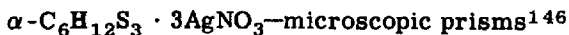
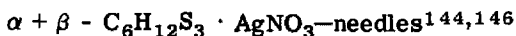
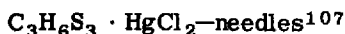
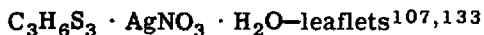
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Reychler¹⁹⁴ reported that *s*-trithiane is soluble in benzyl chloride, nitrobenzene, aniline, phenol, and naphthalene at 150-170°.

The odor of *s*-trithianes is probably a function of their stability and purity. Baumann¹³ reported that *s*-trithiane itself is odorless, as are both isomers of 2, 4, 6-trimethyl-*s*-trithiane. *s*-Trithianes derived from ketones are somewhat less stable, however, and a variety of odors have been reported. Thus, two sources^{40,158} report that 2, 4, 6-trimethyl-2, 4, 6-triethyl-*s*-trithiane has an intensely putrid odor. The *s*-trithianes derived from acetone and from acetophenone are also reported to have unpleasant odors, whereas that derived from cyclohexanone is reported to be odorless.⁴⁰ That the odor of an *s*-trithiane may be related to its purity is illustrated by the experience of Baumann and Fromm,¹¹ who attempted to isolate a volatile material formed as a by-product in the synthesis of trithioacetone. This substance, which they thought might be monomeric thioacetone, must surely hold the record for intensity of obnoxious odor, as it could be smelled a half-mile away shortly after a steam distillation into a chilled receiver. A vacuum distillation, in which no material was lost, led to essentially the same result. As they put it, ethyl mercaptan must be considered a compound with a weak odor compared to this material. Probably, odors attributed to *s*-trithianes are caused by impurities or equilibrium with a trace of monomeric thioketone.

b. Complexes with Heavy Metals Salts

Certain heavy metal salts form crystalline complexes with *s*-trithiane^{105-107,133,134,138} and with 2, 4, 6-trimethyl-*s*-trithiane.^{144,146,228} Determination of the formulas of these complexes was frequently complicated by the questionable purity of the *s*-trithianes, but the following seem to be generally accepted:



2, 4, 6-Triphenyl-*s*-trithiane did not give a crystalline derivative with silver or mercuric salts.¹⁴⁴

c. Thermal Reactions

s-Trithianes derived from aliphatic aldehydes are very stable to heat. Thus, 2, 4, 6-trimethyl-*s*-trithiane distills without decomposition at

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245°. ¹⁴⁴ Those derived from aromatic aldehydes¹⁸ or from ketones⁹¹ are somewhat less stable. Schönberg²⁰⁴ attempted to correlate the dissociation tendency of trithianes with that of the corresponding substituted phenylethanes, as illustrated by the following comparisons:

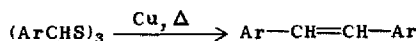
(Ph ₃ C) ₂ unstable	(Ph ₂ CS) ₃ unknown, only monomer isolated
(Ph ₂ CH) ₂ stable	(PhCHS) ₃ monomer unknown
(PhCH ₂) ₂ stable	(CH ₂ S) ₃ monomer unknown
(Ph ₂ CMe) ₂ unstable	(PhCSMe) ₃ decomposes to monomer above 124°
(PhCMe ₂) ₂ stable	(Me ₂ CS) ₃ distillable <i>in vacuo</i>
(PhCHMe) ₂ stable	(MeCHS) ₃ stable at 245°

A number of additional examples of thioketones which have been isolated only as monomers or as both monomers and trimers have already been mentioned (see section II A-1).

A considerable amount of work has been done on the products formed by the thermal decomposition of *s*-trithianes. Eltekow⁷⁴ prepared 2-butene by heating 2, 4, 6-trimethyl-*s*-trithiane with copper in a sealed tube. This general reaction is discussed in greater detail below. Baumann and Fromm^{11,91} claimed that 2, 2, 4, 4, 6, 6-hexamethyl-*s*-trithiane forms monomeric and dimeric thioacetone on being heated at 225°. However, the monomer has never been isolated as a pure compound, and Böhme, Pfeiffer, and Schneider³² asserted that there is no evidence for the existence of the dimer. The latter authors isolated isopropyl mercaptan from the pyrolysis of the hexamethyl-*s*-trithiane at 215° for 10-12 hours. More recently, Kreuz¹⁵² obtained a 50:50 mixture of 2, 4- and 2, 5-dimethylthiophene by passing hexamethyl-*s*-trithiane over porcelain chips at about 600°.

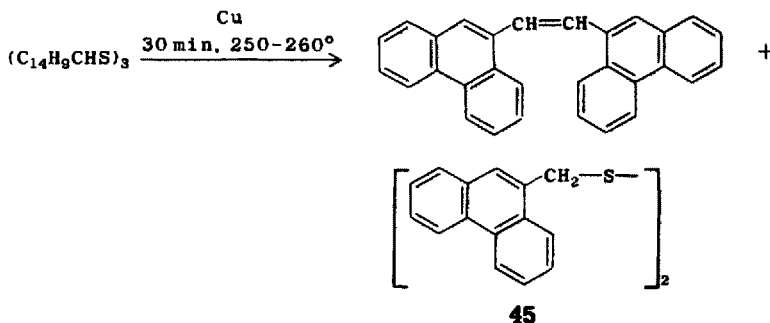
Since monomeric thiocyclohexanone is known,^{189,211} it would have been expected that heating the trimer would give the monomer. However, Fromm⁹⁸ isolated a compound, C₁₈H₂₈S₂, to which he tentatively assigned the structure of a bis(cyclohexene mercaptole) of cyclohexanone.

By far the largest amount of work has been done with triaryl-*s*-trithianes. As early as 1877 Klinger¹⁴⁵ reported that heating β-2, 4, 6-triphenyl-*s*-trithiane above its melting point with copper gives a good yield of stilbene.



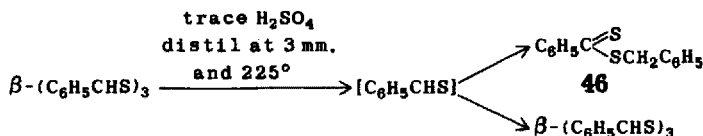
The reaction has been applied to a variety of substituted phenyl compounds by Wood and co-workers,²³⁵ Stanfield and Reynolds,²¹⁷ Fuson and Best,¹⁰⁰ Campaigne and Budde,⁴⁹ Manchot and Zahn,¹⁶² and Richtzenhain and von Hofe.¹⁹⁶ The last authors showed that iron could be used instead of copper. Bergmann and Israelashwili²⁹ applied the

reaction to the *s*-trithiane derived from 9-phenanthraldehyde and isolated a disulfide (45) as a by-product.



This was avoided by using Raney nickel. The versatility of the synthesis is indicated by its successful application to the *s*-trithiane derived from 2-thenylaldehyde by Steinkopf and Jakob.²¹⁸ Yields are generally good and the method constitutes a convenient synthesis of 1, 2-disubstituted ethylenes.

Baumann²⁰ heated 2, 4, 6-triphenyl-*s*-trithiane in the absence of a catalyst. Below 200° the products were stilbene and sulfur, but above this temperature tetraphenylthiophene and hydrogen sulfide were also formed, presumably by a secondary reaction between the initial products. Kopp¹⁵⁰ applied this reaction to a variety of triaryl-*s*-trithianes and Baumann and Fromm²¹ applied it successfully to the 2-furyl derivative. It is not as convenient as the copper-catalyzed reaction because of the temperature limitation to avoid by-products and the slowness of the reaction. Wood and Bost^{233, 234} decomposed triaryl-*s*-trithianes in the presence of a trace of sulfuric acid. Rather surprisingly they isolated benzyl dithiobenzoate (46), the expected product of a Cannizzaro reaction from the phenyl derivative, and postulated, therefore, that monomeric thiobenzaldehyde is an intermediate.



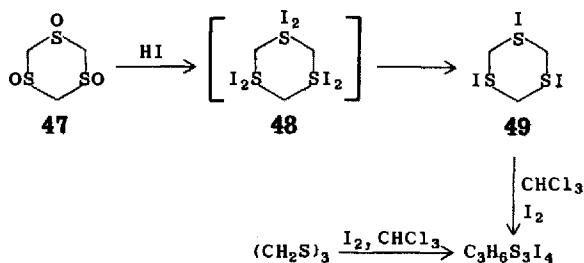
Baumann and Fromm²³ investigated the thermal decomposition of 2, 4, 6-triphenyl-2, 4, 6-trimethyl-*s*-trithiane derived from acetophenone. The reaction was similar to that of triphenyl-*s*-trithiane; the primary products were styrene and sulfur, but these reacted to give a mixture of 2, 4- and 2, 5-diphenylthiophene and hydrogen sulfide. The latter then reduced a portion of the styrene to ethylbenzene. Cline, Campaigne, and Spies⁶¹ found that the trithio derivative, on refluxing with Raney nickel in xylene, gave an 18% yield of the expected *trans*-2, 3-diphenyl-2-butene, but that no olefin was formed under the same conditions with copper. Hauptmann and Wladislaw¹¹⁵ claimed that better yields of olefin

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would have been obtained if the Raney nickel had been heated to remove hydrogen before being used as a desulfurizing agent.

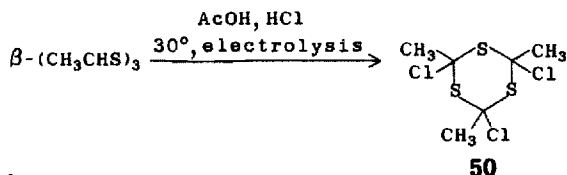
d. Halogenation

s-Trithianes react with halogens readily. A variety of products have been reported depending on the conditions of the reaction. There are not many recorded instances, however, where halogenation takes place without rupture of the *s*-trithiane ring. Fromm and Schultis⁹⁵ reported that the reaction of *s*-trithiane with one mole of iodine in chloroform yields a diiodide, C₃H₆S₃I₂, m.p. 100-110°, while reaction with two moles of iodine gives a tetraiodide, C₃H₆S₃I₄, decomposing at 100-105°. Both compounds gave off iodine on standing and were undoubtedly impure. The compounds probably contain sulfur-iodine bonds, as Hinsberg¹²² isolated similar compounds by treating *s*-trithiane 1, 3, 5-trioxide (**47**) with hydrogen iodide followed by treatment with iodine. The reaction was postulated as proceeding *via* the hexaiodide (**48**), which was not isolated. Hydrogen iodide then dehalogenated **48** to a triiodide, presumably **49**, which was isolated as brown plates or prisms melting at 118-123° with decomposition. Treatment of **49** with iodine yielded a tetraiodide which decomposed at 100°, presumably identical with that prepared by Fromm and Schultis.



Warming the iodides with sodium hydroxide regenerated *s*-trithiane. In contrast to this, Fromm and Engler⁹⁷ reported that the isomeric 2, 4, 6-trimethyl-*s*-trithianes react with iodine to give isomeric diiodides, C₆H₁₂S₃I₂. The α -isomer gave a red crystalline product melting at 76-78°, while the β -isomer gave a red-brown solid which was so unstable that its melting point could not be determined. Both compounds reverted to the parent *s*-trithianes on treatment with silver acetate.

Fichter and Braun⁸⁴ electrolyzed a solution of β -2, 4, 6-trimethyl-*s*-trithiane in acetic acid saturated with hydrogen chloride and isolated an oil, b.p. 85-87° at 10 mm, which they formulated as 2, 4, 6-trimethyl-2, 4, 6-trichloro-*s*-trithiane (**50**). The same product was formed by reacting a solution of the *s*-trithiane in acetic acid with chlorine.

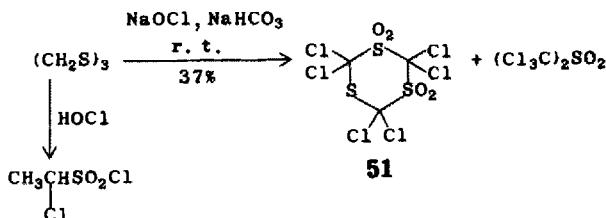


[For references, see pp. 765-773.]

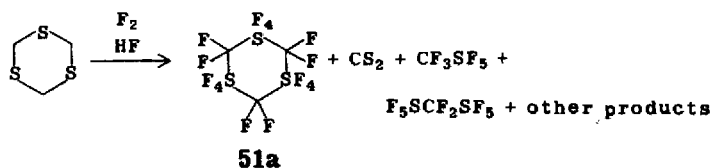
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Müller and Schiller¹⁷⁷ repeated the preparation and obtained the same compound. However, no proof has been advanced for the structure of this material, and the fact that its boiling point is lower than that of the starting material makes the assigned structure doubtful.

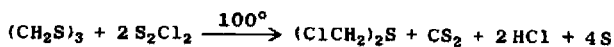
Müller and Schiller¹⁷⁷ found that β -2, 4, 6-trimethyl-*s*-trithiane does not react with alkaline hypochlorite. A vigorous reaction set in, however, when carbon dioxide was added to liberate hypochlorous acid, and impure α -chloroethanesulfonyl chloride was formed.¹⁷⁸ Farrar⁸¹ carried out the reaction of *s*-trithiane with sodium hypochlorite buffered with sodium bicarbonate and found that chlorination and oxidation take place simultaneously; 2, 2, 4, 4, 6, 6-hexachloro-*s*-trithiane 1, 1, 3, 3-tetroxide (**51**), melting at 203-204° with decomposition, was formed.



Infrared analysis showed that **51** is a disulfone and not a sulfone-disulfoxide. The compound liberated iodine from sodium iodide in acetone, and thiophosgene was formed when it was heated above its melting point. A by-product of the chlorination was tentatively identified as bis(trichloromethyl) sulfone. Recently, Dresdner and Young^{72a} treated *s*-trithiane with fluorine, generated electrolytically from hydrogen fluoride. Although the predominant reaction was fragmentation, they isolated in about 2% yield a compound, b.p. 144. 1-144. 5°, n_D^{25} 1. 3258, d_4^{25} 2. 162, to which they assigned the structure perfluoro-*s*-trithiane dodecafluoride (**51a**).



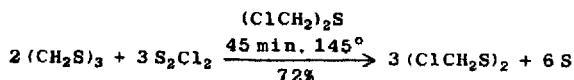
In all other cases, halogenation leads to cleavage of the *s*-trithiane ring. Thus, Bloch and Höhn³¹ chlorinated *s*-trithiane with sulfur monochloride and isolated α , α' -dichlorodimethyl sulfide in 58% yield according to the following equation:



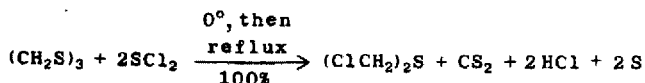
Mann and Pope¹⁶³ and Mayer and Runge^{169b} improved the yield to 70%, while Davies and Hambly⁶³ found that a small amount of α , α' -dichlorodimethyl disulfide is also formed in the reaction. According to

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Joullié and co-workers^{142a} the latter can be made the major product by using the monosulfide as solvent.

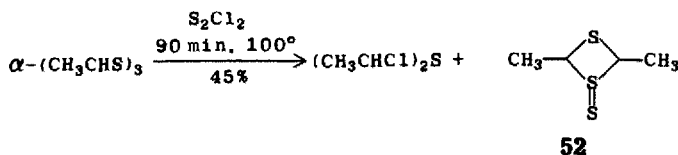


Sulfuryl chloride gave a poor yield under these conditions. According to Mann and Pope¹⁶³ *s*-trithiane reacts quantitatively with sulfur dichloride, while Mayer and Runge^{169b} reported a 70-80% yield of α, α' -dichlorodimethyl sulfide with this reagent.



Truce, Birum, and McBee²²² found that thionyl chloride reacts slowly but almost quantitatively with *s*-trithiane to form α, α' -dichlorodimethyl sulfide, but Mayer and Runge^{169b} reported an 85-90% yield of crude material. The same compound was formed with sulfuryl chloride but in lower yield, 84% according to Joullié and co-workers.^{142a} Birum and co-workers^{30b, 108a} claimed that chlorination of *s*-trithiane with a mixture of thionyl chloride and chlorine yields a mixture of α, α' -dichlorodimethyl sulfide and disulfide, with the sulfide predominating.

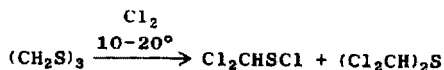
Mann and Pope¹⁶³ extended the reaction with sulfur mono- and dichlorides to α -2, 4, 6-trimethyl-*s*-trithiane. The monochloride gave a better yield of α, α' -dichlorodiethyl sulfide.



The structure of the by-product, diethylidene trisulfide (**52**), is doubtful. Although it might be 3, 5-dimethyl-1, 2, 4-trithiolane, its properties are not in very good agreement with this structure (see Chapter 3, section II A). The same authors found that a small amount of benzal chloride was formed when β -2, 4, 6-triphenyl-*s*-trithiane was heated with sulfur dichloride.

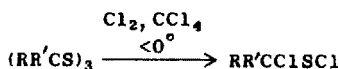
The products formed by the direct halogenation of *s*-trithianes depend on the solvent and on the reaction conditions. Giron¹⁰⁸ claimed that treatment of *s*-trithiane with chlorine in the absence of solvent yields α, α, α' -trichlorodimethyl sulfide, $\text{Cl}_2\text{CHSCH}_2\text{Cl}$, but this is probably in error. According to Wood²³⁶ an exothermic reaction takes place and the product is dichloromethylsulfenyl chloride (**53**). Douglass, Martin, and Addor⁷¹ controlled the temperature in the reaction and isolated two products, dichloromethylsulfenyl chloride (**53**) in 46-60% yield and α, α' -dichlorodimethyl sulfide in 25-35% yield.

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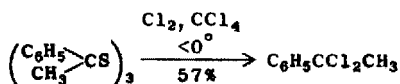
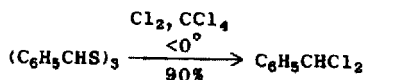
53

Douglass and co-workers⁶⁹⁻⁷¹ investigated the chlorination of a number of *s*-trithianes in methylene chloride or carbon tetrachloride below 0°. With nonaromatic compounds the reaction yielded chlorosulfonyl chlorides (54).



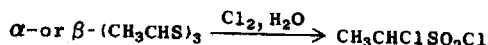
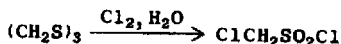
54

With R = H and R' = H, Me, Et, or *n*-Pr the yields were quite low, about 10-20%. Hexamethyl-*s*-trithiane (R = R' = Me) gave a 38% yield. The reaction took a different course with 2, 4, 6-triphenyl-*s*-trithiane and with 2, 4, 6-triphenyl-2, 4, 6-trimethyl-*s*-trithiane, the former giving benzal chloride and the latter α, α -dichloroethylbenzene (55). According to Mayer and Runge^{169b} the Douglass procedure on *s*-trithiane gives an 18% yield of impure of chloromethylsulfonyl chloride.

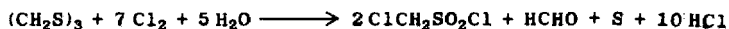


55

Numerous investigators have chlorinated *s*-trithiane^{41, 42, 69, 141, 142, 151, 157, 199} and 2, 4, 6-trimethyl-*s*-trithiane^{142, 177, 178, 214} in aqueous solution, either in the presence or absence of acetic acid. The reactions follow parallel courses to the corresponding chloroalkanesulfonyl chlorides in good yields; apparently it is carried out commercially.¹⁹⁹



According to Lee and Dougherty¹⁵⁷ the stoichiometry of the reaction is as follows, the yield of sulfonyl chloride being 75%:



Douglass, Simpson, and Sawyer⁶⁹ investigated the reaction more care-

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fully and found that a variety of products are formed. At 0-10°, 100 g of *s*-trithiane yielded 90.6 g of ClCH₂SO₂Cl, 3.5 g of methylene chloride, 10 g of a mixture of carbon tetrachloride and sulfur dichloride, 10.2 g of a mixture of ClCH₂SO₂Cl and (ClCH₂)₂S, and formaldehyde, sulfate ion, and an indeterminate amount of Cl₃CSO₂Cl. Exhaustive chlorination increased the amount of the last compound. According to Farrar^{81a} chloromethanesulfonyl chloride prepared by this procedure cannot be obtained pure.

2, 4, 6-Triethyl-*s*-trithiane yielded the expected α -chloropropanesulfonyl chloride.¹⁴²

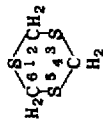
Kostsova¹⁵¹ found that bromine in the presence of water gives an analogous reaction, bromomethanesulfonyl bromide being obtained from *s*-trithiane and α -bromoethanesulfonyl bromide from 2, 4, 6-trimethyl-*s*-trithiane. *N*-Chloroacetamide gave the corresponding chlorides in low yield in water with both *s*-trithianes, but in aqueous ethanol polymers were formed. In chloroform or acetone crystalline, sharp-melting compounds of undetermined structure were obtained.

Although halogenation of *s*-trithianes generally leads to ring cleavage, this is not the case with oxidized *s*-trithianes. This is discussed in section II A-3e.

e. Oxidation

Many sulfoxides and sulfones of *s*-trithianes have been reported, especially those containing aliphatic substituents. The situation is quite confused, since in many cases the derivatives decomposed without melting and the compounds were identified by crystal structure and solubility differences. Frequent arguments arose, therefore, as to the identity of the oxides, and there is little doubt that many of the compounds reported were mixtures. Those compounds for which there is reasonable agreement as to structure are listed in Table 6.

The sulfur-oxygen bond is oriented in space. If *s*-trithiane consists of a symmetrical six-membered ring with alternating sulfur and methylene groups, it should form one monosulfoxide, two disulfoxides and two trisulfoxides. In a very careful study Bell and Bennett²⁷ isolated all of these derivatives by using hydrogen peroxide under various conditions

TABLE 6. Oxides of *s*-Trithianes

Substituents	Yield (%)	M.p. (°C)	Remarks	Ref.
1-Oxide	39	187		27
1, 3-Dioxide	18	dec. 220-280 255	<i>trans</i> isomer probably <i>trans</i> isomer	27 130
1, 3-Dioxide	12	dec. 200-215 210 (dec.)	<i>cis</i> isomer probably <i>cis</i> isomer	27 122
1, 3, 5-Trioxide	100	dec. 230-280	<i>trans</i> isomer by oxidn. of <i>trans</i> 1, 3-dioxide	27
1, 3, 5-Trioxide		dec. 220-260	<i>cis</i> isomer by oxidn. of <i>cis</i> 1, 3-dioxide	27
1, 3, 5-Trioxide		dec. 290	probably <i>trans</i> isomer	121, 125
1, 1-Dioxide		218		124
1, 1, 3, 3-Tetroxide	33			53 124
1, 1, 3, 3, 5-Hexoxide	51	dec. >340 dec. >340		14, 53 104
2-CH ₃ - 1, 1, 3, 3-Tetroxide				
2-C ₂ H ₅ - 1, 1, 3, 3-Tetroxide		280		54

2-C ₂ H ₅ - 1, 1, 3, 3, 5, 5-Hexoxide	dec. > 340		54
2-(CH ₂ =CHCH ₂ -) 1, 1, 3, 3, 5, 5-Hexoxide			79
$\begin{array}{c} \text{CH}_3 \\ \\ 2-(\text{CH}_2=\text{CCH}_2-) \end{array} 1, 1, 3, 3, 5, 5\text{-Hexoxide}$			79
2, 2-(CH ₃ -) ₂ 1, 1, 3, 3-Tetroxide	319		54
2, 2-(CH ₃ -) ₂ 1, 1, 3, 3, 5, 5-Hexoxide	dec. > 340		54
2, 4-(?)-(<i>n</i> -C ₃ H ₇ -) ₂ 1, 1, 3, 3, 5, 5-Hexoxide	297		53
2, 4-(CH ₂ =CHCH ₂ -) ₂ 1, 1, 3, 3, 5, 5-Hexoxide			78, 79
$\begin{array}{c} \text{CH}_3 \\ \\ 2, 4-(\text{CH}_2=\text{CCH}_2-) \end{array} 1, 1, 3, 3, 5, 5\text{-Hexoxide}$	210-212		79
2, 4, 6-(CH ₃ -) ₃ 1-Oxide	87	118. 5	59
2, 4, 6-(CH ₃ -) ₃ 1-Oxide	87	136 93	59
2, 4, 6-(CH ₃ -) ₃ 1, 1-Dioxide	66	190	59
2, 4, 6-(CH ₃ -) ₃ 1, 1-Dioxide	97	157. 5	59
		115-116	
2, 4, 6-(CH ₃ -) ₃ 1, 3-Dioxide		255 (dec.)	97

TABLE 6. Oxides of *s*-Trithianes (contd)

Substituents	Yield (%)	M.p. (°C)	Remarks	Ref.
2, 4, 6-(CH ₃ -) ₃ 1, 3, 5-Trioxide		184	from α-2, 4, 6-trimethyl- <i>s</i> -trithiane	97
2, 4, 6-(CH ₃ -) ₃ 1, 3, 5-Trioxide		153	from β-2, 4, 6-trimethyl- <i>s</i> -trithiane	97
2, 4, 6-(CH ₃ -) ₃ 1, 1, 3, 3-Tetroxide	22-42	283-284		22
2, 4, 6-(CH ₃ -) ₃ 1, 1, 3, 3, 5, 5-Hexoxide	25-35			12, 22, 161
2, 4, 6(?)-(CH ₂ =CHCH ₂ -) ₃ 1, 1, 3, 3, 5, 5-Hexoxide		260-270		79
2, 4, 6(?)-(CH ₂ =C(CH ₃)CH ₂ -) ₃ 1, 1, 3, 3, 5, 5-Hexoxide		195		79
2, 4, 6-(ClCH ₂ -) ₃ 1, 3-Dioxide		250 (dec.)		168a
2, 4, 6-(C ₆ H ₅ -) ₃ 1, 3, 5-Trioxide		240		95
2, 4, 6-(C ₆ H ₅ -) ₃ 1, 1, 3, 3, 5, 5-Hexoxide		>340		95
2, 2, 4, 6(?)-(C ₂ H ₅ -) ₄ 1, 1, 3, 3, 5, 5-Hexoxide		175		53

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2, 2, 4, 6(?)-($C_6H_5CH_2$) ₄ 1, 1, 3, 3, 5, 5-Hexoxide	171-172	53	
2, 2, 4, 4, 6-($CH_2=CHCH_2$) ₅ 1, 1, 3, 3, 5, 5-Hexoxide	91 100-102	216	
2, 4, 6-(CH_3) ₃ -2, 4-(C_2H_5) ₂ 1, 1, 3, 3, 5, 5-Hexoxide	239-240	161	
2, 4, 6-(C_6H_5) ₃ -2, 4-(CH_3) ₂ 1, 1, 3, 3, 5, 5-Hexoxide	248	95	
2, 2, 4, 4, 6, 6-(CH_3) ₆ 1, 1, 3, 3-Tetroxide	208	11	
2, 2, 4, 4, 6, 6-(CH_3) ₆ 1, 1, 3, 3, 5, 5-Hexoxide	302	11	by oxidation of hexamethyl-s-trithiane
2, 2, 4, 4, 6-(CH_3) ₅ -6- C_2H_5 -1, 1, 3, 3, 5, 5-Hexoxide	100 302	12, 14, 53, 54, 161	by alkylation of 1, 1, 3, 3, 5, 5-hexoxide
2, 2, 4, 4, 6-(CH_3) ₅ -6- C_2H_5 -1, 1, 3, 3, 5, 5-Hexoxide	241	54	
2, 4, 6-(CH_3) ₃ -2, 4, 6-(C_2H_5) ₃ 1, 1, 3, 3, 5, 5-Hexoxide	269	161	
2, 4, 6-(CH_3) ₃ -2, 4, 6-($CH_2=CHCH_2$) ₃ 1, 1, 3, 3, 5, 5-Hexoxide	267	161	
2, 4, 6-(CH_3) ₃ -2, 4, 6-($C_6H_5CH_2$) ₃ 1, 1, 3, 3, 5, 5-Hexoxide	100 268	161	
2, 4, 6-(CH_3) ₃ -2, 4, 6-($C_6H_5CH_2$) ₃ 1, 1, 3, 3, 5, 5-Hexoxide	dec. > 132	161	

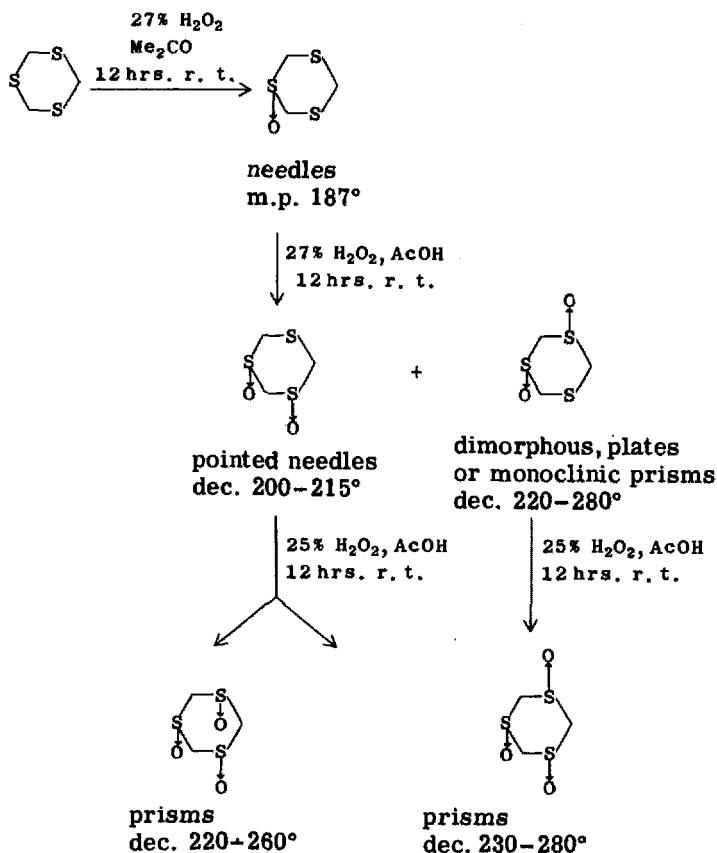
TABLE 6. Oxides of *s*-Trithianes (contd)

Substituents	Yield (%)	M.p. (°C)	Remarks	Ref.
2, 4, 6-(CH ₃) ₃ -2, 4, 6-(<i>o</i> -CH ₃ C ₆ H ₄ CH ₂) ₃ 1, 1, 3, 3, 5, 5-Hexoxide	100	206		161
2, 4, 6-(CH ₃) ₃ -2, 4, 6-[(NO ₂) ₂ - <i>o</i> -CH ₃ C ₆ H ₄ CH ₂] ₃ 1, 1, 3, 3, 5, 5-Hexoxide		191 (dec.)		161
2, 2, 4, 4, 6, 6-(C ₂ H ₅) ₆ 1, 1, 3, 3, 5, 5-Hexoxide		208		53
2, 2, 4, 4, 6, 6-(<i>n</i> -C ₃ H ₇) ₆ 1, 1, 3, 3, 5, 5-Hexoxide		133		53
2, 2, 4, 4, 6, 6-(CH ₂ =CHCH ₂) ₆ 1, 1, 3, 3, 5, 5-Hexoxide				216
Trithiocyclopentanone 1, 1, 3, 3, 5, 5-Hexoxide		172		98
Trithiocyclohexanone 1, 1, 3, 3-Tetroxide		175. 5-176. 5		98
Trithio-3-methylcyclohexanone 1, 1, 3, 3-Tetroxide		266-267		98
Trithio-4-methylcyclohexanone 1, 1, 3, 3-Tetroxide		253-254		98
2-C ₂ H ₅ -2-Br 1, 1, 3, 3-Tetroxide		204 (dec.)		54

2, 2-Br ₂ 1, 1, 3, 3-Tetroxide				54, 181
2-CH ₃ -Br ₄ 1, 1, 3, 3-Tetroxide				104
2, 2-(CH ₃ -) ₂ -4, 4, 6, 6-Br ₄ 1, 1, 3, 3, 5, 5-Hexoxide		231 (dec.)		54
2-C ₂ H ₅ -2, 4, 4, 6, 6-Br ₅ 1, 1, 3, 3, 5, 5-Hexoxide		221 (dec.)		54
2, 4, 6-(CH ₃ -) ₃ -2, 4-(C ₂ H ₅ -) ₂ -6-Br 1, 1, 3, 3, 5, 5-Hexoxide		221		161
2, 4, 6-(CH ₃ -) ₃ -2, 4, 6-Cl ₃ 1, 1, 3, 3, 5, 5-Hexoxide		270 (dec.)		161
2, 4, 6-(CH ₃ -) ₃ -2, 4, 6-Br ₃ 1, 1, 3, 3, 5, 5-Hexoxide		240 (dec.)		161
2, 2, 4, 4, 6, 6-Cl ₆ 1, 1, 3, 3-Tetroxide	37	203-204 (dec.)	might be 2, 2, 4, 4, 5, 5-Cl ₆	81
2, 2, 4, 4, 6, 6-Br ₆ 1, 1, 3, 3-Tetroxide		132	might be 2, 2, 4, 4, 5, 5-Br ₆	54, 181
2, 2, 4, 4, 6, 6-Cl ₆ 1, 1, 3, 3, 5, 5-Hexoxide	89	252 (dec.)		53, 81, 199
2, 2, 4, 4, 6, 6-Br ₆ 1, 1, 3, 3, 5, 5-Hexoxide		146		53
2, 4, 6-(C ₆ H ₅ N=N-) ₃ 1, 1, 3, 3, 5, 5-Hexoxide	4	149		199

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as the oxidizing agent. The relationship among the various sulfoxides is shown in the following set of equations:



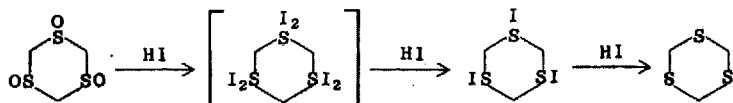
Since the di- and trisulfoxides do not have sharp melting points, non-identity was shown by differences in crystal structure and solubility. All the oxides were reduced to *s*-trithiane with zinc and hydrochloric acid, showing that no sulfones had been formed. The assignments of configuration are obvious. Of the two disulfoxides one gave one trisulfoxide in quantitative yield. Thus, both the disulfoxide and the trisulfoxide must be *trans* isomers. The other disulfoxide, which must be the *cis* isomer, gave two trisulfoxides, the previously prepared *trans* isomer and a new *cis* isomer. Whitaker and Sisler^{228a} have shown that N_2O_4 cannot be used to prepare sulfoxides from *s*-trithiane.

Prior to this work Hinsberg¹²² isolated a disulfoxide from the oxidation of *s*-trithiane with hydrogen peroxide, which Bell and Bennet identified as the *cis* isomer. Subsequently, Hinsberg¹³⁰ isolated the *trans*

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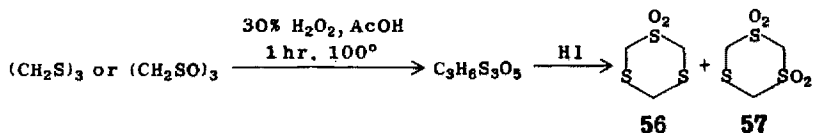
isomer from the oxidation of "s-trithiane perchlorate" with hydrogen peroxide. Hinsberg claimed to have isolated two trisulfoxides. One¹²¹ was shown by Bell and Bennett to be identical with their *trans* isomer. The second¹²⁴ was different from Bell and Bennett's *cis* isomer, thus confirming Fromm's contention^{95,96} that the compound was not an s-trithiane derivative.

Hinsberg^{121,122} investigated the chemistry of his trisulfoxide. Like all the sulfoxides it was reduced to s-trithiane by warming with concentrated hydrogen iodide. As already mentioned (see section IIA-3d), under milder conditions a triiodide was isolated, the reduction presumably taking place in steps.

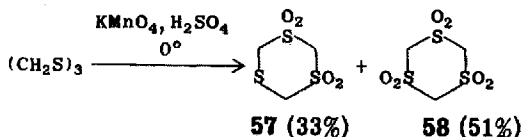


The trisulfoxide was a weak acid, soluble in dilute sodium hydroxide and insoluble in sodium carbonate. Sodium ethoxide in ethanol gave a mono-sodium salt. The trisulfoxide decomposed on standing in dilute sodium hydroxide or in concentrated hydrochloric acid. The hydrogens were shown to be acidic also by treating an alkaline solution with benzaldehyde, an amorphous solid being formed, and with aromatic diazonium salts, brown dyes being formed. Whether these reactions are reactions of the trisulfoxide or of impurities is not known. According to Hepworth and Clapham¹²⁰ the trisulfoxide is completely unreactive with methylmagnesium iodide, no gas being evolved in anisole at 70°. They attributed this to lack of solubility in the reaction medium.

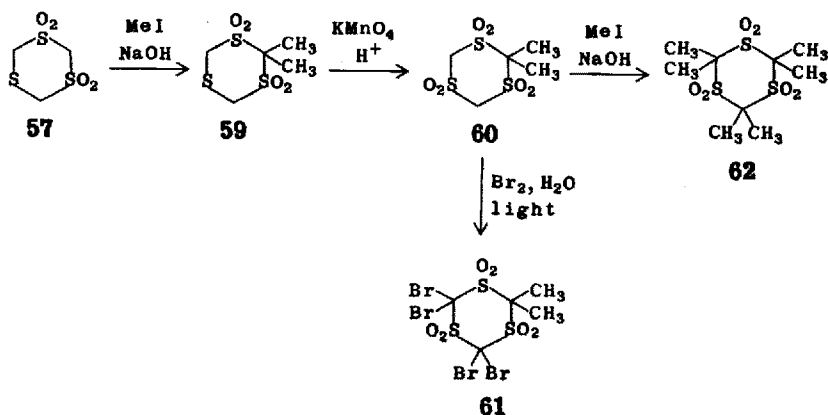
Hinsberg¹²⁴ prepared s-trithiane monosulfone (56) and disulfone (57) by oxidizing s-trithiane or its trisulfoxide with hydrogen peroxide and reducing the mixture of sulfones and sulfoxides with hydrogen iodide.



Camps^{53,54} had previously prepared the disulfone (57) by oxidizing s-trithiane with acidic potassium permanganate and separating it from the trisulfone (58) formed concurrently by the difference in solubility of their potassium salts, the trisulfone being insoluble.

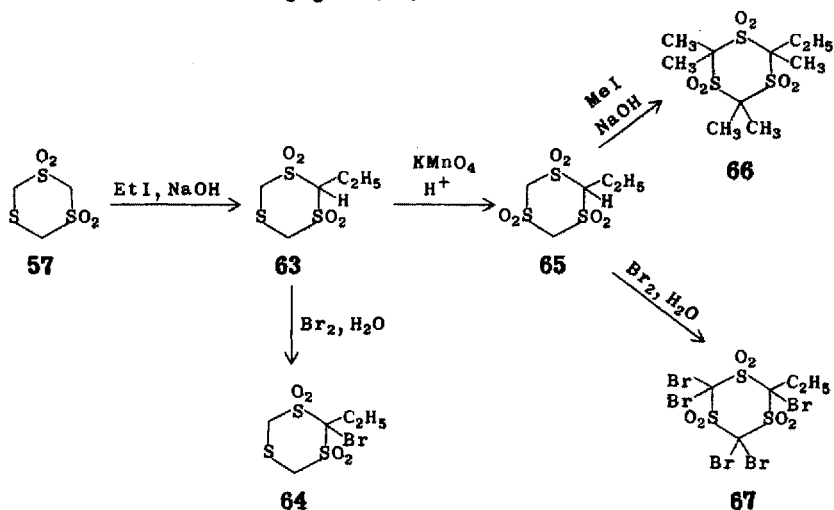


The disulfone was soluble in hot water and had no sharp melting point. It was soluble in dilute sodium hydroxide, sodium carbonate and ammonium hydroxide, showing that it had the acidic hydrogens expected of a disulfone, but it did not form stable salts. It decomposed slowly in hot caustic and rapidly in concentrated sulfuric acid. Potassium permanganate slowly oxidized it to the trisulfone. According to Gibson¹⁰⁴ treatment of the disulfone with dimethyl sulfate gives the 2-methyl derivative. However, no properties of this compound were given. Bromination below 50° gave a tetrabromide of undetermined structure. Camps⁵⁴ found that in the presence of sodium hydroxide methyl iodide gives a dimethyl derivative rapidly. The product (**59**) was now insoluble in alkali, showing the absence of acidic hydrogens, and it gave the reactions expected of 2, 2-dimethyl-*s*-trithiane 1, 1, 3, 3-tetroxide. Thus, oxidation yielded 2, 2-dimethyl-*s*-trithiane trisulfone (**60**), which had the expected properties, being soluble in dilute base and stable in hot sodium hydroxide solution. Bromination of **60** gave 2, 2-dimethyl-4, 4, 6, 6-tetrabromo-*s*-trithiane trisulfone (**61**). The tetrabromide lost bromine readily and oxidized ethanol to acetaldehyde. Methylation of **60** gave 2, 2, 4, 4, 6, 6-hexamethyl-*s*-trithiane trisulfone (**62**), identical with the compound formed by oxidizing trithioacetone.

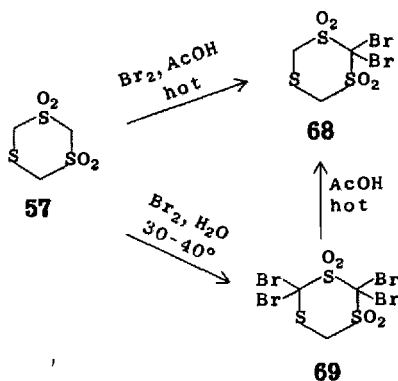


In contrast to methyl iodide, the reaction of **57** with ethyl iodide gave only a monoethyl derivative, presumably 2-ethyl-*s*-trithiane 1, 1, 3, 3-tetroxide (**63**). Since this still contained an active hydrogen, it was soluble in dilute sodium hydroxide and it reacted with bromine to give presumably 2-bromo-2-ethyl-*s*-trithiane 1, 1, 3, 3-tetroxide (**64**). The monoethyl compound (**63**) was also oxidized to 2-ethyl-*s*-trithiane trisulfone (**65**), which was methylated to 2-ethyl-2, 4, 4, 6, 6-pentamethyl-*s*-trithiane trisulfone (**66**) and brominated to 2-ethyl-2, 4, 4, 6, 6-penta-bromo-*s*-trithiane trisulfone (**67**).

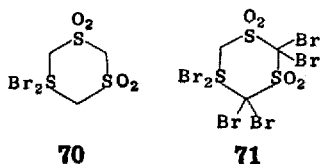
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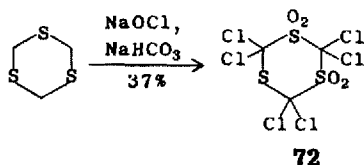
Some question exists as to the structure of the bromination products of the disulfone (**57**). Camps considered that they contain carbon-bromine bonds, the dibromide being 2,2-dibromo-*s*-trithiane 1,1,3,3-tetroxide (**68**) and the hexabromide being 2,2,4,4,6,6-hexabromo-*s*-trithiane 1,1,3,3-tetroxide (**69**).



Peters,¹⁸¹ however, showed that two bromines are readily removed from both compounds by treatment with potassium iodide, whereas 2,2,4,4,6,6-hexabromo-*s*-trithiane trisulfone is inert to this reagent. He therefore formulated these compounds as containing sulfur-bromine bonds, 5,5-dibromo-*s*-trithiane 1,1,3,3-tetroxide (**70**) and 2,2,4,4,5,5-hexabromo-*s*-trithiane 1,1,3,3-tetroxide (**71**).



It is difficult to see why heating the hexabromide should liberate the more stable bromines and it is apparent that additional evidence is needed. In more recent work Farrar⁸¹ prepared the analogous hexachloride from *s*-trithiane and sodium hypochlorite, which he formulated as 2, 2, 4, 4, 6, 6-hexachloro-*s*-trithiane 1, 1, 3, 3-tetroxide (**72**).

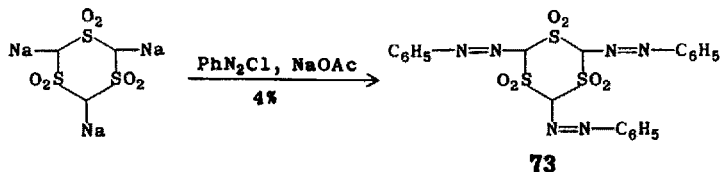


s-Trithiane trisulfone was first prepared by permanganate oxidation by Baumann and Camps¹⁴ and investigated more thoroughly by Camps.⁵³ The compound has no sharp melting point and is quite insoluble in water and in organic solvents. It is unaffected by concentrated sulfuric acid and by hot sodium hydroxide solution, in both of which it is soluble. By virtue of its six acidic hydrogens it is also soluble in dilute sodium carbonate and warm ammonium hydroxide. Unlike the disulfone it forms stable salts by replacement of one hydrogen, the sodium, potassium, lithium, barium, and silver salts having been prepared. Treatment of the sodium salt with methyl or ethyl iodide did not lead to the expected monoalkyl derivatives. The trisulfone was alkylated, however, rapidly and quantitatively to the hexamethyl derivative by treating a solution of the trisulfone in sodium hydroxide with methyl iodide. The product was identical with that obtained by the permanganate oxidation of 2, 2, 4, 4, 6, 6-hexamethyl-*s*-trithiane. Ethylation was much more difficult, the trisulfone of 2, 2, 4, 4, 6, 6-hexaethyl-*s*-trithiane being obtained only in low yield. There was also isolated an alkali-soluble tetraethyl compound, probably the 2, 2, 4, 6-derivative. *n*-Propyl iodide gave a dipropyl derivative, probably the 2, 4-substituted compound, while longer heating gave the completely substituted hexa-*n*-propyl derivative. Benzyl chloride reacted as rapidly as did methyl iodide, but the reaction stopped at the tetrabenzyl stage. The compound, perhaps the trisulfone of 2, 2, 4, 6-tetrabenzyl-*s*-trithiane, was insoluble in alkali.

According to the patent literature^{76,79,216} treatment of the trisulfone of *s*-trithiane with allyl chloride or bromide can give substituted allyl derivatives containing one to six allyl groups, while one to three methallyl groups can be introduced. Similarly, the trisulfone can be cyanoethylated^{77,135} and yields cross-linked resins with formaldehyde in the presence of base.^{80,194,195} Runge, El-Hewehei, and Hempel¹⁹⁹ have confirmed the formation of an insoluble resin in the reaction of the trisulfone with formaldehyde and sodium hydroxide; analysis indicated that the trithiane rings are linked by methylene bridges. Two laboratories^{189a,1} have claimed that resins can be prepared by treating *s*-trithiane disulfone or trisulfone with tris(1-aziridinyl)phosphine sulfides or oxides in the presence of caustic; the resins can be insolubilized by heat.

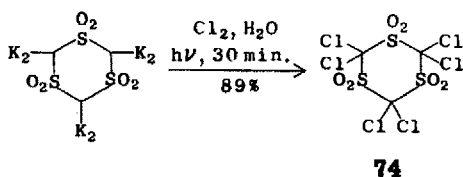
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These reactions are all based on the acidity of *s*-trithiane trisulfone. Peters¹⁸¹ and Reychler^{194,195} reported that the trisulfone is only a weak acid, excess base being required to keep it in solution. Hinsberg¹²¹ claimed that it did not react with benzaldehyde or with phenyldiazonium chloride, although Runge, El-Hewehei, and Hempel¹⁹⁹ succeeded in isolating a low yield of 2, 4, 6-tris(phenylazo)-*s*-trithiane trisulfone (**73**) from the latter reaction.



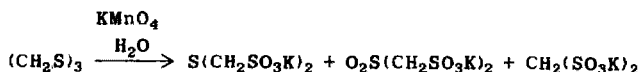
Arndt and Martius² have shown, however, that *s*-trithiane trisulfone is more acidic than a simple alkyl disulfone, (RSO₂)₂CH₂, since it reacted with diazomethane to yield 2, 2, 4, 4, 6, 6-hexamethyl-*s*-trithiane trisulfone, whereas the latter was unreactive. The finding of Hepworth and Clapham¹²⁰ that *s*-trithiane trisulfone gave no gas evolution with methylmagnesium iodide is undoubtedly a reflection of its insolubility in the reaction medium rather than its lack of acidity.

Camps⁵³ found that chlorine reacts with an aqueous suspension of *s*-trithiane trisulfone to give 2, 2, 4, 4, 6, 6-hexachloro-*s*-trithiane trisulfone (**74**). Runge, El-Hewehei, and Hempel¹⁹⁹ improved the synthesis by photochemically chlorinating the hexapotassium salt.



The same product was obtained by Farrar⁸¹ with sodium hypochlorite buffered with sodium bicarbonate. Bromine reacted similarly, but iodine was inert. The compounds were decomposed by base and oxidized ethanol to acetaldehyde.⁵³

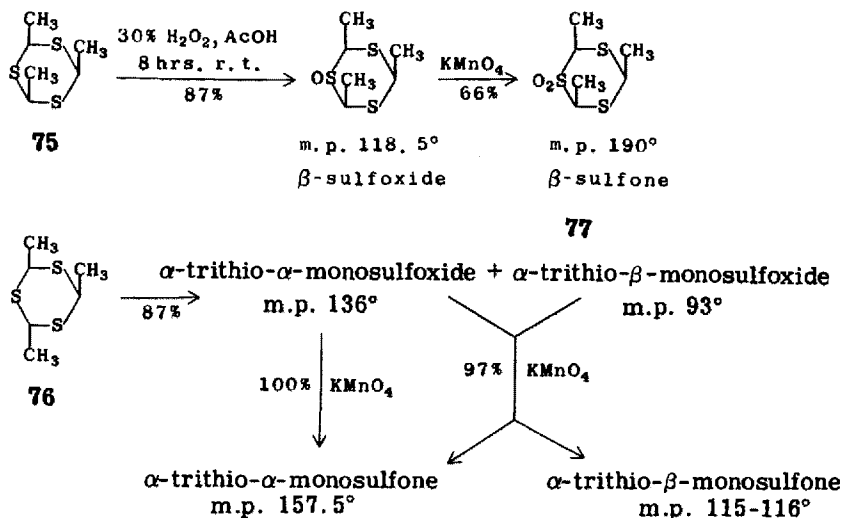
According to Husson¹³⁹ permanganate in the absence of acid cleaves the *s*-trithiane ring.



The number of possible sulfoxides and sulfones of 2, 4, 6-trimethyl-*s*-trithiane is much larger than for *s*-trithiane itself. Thus, the *cis* isomer can have two monosulfoxides and the *trans* isomer four. Chattaway and Kellett⁵⁹ managed to isolate two monosulfoxides from the α -isomer (**76**) and one from the β -isomer (**75**). Each sulfoxide yielded a different sulfone, thus proving that the α -isomer has the *trans* configur-

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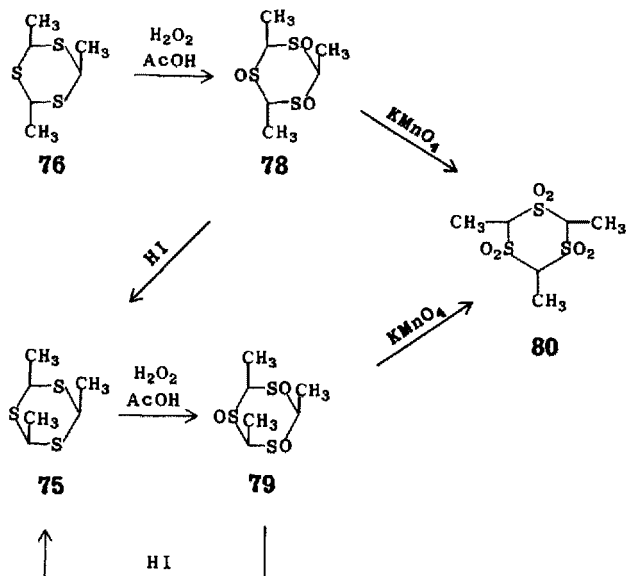
ation and the β -isomer the *cis*. The relationship among the isomers is shown by the following set of reactions:



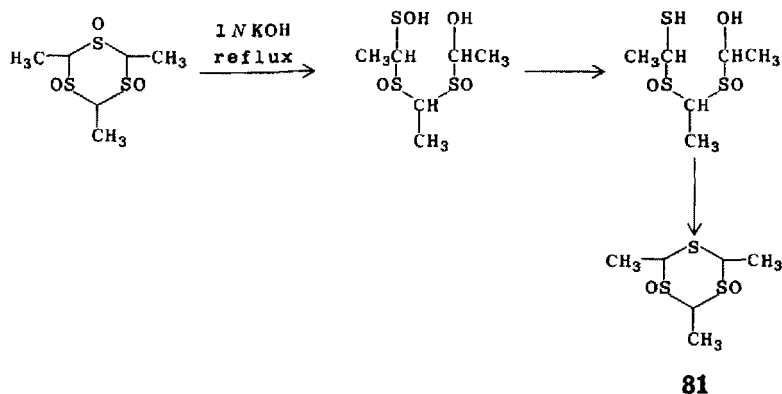
The three monosulfoxides lowered the melting points of each other. Reduction with zinc and hydrochloric acid in each case regenerated the parent *s*-trithiane, indicating no rearrangement during formation of the monosulfoxide. The dioxides could not be reduced and were not interconverted with hydrogen iodide, iodine, or acetyl chloride. Only the β -sulfone (**77**) can be assigned a definite configuration.

Fromm and Engler⁹⁷ claimed to have isolated two different trisulfoxides, one melting at 184° (**78**) from α -2, 4, 6-trimethyl-*s*-trithiane (**76**) and one melting at 153° (**79**) from β -2, 4, 6-trimethyl-*s*-trithiane (**75**), by oxidizing the *s*-trithianes with hydrogen peroxide in acetic acid. It is most surprising, considering the possible number of isomers, that pure compounds could be isolated. That they were both trisulfoxides was shown by the fact that both were reduced to β -2, 4, 6-trimethyl-*s*-trithiane (**75**) with hydrogen iodide. This was not unexpected, since hydrogen iodide is known to isomerize the α -isomer to the β . Both trisulfoxides were oxidized by potassium permanganate to the same trisulfone (**80**). This too was expected, since, as will be described below, only one 2, 4, 6-trimethyl-*s*-trithiane trisulfone has ever been isolated.

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The instability of cyclic sulfoxides to base has already been mentioned. Fromm and Engler⁹⁷ claimed that treating either of the two tri-sulfoxides (78 or 79) with base yields a disulfide, 2, 4, 6-trimethyl-*s*-trithiane 1, 3-dioxide (81), according to the following scheme:

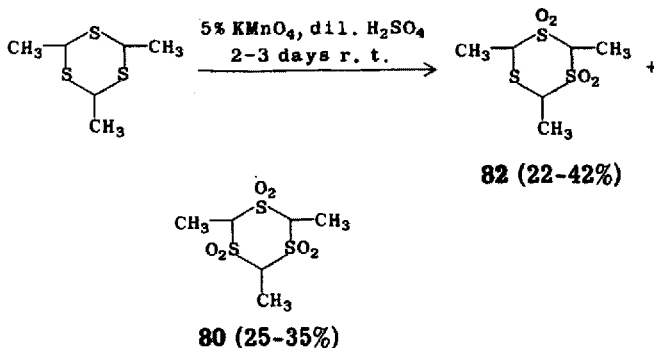


The disulfide was reduced with hydrogen iodide to β-2, 4, 6-trimethyl-*s*-trithiane and oxidized to the known trisulfone (80), indicating the correctness of the assigned structure. Sulfenic acids are known to form mercaptans by oxidation-reduction, and displacement of hydroxide ion by mercaptide ion to regenerate the trithiane ring is not too unreasonable.

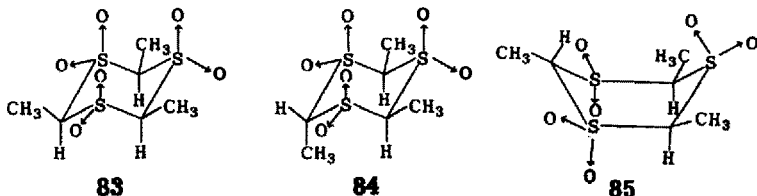
2, 4, 6-Trimethyl-*s*-trithiane was first oxidized with permanganate by Guareschi.¹⁰⁹ However, his starting material was so impure that his

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compounds were undoubtedly mixtures. Baumann and Fromm¹² and Baumann²² showed that oxidation with potassium permanganate and sulfuric acid gave a mixture of disulfone (**82**) and trisulfone (**80**), the same compounds being formed from either isomer. This was confirmed by Lomnitz.¹⁶¹



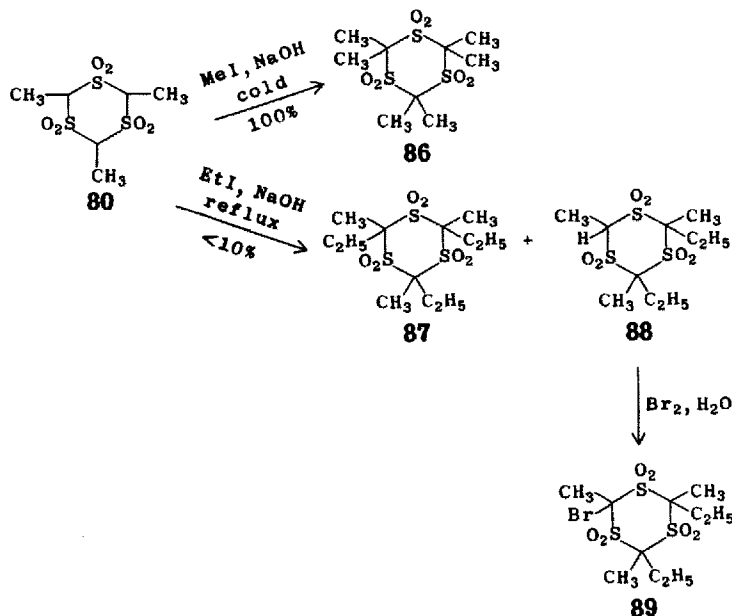
The two compounds were separated by treatment with dilute alkali, the trisulfone being soluble and the disulfone insoluble. That isomerization did not precede oxidation was shown by isolating unisomerized starting material from the oxidation. Roberts and Cheng¹⁹⁸ have shown, using 1,3-dithiolanes as model compounds, that the isomerization is a result of the acidity of the hydrogens located between two sulfone groups (see Chapter 5, section II A-1b). An inspection of models indicates that the most stable isomer should be the *cis* isomer (**83**) with the ring in the chair form and the methyl groups equatorial. The *trans* isomer (**84**) with one axial methyl group shows greater steric hindrance, while the boat form (**85**) is unlikely because of interaction between the sulfone oxygen and the hydrogen on the carbon in the 4-position.



Little is known about the disulfone (**82**). It contains an acidic hydrogen and therefore dissolves in hot sodium hydroxide; however, it does not form crystalline salts. It can be oxidized to the trisulfone (**80**) with acid permanganate and is destroyed by fuming nitric acid. The trisulfone was investigated thoroughly by Lomnitz.¹⁶¹ It has no sharp melting point. It is soluble in cold sodium hydroxide and ammonium hydroxide and in warm sodium carbonate. A number of salts were isolated in which one hydrogen was displaced by sodium, potassium, barium, strontium, and silver; the same salts were isolated from the trisulfone prepared from either α - or β -2, 4, 6-trimethyl-*s*-trithiane. The trisulfone could be recovered unchanged from solution in concentrated sulfuric or

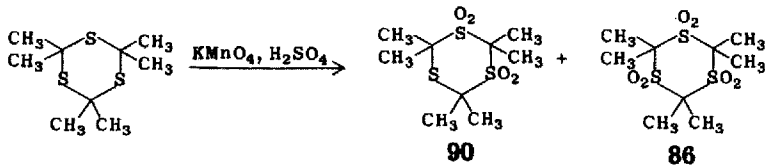
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nitric acids. Alkylation took place rapidly and quantitatively with methyl iodide in the presence of sodium hydroxide, the hexamethyl compound (86) being identical with that formed by the oxidation of 2, 2, 4, 4, 6, 6-hexamethyl-*s*-trithiane. The reaction with ethyl iodide, however, was very slow and incomplete, a mixture 2, 4-diethyl-2, 4, 6-trimethyl-*s*-trithiane trisulfone (88) and 2, 4, 6-triethyl-2, 4, 6-trimethyl-*s*-trithiane trisulfone (87) being isolated. The compounds had the expected properties. The triethyl compound (87) was insoluble in hot alkali and the diethyl compound (88) was soluble, crystalline sodium and potassium salts being isolated. The diethyl compound reacted with bromine to give 6-bromo-2, 4-diethyl-2, 4, 6-trimethyl-*s*-trithiane trisulfone (89), unstable to alkali. Allyl bromide reacted slowly and benzyl chloride and *o*-xylyl bromide rapidly with 2, 4, 6-trimethyl-*s*-trithiane trisulfone (80), all giving complete substitution. The aromatic derivatives could be nitrated, the benzyl compound to a trinitro derivative and the *o*-xylyl compound to a hexanitro derivative. Chlorination and bromination of the trisulfone (80) took place readily in aqueous solution; the trihalides formed were relatively unstable, decomposing in the presence of base and oxidizing ethanol to acetaldehyde. It is quite surprising that never more than one isomer has been reported for these compounds, in spite of the fact that more than one isomer is possible. However, in most cases yields were not reported, and it is quite possible that other isomers were present but were not isolated.

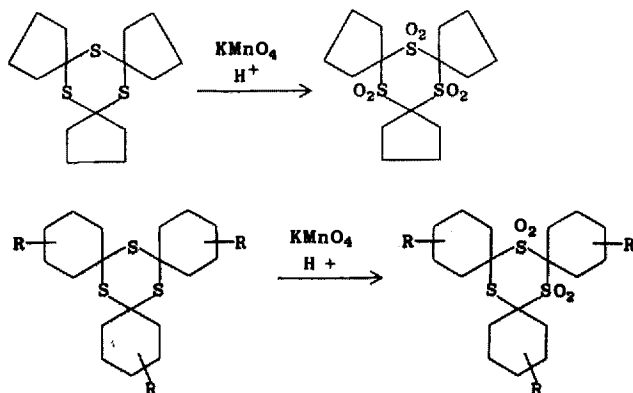


Very few oxidation products from the direct oxidation of hexasubstituted *s*-trithianes are known. Baumann and Fromm¹¹ oxidized 2, 2, 4, 4, 6, 6-hexamethyl-*s*-trithiane to a mixture of disulfone (90) and trisulfone (86).

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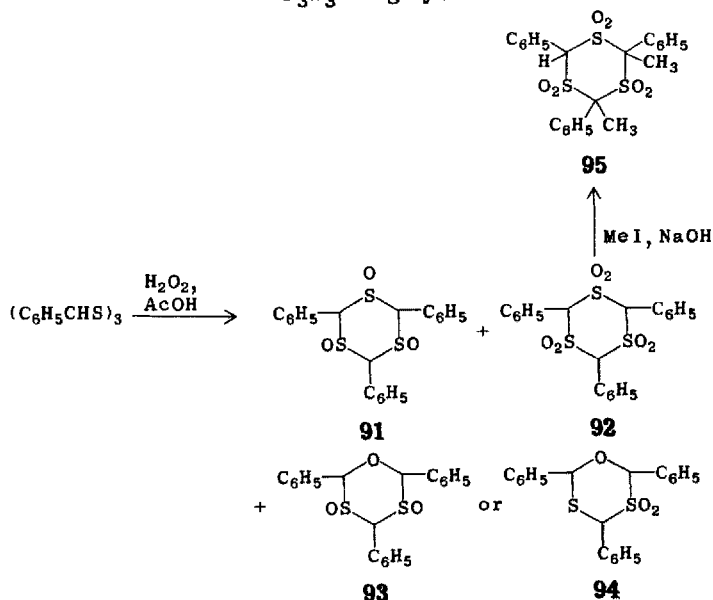


Fromm⁹⁸ oxidized the *s*-trithiane derived from cyclopentanone to a trisulfone, while those derived from cyclohexanone, 3-methylcyclohexanone and 4-methylcyclohexanone yielded only disulfones.



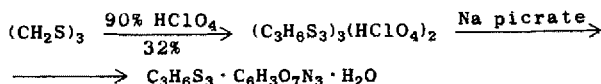
2, 4, 6-Triaryl-*s*-trithianes are less stable to oxidation than the corresponding alkyl derivatives and fewer compounds are known. Hinsberg^{123,126} claimed that oxidation of α -2, 4, 6-triphenyl-*s*-trithiane with hydrogen peroxide in acetic acid yielded a sulfoxide-disulfone, while the β -isomer gave a disulfoxide-sulfone. Both compounds yielded the same trisulfone with permanganate, and both were reduced with hydrogen iodide to the β -*s*-trithiane. Since it is most unusual for sulfones to be reduced to sulfides with hydrogen iodide, the statement by Fromm and Schultis⁹⁵ that Hinsberg's compounds were mixtures is probably correct. According to the latter authors both α - and β -2, 4, 6-triphenyl-*s*-trithiane are oxidized to the same mixture of 2, 4, 6-triphenyl-*s*-trithiane trisulfoxide (**91**), 2, 4, 6-triphenyl-*s*-trithiane trisulfone (**92**), and either 2, 4, 6-triphenyl-1, 3, 5-oxadithiane 3, 5-dioxide (**93**) or 3, 3-dioxide (**94**). The trisulfoxide (**91**) was reduced with hydrogen iodide to β -2, 4, 6-triphenyl-*s*-trithiane. However, its reported stability to aqueous sodium hydroxide is unusual, sulfoxides being generally unstable to base in the trithiane series. The trisulfone (**92**) had the expected properties, being soluble in sodium hydroxide, forming insoluble sodium, potassium, and pyridinium salts, and being alkylated by methyl iodide to 2, 4-dimethyl-2, 4, 6-triphenyl-*s*-trithiane trisulfone (**95**). The dimethyl derivative, as expected, was soluble in base.

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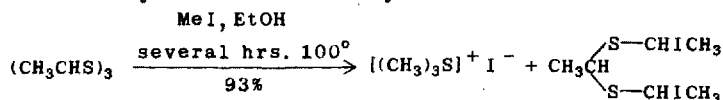
f. Miscellaneous Reactions

Hinsberg^{128,130} claimed that *s*-trithiane forms a perchlorate salt which melts at 138° (dec.) and a picrate salt which decomposes at 134°.



Hinsberg believed this to be a new form of *s*-trithiane stable only as its salt and postulated a complicated relationship among the compounds formed on oxidation with hydrogen peroxide. As the sulfoxides and sulfones of *s*-trithiane generally decompose without having sharp melting points, there is a good possibility that Hinsberg's compounds were mixtures and little credence can be given to this work without further verification.

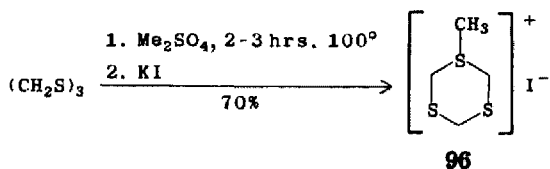
As early as 1877 Klinger¹⁴⁵ showed that 2, 4, 6-trimethyl-*s*-trithiane reacts with methyl iodide to form trimethylsulfonium iodide. He postulated that only one sulfur was alkylated.



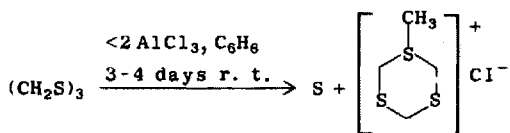
The by-product was not isolated. Reyckler¹⁹⁴ isolated trimethylsulfonium iodide by carrying out the same reaction with *s*-trithiane in methanol, but claimed that all the sulfurs react to yield the iodide and methylal. More recently Selker²¹⁰ used the slowness of this reaction at room temperature as proof that sulfur-vulcanized rubber does not contain any *s*-trithiane rings.

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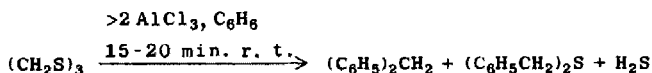
Lee and Dougherty¹⁵⁶ isolated the primary alkylation product of *s*-trithiane, 1-methyl-*s*-trithianium iodide (**96**), by reacting it with dimethyl sulfate.



The sulfonium compound formed a picrate, m.p. 135-137°. The same product was obtained when *s*-trithiane in benzene was treated with less than two moles of aluminium chloride.

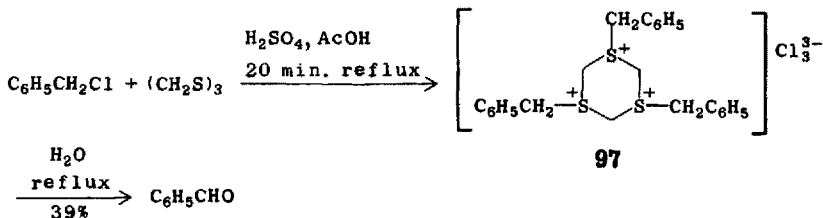


Treatment with potassium iodide gave a 50-60% yield of product identical with that obtained by direct alkylation. With greater than two moles of aluminum chloride the reaction took a different course, yielding diphenylmethane, dibenzyl sulfide, and hydrogen sulfide.



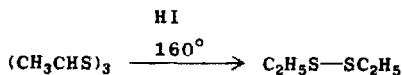
The authors took this as evidence for the formation of a complex, $\text{C}_3\text{H}_6\text{S}_3 \cdot 2 \text{ AlCl}_3$.

An unusual reaction which perhaps involves alkylation of *s*-trithiane was described by Horák and Gerovová.¹³⁶ Benzyl chloride reacted with *s*-trithiane gave benzaldehyde after hydrolysis; the authors postulated the intermediate formation of 1, 3, 5-tribenzyl-*s*-trithianium trichloride (**97**).



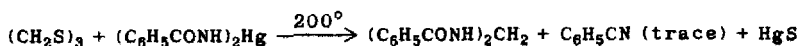
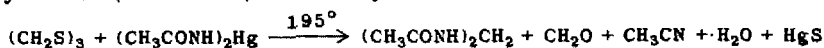
This would be the sulfur equivalent of the Sommelet reaction.

Böttinger³⁴ claimed that heating 2, 4, 6-trimethyl-*s*-trithiane with hydrogen iodide forms diethyl disulfide.

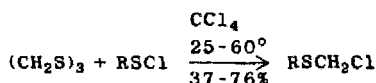


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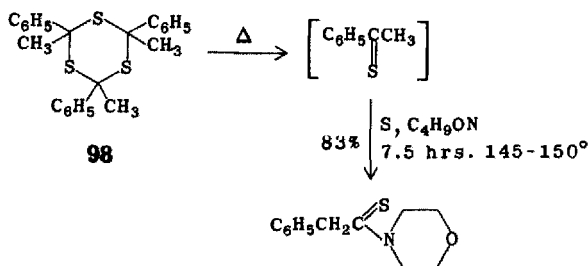
According to Pulvermacher¹⁸⁷ long refluxing of *s*-trithiane with aqueous mercuric oxide gives mercuric sulfide and formaldehyde. On this basis he used *s*-trithiane as a source of formaldehyde to prepare methylene bis(acetamide) and methylene bis(benzamide).



Birum^{30,30a} claimed that *s*-trithiane reacts with sulfenyl chlorides to give 1:1, 2:1, and 3:1 adducts as viscous, high-boiling oils, but offered no suggestions as to structure. According to Petrov and Sokol'skiĭ,¹⁸² however, *s*-trithiane reacts vigorously with sulfenyl chlorides to give alkyl chloromethyl sulfides.



Campaigne and Rutan⁴⁸ used 2, 4, 6-triphenyl-2, 4, 6-trimethyl-*s*-trithiane (**98**) as a source of monomeric thioacetophenone in order to prove that this is an intermediate in the Willgerodt reaction.



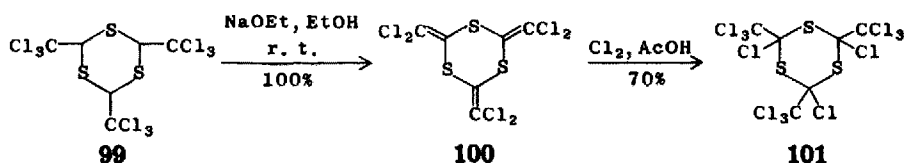
Acetophenone under the same conditions gave only a 72% yield.

g. Methylene Derivatives

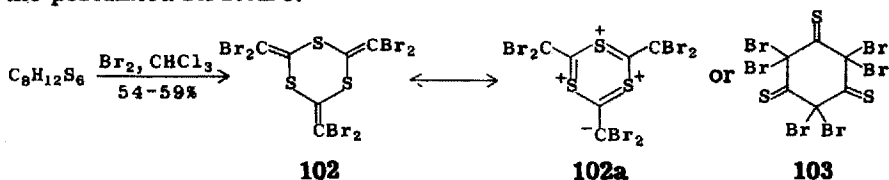
A number of methylene derivatives of *s*-trithiane have been reported; these are listed in Table 7 (page 757).

Chattaway and Kellett⁵⁸ investigated the chemistry of 2, 4, 6-tris(trichloromethyl)-*s*-trithiane (**99**) formed from chloral. As already mentioned only one of the two possible isomers was isolated. It was stable to hydrogen peroxide and completely disrupted by potassium permanganate. Basic reagents—alcoholic sodium ethoxide, potassium acetate or ammonia, as well as hydrated manganese dioxide—eliminated three molecules of hydrogen chloride rapidly and quantitatively, yielding 2, 4, 6-tris(dichloromethylene)-*s*-trithiane (**100**). Chlorination gave the expected 2, 4, 6-trichloro-2, 4, 6-tris(trichloromethyl)-*s*-trithiane (**101**), melting at 175° with decomposition; again only one isomer was isolated.

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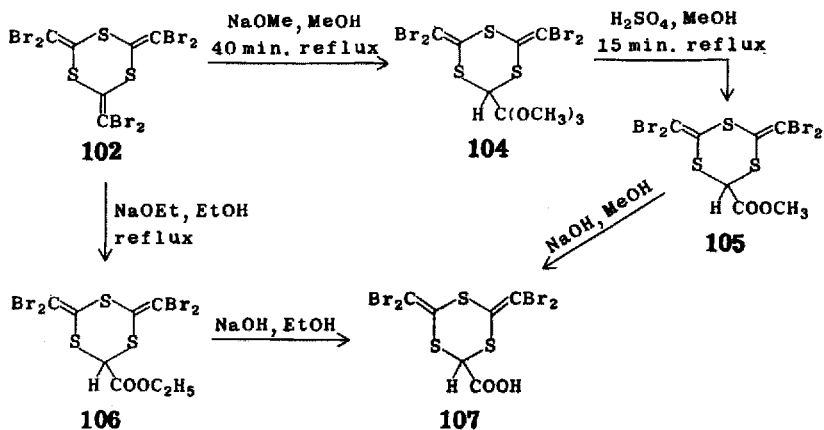


In an attempt to elucidate the structure of tetraethenyl hexasulfide or 1, 3, 5, 7-tetramethyl-2, 4, 6, 8, 9, 10-hexathiaadamantane (see section II B), Fromm and Mangler⁹² brominated the compound and isolated a hexabromotrissulfide, $\text{C}_6\text{H}_2\text{Br}_6\text{S}_3$, as a crystalline compound. They prepared a number of derivatives, but were unable to propose rational structures. More recently, Mecke and Spiesecke¹⁷¹ investigated the structure of this compound. They found the correct analysis to be $\text{C}_6\text{Br}_6\text{S}_3$ and formulated the compound as 2, 4, 6-tris(dibromomethylene)-s-trithiane (102) on the following evidence: Infrared analysis showed the presence of carbon-carbon double bonds, the absence of carbon-hydrogen bonds, and the presence of carbon-sulfur and carbon-bromine bonds. The ultraviolet spectrum was similar to that of s-trithiane, with weak maxima at 304 and 275 $\text{m}\mu$, and indicated a quasi-aromatic structure for the compound, although from the infrared spectrum they could not decide whether the molecule is staggered or has the planar configuration required for the quasi-aromatic structure (102a). The isomeric structure, 2, 2, 4, 4, 6, 6-hexabromo-1, 3, 5-cyclohexanetrithione (103), was ruled out because of the lack of color and the absence of carbon-sulfur double bonds in the infrared spectrum. The spectra of several derivatives prepared by Fromm and Mangler were in agreement with the postulated structure.

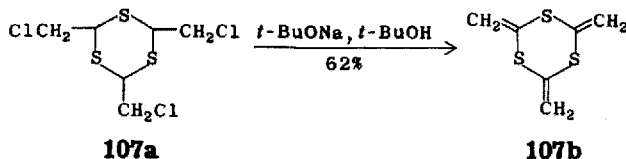


The other compounds reported by Fromm and Mangler are readily formulated if this assignment is correct. Thus, treatment of the tris(dibromomethylene) compound (102) with sodium methoxide gave an ortho ester (104), which was converted with sulfuric acid in methanol to the methyl ester (105). Sodium ethoxide gave the ethyl ester (106) with no indication of the formation of an ortho ester. Both esters yielded the acid (107) on alkaline saponification. The one unresolved question is the reason for the lack of reactivity of the other two dibromomethylene groups.

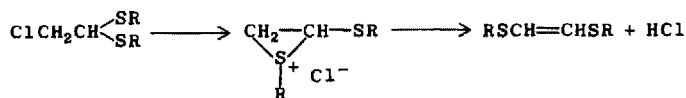
C₃S₃ Ring Systems



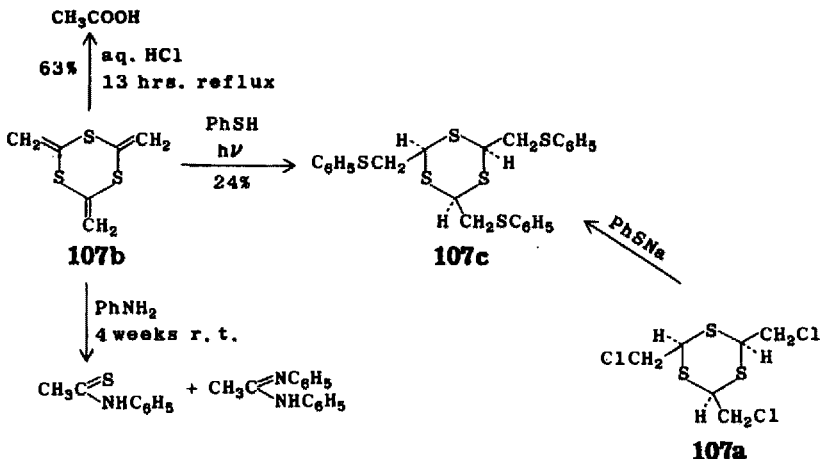
Matlack, Chien, and Breslow^{168a} prepared the parent member of this class of compounds, 2, 4, 6-tris(methylene)-s-trithiane (**107b**), by dehydrohalogenation of *cis*- or *trans*-2, 4, 6-tris(chloromethyl)-s-trithiane (**107a**).



Reaction of **107a** with other nucleophilic reagents, trimethylamine and sodium 3, 5-dinitrobenzoate, indicated that dehydrohalogenation is more difficult than with 2, 4, 6-tris(trichloromethyl)-s-trithiane (**99**),⁵⁸ presumably because of the lower acidity of the ring hydrogens. **107a** was also more stable than simple α -halomercaptals, which are reported to eliminate hydrogen chloride spontaneously with rearrangement.^{180b}

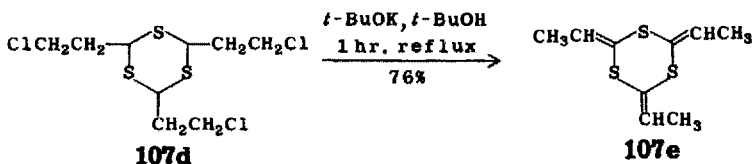


The structure of 2, 4, 6-tris(methylene)-s-trithiane (**107b**) was assigned on the following grounds. The infrared spectrum showed the presence of exocyclic double bonds, as well as possessing several bands also present in the spectrum of 1, 1-bis(ethylthio)ethene.^{226a} A band at 240-244 μ in the ultraviolet is attributable to an s-trithiane structure.^{82a} Reaction of the tris(methylene) compound with thiophenol in the presence of light yielded *cis*-2, 4, 6-tris(phenylthiomethyl)-s-trithiane (**107c**), identical with the compound prepared from *cis*-2, 4, 6-tris(chloromethyl)-s-trithiane (**107a**) and sodium thiophenoxide. Acid hydrolysis of the tris(methylene) compound gave acetic acid, while aniline yielded thioacetanilide and *N, N'*-diphenylacetamidine. According to Arens and co-workers^{197b, 226a} 1, 1-bis(ethylthio)ethene yields the same products.

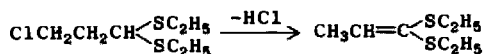


2, 4, 6-Tris(methylene)-s-trithiane (**107b**), the cyclic trimer of the unknown thioketene, was isolated as an unstable yellow oil. It polymerized on standing, even at -40° , and copolymerized with styrene in the presence of a free radical catalyst to yield an insoluble, cross-linked polymer.

Matlack, Chien, and Breslow^{168a} also prepared 2, 4, 6-triethylidene-*s*-trithiane (**107e**) by the dehydrohalogenation of 2, 4, 6-tris(2-chloroethyl)-*s*-trithiane (**107d**).



The triethylidene structure, rather than the expected trivinyl structure, was assigned to **107e** on the basis of a strong $7.28\ \mu$ band in the infrared spectrum attributable to a methyl group. Rothstein^{198a} has reported that 3-chloro-1, 1-bis(ethylthio)propane reacts analogously, giving 1, 1-bis(ethylthio)-1-propene instead of the 2-propene:



4. Uses

It is quite surprising that apparently no large-scale commercial uses have evolved for these relatively inexpensive and readily obtainable compounds.

Allylated *s*-trithiane trisulfone sets to an insoluble film on heating and its use as a stoving varnish has been patented.⁷⁸ Penta- and hexallyl-*s*-trithiane trisulfones yield thermosetting plastics either alone or with other monomers such as glycol maleate.²¹⁶ The reaction product of *s*-

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trithiane trisulfone with formaldehyde in the presence of base sets to an insoluble film on heating; the film is reported to be tough, flexible, and alkali-resistant.⁸⁰ Two patents^{1,189a} claim that the resins obtained by condensing tris(1-aziridinyl)phosphine oxides or sulfides with *s*-trithiane disulfone or trisulfone are useful flame-proofing agents for textiles. The use of *s*-trithiane as a regulator of molecular weight in the polymerization of vinyl chloride has been patented,²¹⁵ as has the use of 2, 4, 6-trimethyl-*s*-trithiane as a solvent or plasticizer for polyvinyl chloride.²⁰⁰

The reaction product formed by heating a trithioketone, such as hexamethyl-*s*-trithiane, with an arylamine is reported to be an oxidation inhibitor for hydrocarbons.¹¹⁸ *s*-Trithiane is claimed to be a corrosion inhibitor for the acid pickling of metals.²⁰⁹ It is also reported to decrease carbon formation during the pyrolysis of acetone to ketene in stainless steel tubes.¹¹⁹ *s*-Trithiane is reported to be an antioxidant for vitamin A,^{142b} as well as for transformer and turbine oils.⁹⁹ 2, 2, 4, 4, 6, 6-Hexamethyl-*s*-trithiane is claimed to have use as an extreme pressure lubricant additive,^{160a} while *s*-trithiane is reported to be a vulcanization accelerator.⁴³

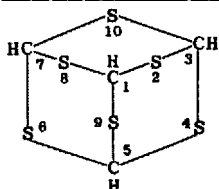
Trithiocyclohexanone, 2, 4, 6-trimethyl-2, 4, 6-triethyl-*s*-trithiane, and hexaethyl-*s*-trithiane are reported to have therapeutic properties.¹⁵⁹ 2, 4, 6-Tris(*p*-dimethylaminophenyl)-*s*-trithiane is ineffective against avian malaria.²⁴ *s*-Trithiane, when admixed with nicotine sulfate, is

TABLE 7. Methylene Derivatives of *s*-Trithianes

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	B.p. (mm)	Ref.
2, 4, 6-(CH ₂ =) ₃	62		73-74	0. 25	168a
2, 4, 6-(Cl ₂ C=) ₃	100	126			58
2, 4, 6-(Br ₂ C=) ₃	54-59	needles			92, 171
2, 4-(Br ₂ C=) ₂ -6-[(CH ₃ O) ₃ C-]		125-126			92, 171
2, 4-(Br ₂ C=) ₂ -6-CO ₂ CH ₃		146-147			92, 171
2, 4-(Br ₂ C=) ₂ -6-CO ₂ C ₂ H ₅		115-116			92
2, 4-(Br ₂ C=) ₂ -6-CO ₂ H		162			92
2, 4-(Br ₂ C=) ₂ -6-CO ₂ NH ₄		193-194			92
2, 4, 6-(CH ₃ CH=) ₃	76		109	0. 15	168a

toxic to southern army worms.¹⁶⁹ 2, 4, 6-Tris(*o*-hydroxyphenyl)-*s*-trithiane and its chlorinated derivatives are reported to have fungicidal and insecticidal action.²⁰¹ The insecticidal action of a number of other *s*-trithiane derivatives has been investigated.¹⁸⁵ According to Runge, El-Hewehei, and Hempel,¹⁹⁹ hexachloro-*s*-trithiane trisulfone is an excellent fungicide. Birum³⁰ claimed herbicidal, fungicidal, and insecticidal activity for the *s*-trithiane-sulfenyl chloride adducts. He also claimed similar activity for the sulfenyl chloride adducts treated with trialkyl phosphites,^{30a} for the reaction products of chlorinated *s*-trithiane with trialkyl phosphites and xanthate salts.^{30b,108a} According to Birum^{30c} the residue obtained after heating *s*-trithiane for 19 hours to 149° and distilling off volatile material has fungicidal and bactericidal activity.

B. $C_3S_3-C_3S_3-C_3S_3$ 2, 4, 6, 8, 9, 10-HEXATHIAADAMANTANE (108)

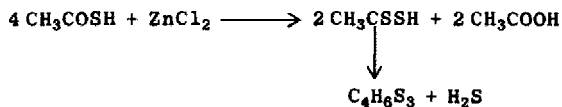


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This ring system is indexed under the above name by Chemical Abstracts, following the suggestion of Stetter,²¹⁹ who has reviewed this class of compounds. Before 1956 it was indexed as 2, 4, 6, 8, 9, 10-hexathiatricyclo[3. 3. 1. 1^{3,7}]decane. Prior to the elucidation of the structure the 1, 3, 5, 7-tetramethyl derivative was called tetraethenyl hexasulfide.

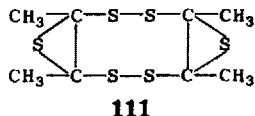
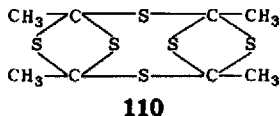
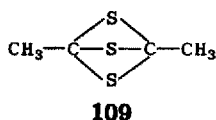
In 1886 Bongartz³⁶ treated thioacetic acid with zinc chloride and isolated a crystalline solid melting at 224-225°. He postulated that the reaction takes place as follows, in order to account for the acetic acid and hydrogen sulfide formed:



That the actual intermediate is dithioacetic acid and not thioacetic acid was indicated by Stetter and Krause,²¹⁹ who obtained an 80% yield with the former while the latter gave only a 33% yield.⁹²

The compound was volatile, extremely stable to base at temperatures as high as 200°, and could be oxidized with potassium permanganate. Bongartz postulated the unlikely structure 109. Candiani^{55,56} found that the same product is formed from thioacetic acid and bromine, the actual condensing agent being hydrogen bromide. Molecular weight determinations showed the compound to be dimeric, and he proposed two alternative structures, 110 and 111.

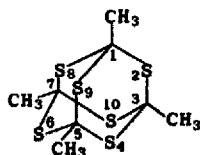
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Fromm and Mangler⁹² ruled out 111 by showing that the compound is stable to a variety of reducing agents and therefore could not contain sulfur-sulfur linkages. The compound was stable to alkyl halides and to acetic anhydride, while chlorine and bromine reacted to give compounds for which Fromm and Mangler could not write reasonable structures. Quite recently Mecke and Spiesecke¹⁷¹ showed that the bromine reaction product is 2, 4, 6-tris(dibromomethylene)-*s*-trithiane (see section II A-3g). Acid permanganate gave a disulfone, stable to chromic anhydride and to hot nitric acid, and Fromm and Mangler therefore preferred 110, since it contains two sulfurs different from the other four.

Borgeson and Wilkinson,³⁷ who were apparently unaware of the previous work, obtained the same compound by treating acetyl chloride or bromide with liquid hydrogen sulfide. They proposed that the compound is the anhydride of dithioacetic acid, (CH₃CS)₂S, and attributed the high molecular weight to association in solution.

The presently accepted formula for the compound was proposed by Fredga⁸⁸ on the basis of its chemical and crystallographic properties. He considered the molecule to consist of four six-membered *s*-trithiane rings with each sulfur common to two rings. Models show this to be a strainless configuration if the rings are in the chair form. The structure can perhaps be visualized most readily from 112.



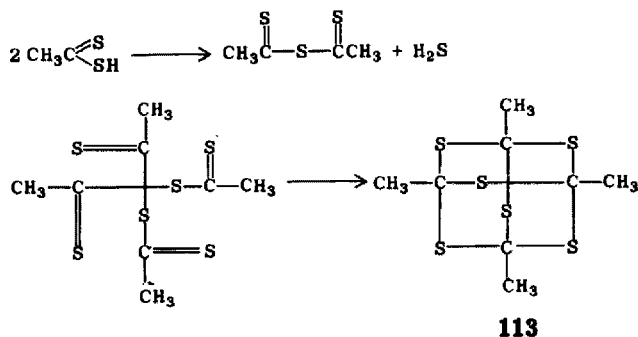
It is related in structure, therefore, to adamantane and to urotropine (or hexamethylenetetramine), and Fredga found that its ultraviolet absorption spectrum is similar to that of other molecules containing this structure. According to Hagg and Nygårdh, as quoted by Fredga,⁸⁸ its crystallographic properties are in agreement with the proposed structure, although an earlier crystallographic determination by Déverin⁶⁵ was at variance with theirs. However, the infrared and Raman spectra determined more recently by Mecke and Spiesecke^{170,216a} are in complete agreement with the assigned structure, as is the crystallographic investigation of the unsubstituted parent compound by Andersen and Lindqvist.^{1b} The unsubstituted parent compound was prepared by Fredga and Olsson⁹⁰ in low yield by reacting formic acid with hydrogen sulfide

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either in nitrobenzene with hydrogen chloride as the condensing agent or in ether with boron trifluoride.

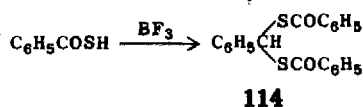
Fredga⁸⁸ attributed the lack of oxidizability past the disulfone stage to steric hindrance. An inspection of models shows that conversion of the sulfurs in the 2- and 6-positions to sulfones effectively blocks the other sulfurs from being oxidized. His assignment of a 2, 2, 6, 6-tetr-oxide structure to the disulfone is therefore reasonable.

Stetter²¹⁹ has proposed a reasonable mechanism for the formation.



113 is an equivalent projection of **112**. The carbon-sulfur double bond undoubtedly has some ionic character $\text{>}\ddot{\text{C}}-\text{S}$, and the zipping up of the ring is analogous to the formation of paraldehyde from acetaldehyde or of *s*-trithiane from thioacetaldehyde.

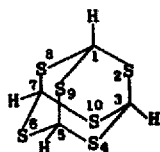
Fredga and Bauer⁸⁹ prepared a number of homologs of the parent compound. The yield decreased as the chain lengthened, and the reaction was unsuccessful with branched-chain acids. According to Bongartz³⁶ aromatic acids do not condense in the same fashion. Behringer and Grunwald²⁶ found that thiobenzoic acid yields benzylidene bis(thiobenzoate) (**114**) with acid, although 3-phenylthiopropionic acid reacts normally to give 1, 3, 5, 7-tetraphenethyl-2, 4, 6, 8, 9, 10-hexathiaadamantane.



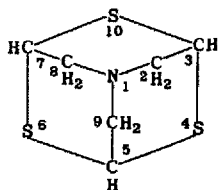
Olsson^{180,180a} prepared the only unsymmetrically substituted compounds by condensing thioacetic acid with formic acid in the presence of anhydrous zinc chloride. By varying the ratios of the two acids, he was able to isolate 2, 4, 6, 8, 9, 10-hexathiaadamantane and its 1-methyl, 1, 3-dimethyl, 1, 3, 5-trimethyl, and 1, 3, 5, 7-tetramethyl derivatives. The corresponding ethyl and *n*-propyl derivatives were prepared similarly. Both the solubility and volatility increased with increasing alkyl content. The compounds which have been reported are listed in Table 8.

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TABLE 8. 2, 4, 6, 8, 9, 10-Hexathiaadamantane Derivatives



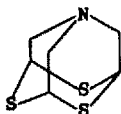
Substituents	M.p.(°C)	Ref.
None	dec. 330	90, 180, 180a
1-CH ₃ -	dec. 300	180, 180a
1-C ₂ H ₅ -	dec. 300	180a
1- <i>n</i> -C ₃ H ₇ -	dec. 300	180a
1, 3-(CH ₃ -) ₂	dec. 300	180, 180a
1, 3-(C ₂ H ₅ -) ₂	<i>ca.</i> 250(dec.)	180a
1, 3-(<i>n</i> -C ₃ H ₇ -) ₂	179-182	180a
1, 3, 5-(CH ₃ -) ₃	dec. 300	180, 180a
1, 3, 5-(C ₂ H ₅ -) ₃	209-210	180a
1, 3, 5-(<i>n</i> -C ₃ H ₇ -) ₃	198-199	180a
1, 3, 5, 7-(CH ₃ -) ₄	224-225	36, 37, 55, 56, 92, 180, 180a, 219
1, 3, 5, 7-(CH ₃ -) ₄ 2, 2, 6, 6-tetroxide	250(dec.)	92
1, 3, 5, 7-(C ₂ H ₅ -) ₄	122. 5-123. 5	89, 180a
1, 3, 5, 7-(<i>n</i> -C ₃ H ₇ -) ₄	133. 5-134. 0	89, 180a
1, 3, 5, 7-(<i>n</i> -C ₄ H ₉ -) ₄	66-67	89
1, 3, 5, 7-(<i>n</i> -C ₅ H ₁₁ -) ₄	45. 5-46. 5	89
1, 3, 5, 7-(<i>n</i> -C ₆ H ₁₃ -) ₄	79. 5-80. 5	89
1, 3, 5, 7-(<i>n</i> -C ₇ H ₁₅ -) ₄	65. 0-65. 5	89
1, 3, 5, 7-(<i>n</i> -C ₈ H ₁₇ -) ₄	44-45	89
1, 3, 5, 7-(C ₆ H ₅ CH ₂ CH ₂ -) ₄	183-183. 5	26

C. $C_3S_3-C_4NS-C_4NS$ 4, 6, 10-TRITHIA-1-AZAADAMANTANE (115)

115

(RRI 3306)

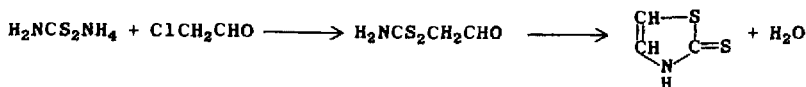
Chemical Abstracts indexed this ring system under the above name. Although they listed the compound under the ring system $C_4NS-C_4NS-C_4NS$, it may also be considered to contain an *s*-trithiane ring, as shown in formula 116.



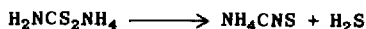
116

Craig, Shipman, Hawthorne, and Fowler,⁶² who were the first to report the compound, named it 5-aza-2, 8, 10-trithiaadamantane, or trithiotri-morpholine.

Mathes and Beber¹⁶⁸ prepared 4-thiazoline-2-thione (117) by reacting chloroacetaldehyde with excess ammonium dithiocarbamate. From the crude product Craig and co-workers⁶² isolated, by extraction with hot ethanol, a crystalline compound, $C_6H_9NS_3$, melting at 147-148°. The compound was soluble in dilute or in concentrated sulfuric acid but was insoluble in aqueous hydrochloric acid. Dry hydrogen chloride in benzene gave a water-insoluble hydrochloride, m.p. 223-225°, and a methiodide, $C_7H_{12}NS_3I$, was formed rapidly in hot methanol. The adamantane-like structure was assigned on the basis of the infrared spectrum, which showed the absence of SH, NH, C=C, C=S and C=N groups. A reasonable course for the reaction was postulated by these workers.



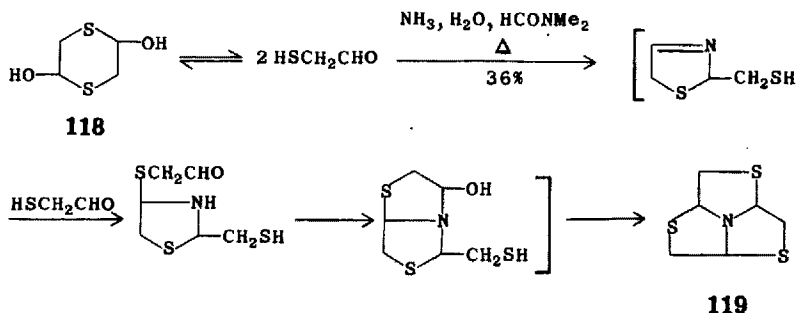
117



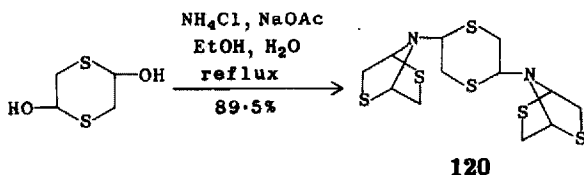
115

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Several years later Thiel, Asinger, and Schmiedel²²¹ reacted the dimer of mercaptoacetaldehyde, *p*-dithiane-2, 5-diol (**118**), with aqueous ammonia and isolated a compound with the same molecular formula and melting at 144°. To this they assigned the structure 1, 4, 7-trithia-2, 5, 8-endazacyclononane (**119**), and postulated that it formed in the following manner:



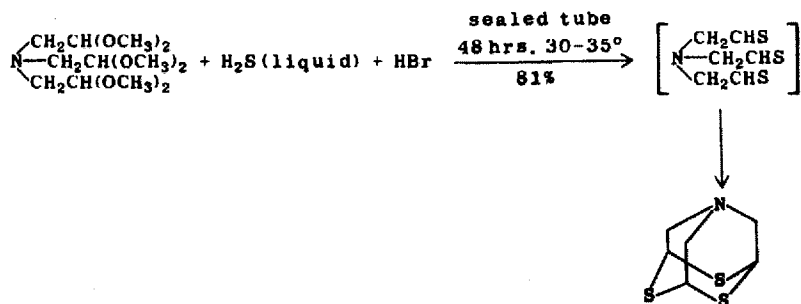
The structure of **119** was assigned on the basis of a 71% yield of triethylamine on Raney nickel desulfurization. Shortly thereafter, Asinger and Thiel³ suggested that the Craig compound (**115**) might have the same structure. However, **115** would also yield triethylamine on desulfurization. Asinger and Thiel also suggested that the reaction product, m.p. 143.5–144°, obtained by Haberl and Hromatka¹¹⁰ from mercaptoacetaldehyde dimer and ammonia under somewhat different conditions, and which Haberl and Hromatka formulated as a *p*-dithiane derivative (**120**) (see Chapter 12, section III A-1j), might be identical with and have the same structure as **119**.



In a joint paper from these two schools,^{221a} it was shown that the three compounds are identical and have the structure **119**. Repetition of the three syntheses yielded the same compound, as shown by infrared spectra, melting points and mixed melting points of the free base, the methiodide, and the hydrochloride. The *p*-dithiane formulation (**120**) was eliminated as a possibility by showing by several molecular weight determinations that the correct formula is C₆H₉NS₃ and not C₁₂H₁₈N₂S₆; abnormally high results were obtained by the Rast method used originally by Haberl and Hromatka. The adamantane structure (**115**) appeared unlikely because of the low melting points of the free base (144°), the methiodide (210° with decomposition), and the hydrochloride (223°), the highly symmetrical adamantane-like compounds having much higher melting points (see section II B). What would appear

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to be an unequivocal synthesis of 115 was carried out in the following manner:



115

The compound was isolated as a yellow, crystalline solid, which sublimed above 100° and decomposed above 285° , properties more in keeping with this structure. It yielded a methiodide, hydrochloride, hydrobromide, and picrate, all of which did not melt below 420° .

It would appear, therefore, that the Asinger structure (119) is correct for the Craig, Asinger, and Haberl and Hromatka preparations, and this has been confirmed crystallographically by Hofer and Preisinger.^{221a}

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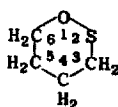
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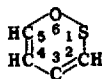
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C₄ OS RING SYSTEMSI. *o*-OXATHIA COMPOUNDSA. C₄OS *o*-OXATHIANE (1) AND *o*-OXATHIIN (2)

The following two ring systems characterize this class:



1



2

(RRI 253)

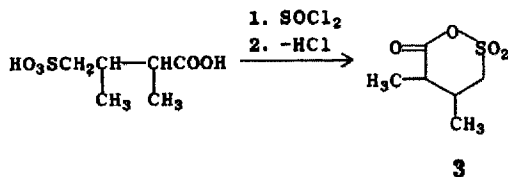
The parent compounds are not known. They are represented by their 2, 2-dioxides, or sultone forms. They are indexed by Chemical Abstracts as *δ*-sultones under the 4-hydroxy-alkane, -alkene, or -alkadiene sulfonic acid from which they might be derived or to which they would be converted by hydrolysis. The common name for *o*-oxathiane 2, 2-dioxide in the literature is 1, 4-butanedisulfone.

1. *o*-Oxathiane

a. Preparation

o-Oxathiane 2, 2-dioxide was first prepared in 1940 by Nilsson,²²³ who obtained it as an intermediate in the conversion of 4-bromobutanedisulfonic acid to the corresponding hydroxy compound.

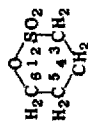
Only one study in the literature refers to the cyclic anhydride form, and this was in connection with a study on the constitution of biotin from egg yolk. In this study, 4, 5-dimethyl-6-oxo-*o*-oxathiane 2, 2-dioxide (3) was isolated as an oil on treating γ -sulfo- α , β -dimethylbutyric acid with thionyl chloride.¹⁷⁸



3

Table 1 summarizes the various *o*-oxathiane 2, 2-dioxides whose preparations have been reported in the literature. Most of the preparative

TABLE 1. 1, 2-Oxathiane 2, 2-Dioxides



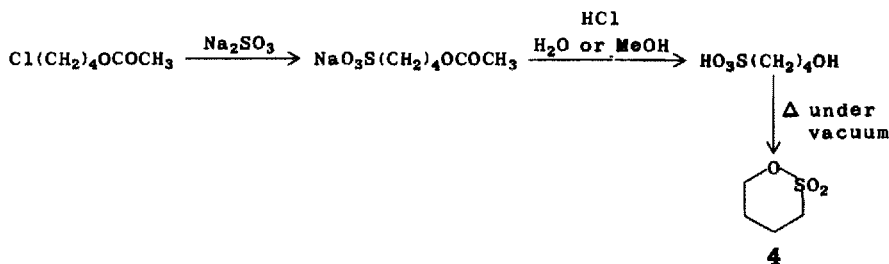
Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	B.p. (mm)	Other properties	Ref.
None	50-89	15	153	14	d_4^{25} 1.3319	313
					n_D^{25} 1.4615	133
		14.5	152-153	16		223
		14.0	150	12	d_4^{18} 1.336	145
	94	14.5	149-150	13		146
			152-154	14	n_D^{23} 1.4545	129
	77					131
	82		112-113	1.5	d_4^{25} 1.3322	304
					n_D^{25} 1.4620	
	97					27
	72-80	12.5-14.5	134-136	4	d_4^{25} 1.3347	
<i>x</i> -Cl		49			n_D^{25} 1.4619-1.4625	282
<i>x</i> -Br		54				133, 136
						133, 136

4-CH ₃ -	68	155-157	15	n_D^{20}	1.4612	7
6-CH ₃ -	49	121-123	2	d_4^{20}	1.2516	304
6-CH ₃ CH ₂ CH ₂ -	25	126	0.4	n_D^{25}	1.4586	313
4, 6-(CH ₃ -) ₂	58	45				129
4, 6-(C ₆ H ₅ -) ₂	85					29, 31
	25	147-149				248
5-Br-4, 6-(C ₆ H ₅ -) ₂	80	204.5-205.0				31
4, 5-(CH ₃) ₂ -6-(O=)						178
4, 4, 6, 6-(CH ₃ -) ₄	31	99-100				32b
6-BrCH ₂ -4, 4, 6-(CH ₃ -) ₃						
or 5-Br-4, 4, 6, 6-(CH ₃ -) ₄	48	130.5-131.0				32b
4, 4, 6, 6-(C ₆ H ₅ -) ₄	8	94-95				32a
5-Br-4, 4, 6, 6-(C ₆ H ₅ -) ₄	90					32a

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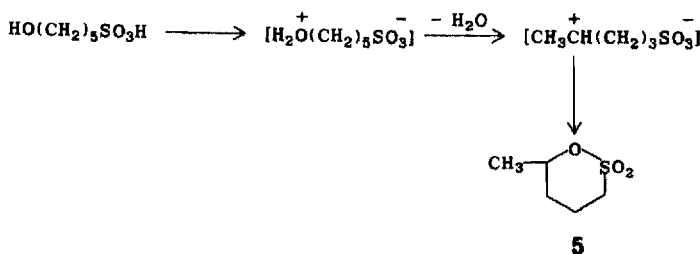
methods have been based on the dehydration of a δ -hydroxysulfonic acid or on the dehydrohalogenation of a δ -halosulfonic acid.

Butanesultone (4) has been prepared in excellent yields (82-89%) by the following series of reactions:^{146,303,304}



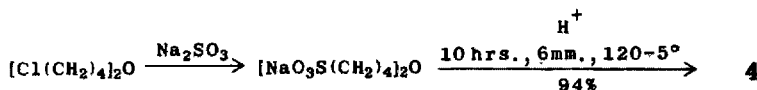
Using butylene chlorohydrin instead of the acetate in the above series of reactions gave only a 58% yield of 4, probably because of the competing reaction of the chlorohydrin to lose hydrogen chloride to form tetrahydrofuran.³⁰⁴

On subjecting 5-chloropentyl acetate to the above reactions, 6-methyl-*o*-oxathiane 2, 2-dioxide (5) was formed in an over-all yield of 49%. Truce and Hoerger³⁰⁴ suggested the following mechanism for the formation:



The temperature used, 130°, in the dehydration favors the suggested isomerization.

Starting with 4-chlorobutyl ether, Helberger and Lantermann obtained a 94% yield of butanesultone.^{142, 146, 282}

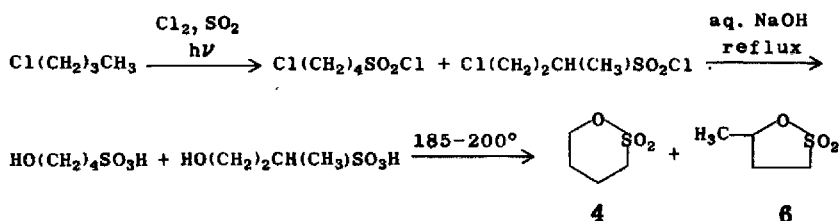


They also obtained the sultone (4) on heating 4-methoxybutanesulfonic acid under vacuum at 150-180°.¹⁴²

Chlorosulfonation of butyl bromide or chloride gives a mixture of 4 and the 2, 4-butanesultone (6) which can be separated by virtue of their different reactivities towards methanolysis (see section I A-1b).¹⁴⁵ This

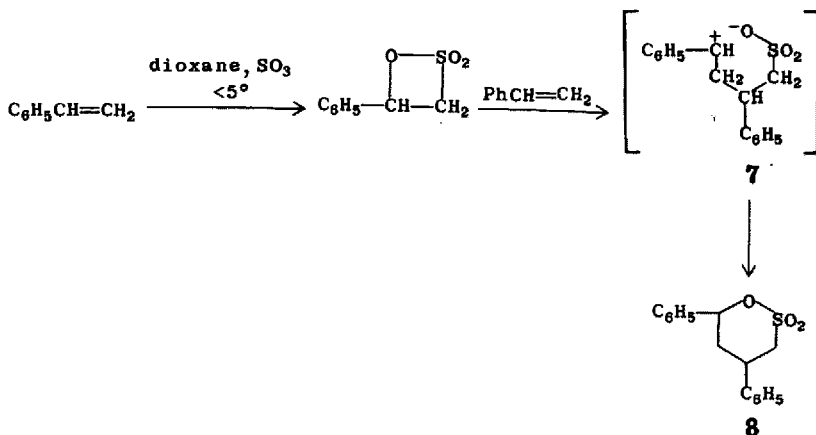
Chapter 11

sultone synthesis (more fully discussed in Chapter 4, section I A-3, under 1,2-oxathiolane) proceeds as follows:^{129,133}



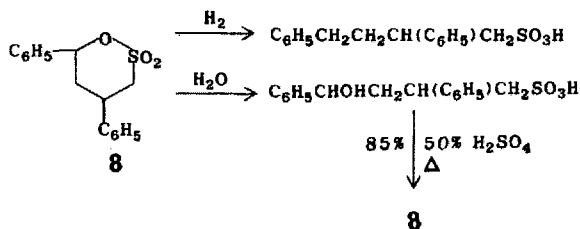
According to Helberger, the ring closure of 4-chlorosulfonic acids to the sultone is improved by heating at 20-25 mm and 150-160° in the presence of copper compounds, such as copper oxide.¹³¹

In studying the sulfonation of styrene with dioxane-sulfur trioxide, Bordwell and Rondestvedt^{29,248} obtained 4,6-diphenyl-*o*-oxathiane 2,2-dioxide (8) in a yield of 5-25%, a higher yield being obtained by using three moles of styrene per mole of sulfur trioxide. The butane-sultone formation was believed to occur through a styrene dimer intermediate (7).

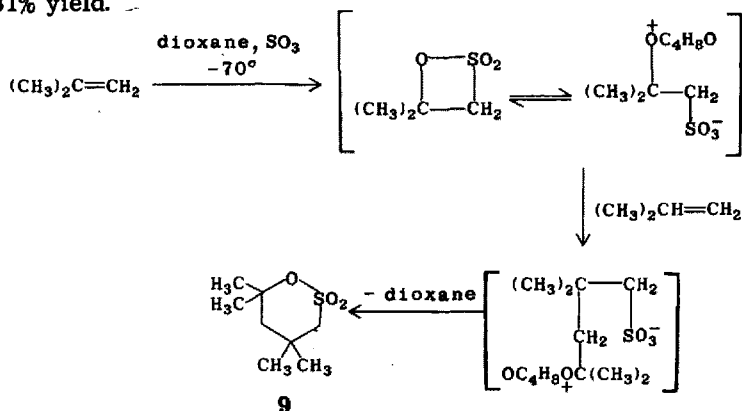


The structure of the butanesultone (8) was proved by its hydrogenolysis over palladium-on-charcoal to 2,4-diphenyl-1-butanesulfonic acid. The salts obtained in the hydrolysis of the sultone were converted to the sultone in 75% yield by concentration of the salts with sulfuric acid *in vacuo* or in 85% yield by heating the salts with 50% sulfuric acid. The ready formation of the sultone from 4-hydroxy-2,4-diphenyl-1-butane-sulfonic acid indicated a reactive benzyl-type hydroxyl, since other sultones are prepared from the hydroxysulfonic acids only under more drastic conditions.

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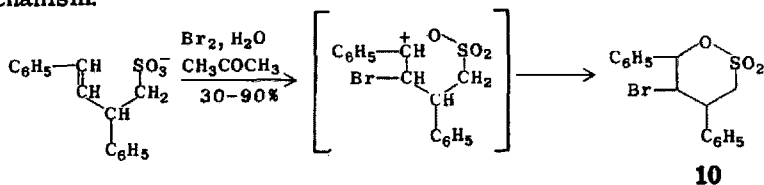


The dimerization-sulfonation reaction was extended to other olefins.^{32a,32b} Carrying out the sulfonation of isobutylene with dioxane-sulfur trioxide reagent at -70° , the tetramethyl sultone (9) was obtained in 31% yield.



Similar sulfonation of 1, 1-diphenylethene gave about a 10% yield of the sultone, the major product being 2, 2-diphenyl-1-ethene-1-sulfonic acid (70% yield).

The sultone ring is readily formed from 3-butene-1-sulfonates by treatment with bromine water^{31,32a,32b} through the following mechanism:



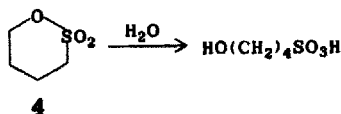
In the ring closure of hydroxysulfonic acids to the sultone, Willems³¹³ found that hydrogen ion is without effect. The reaction is monomolecular and accordingly

$$-dc/dt = kc$$

$$-d(a-x)/dt = k(a-x)$$

$$\text{and } k = \frac{2.3}{t} \log \frac{a}{a-x} = 1.80 \times 10^{-5}$$

where a is the initial concentration of the sultone and x is the decrease in concentration in time t for the hydrolysis reaction.

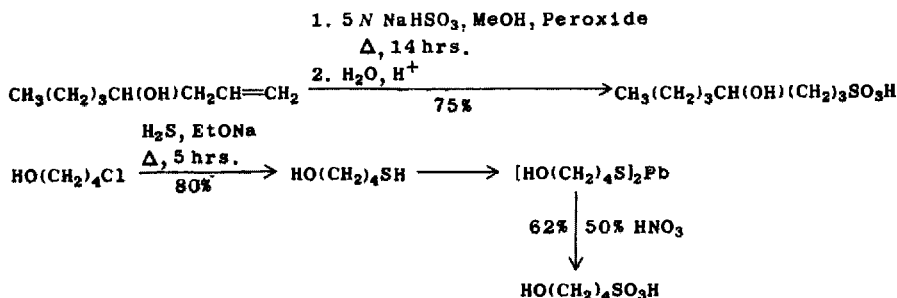


Willems converted hydroxysulfonic acids to the sultones by three methods:

1. Distillation under reduced pressure.
2. Azeotropic distillation with butylcellosolve at 170° until water is distilled, then distillation of the sultone under reduced pressure.
3. Addition of an alcoholic solution of the hydroxysulfonic acid dropwise to boiling xylene, distilling the water-alcohol-xylene ternary azeotrope, and crystallizing or distilling the sultone.

Using these three methods, *o*-oxathiane 2, 2-dioxide was prepared in 50, 85, and 89% yield, respectively, and 6-propyl-*o*-oxathiane 2, 2-dioxide in 0, 21, and 25% yield, respectively.³¹³

Willems³¹² prepared hydroxysulfonic acids by two methods:



Blaser, Haas, and Helberger²⁴ obtained almost 100% yields of 4-hydroxybutanesulfonic acid by treating $\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{OH}$ with sodium bisulfite under neutralizing conditions.

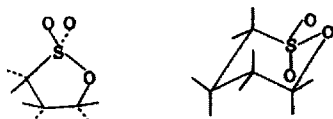
b. Properties, Reactions, and Uses

o-Oxathiane 2, 2-dioxides are colorless, odorless, high-boiling liquids, insoluble in cold water, somewhat soluble in hot water, easily soluble in ether, chloroform, benzene, methanol, and ethanol, but insoluble in carbon tetrachloride.¹⁴⁶

The six-membered ring sultone is apparently more easily formed than the five-membered ring sultone (see 1, 2-oxathiolane in Chapter 4). The studies on methanolysis (see later) also support the observation that the six-membered ring sultone is the more stable. This of course is the opposite of the lactone series in which the five-membered ring is the more stable. The greater stability of the six-membered

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ring was explained by Hoerger¹⁵⁹ by its existence in a staggered chair-type structure as compared to the planar structure for the five-membered ring sultone.

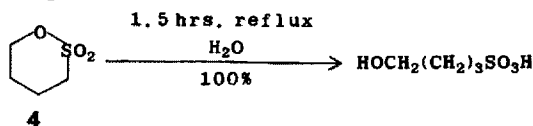


Because the valence angle of tetravalent sulfur approximates that of tetrahedral carbon, the geometry of sultones should approximate that of the rings of the corresponding hydrocarbon. Also, an oxygen can replace a methylene without affecting the structural conformation.

This assumption has an important consequence on the possible effect of the transition state of sultones on their reactivity. Thus, in the reaction of the sultones with nucleophilic reagents, such as methanol, alkoxides, or salts, by the S_N2 mechanism, the transition state will be:



o-Oxathiane 2, 2-dioxides are hydrolyzed by refluxing with water to give a quantitative yield of hydroxysulfonic acid.^{129, 146}



Helberger and co-workers have studied the reactions of a variety of nucleophilic reagents with *o*-oxathiane 2, 2-dioxides.^{129a, 130, 132, 134, 135, 137-141, 143-147} In a study of the methanolysis of *o*-oxathiane 2, 2-dioxide and 5-methyl-1, 2-oxathiolane 2, 2-dioxide at 100°, it was found that the reactivity of the oxathiolane is about ten times greater than for the oxathiane, as shown in Table 2.

TABLE 2. Reaction of Sultones with CH₃OH at 100°

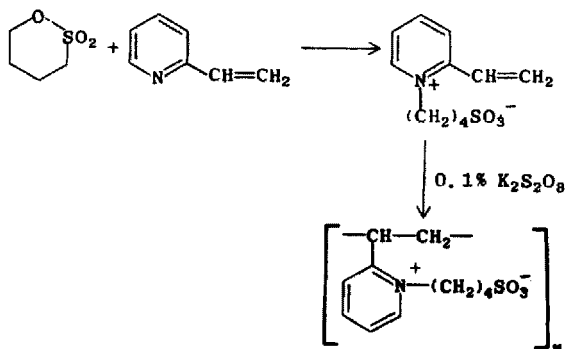
$\text{CH}_3\text{CH}(\text{CH}_2)_2\text{SO}_2\text{O}$		$\longrightarrow$	$\text{CH}_3\text{OCH}(\text{CH}_2)_2\text{SO}_3\text{H}$
Time, hrs.:	0.5 1 1.5 2 2.5 3.5 7.5 18 22 34.5		
Acid, %:	27 58 79 82 84 88 90 92 93 94		
$\text{CH}_2(\text{CH}_2)_3\text{SO}_2\text{O}$		$\longrightarrow$	$\text{CH}_3\text{O}(\text{CH}_2)_4\text{SO}_3\text{H}$
Time, hrs.:	1 4 6 16.5 32.5 47.75 76.75		
Acid, %:	1 21 31 73 92 96 98		

This difference in reactivity was used to separate the sultones in their preparation by the sulfochlorination of 1-chlorobutane.¹⁴⁵

In general, *o*-oxathiane 2,2-dioxides react with nucleophilic reagents with heating or under reflux to give δ -substituted alkylsulfonates. Table 3 summarizes the various reactions, including the ones involving nucleophilic reactants.

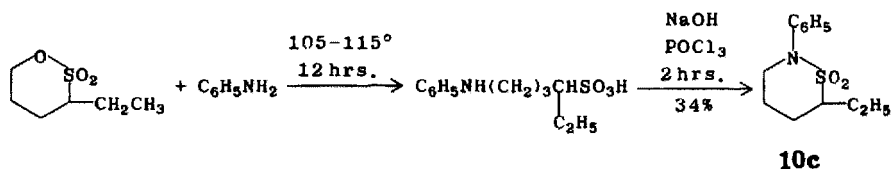
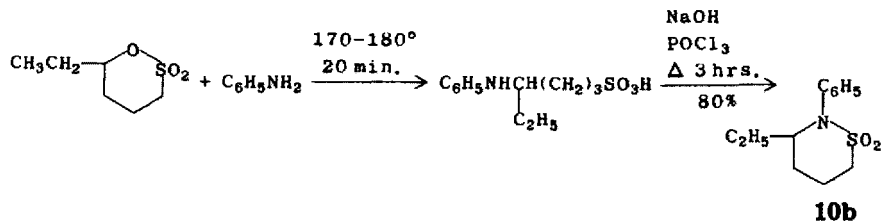
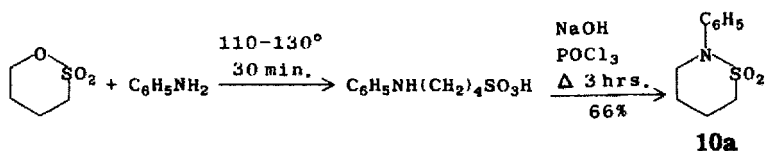
The products of these reactions are stated to be useful as detergents, wetting agents, dispersing agents, intermediates for the manufacture of dyes, pharmaceuticals, and as softeners for use in lacquers in many patents assigned to Böhme Fettchemie. 28,118,129,130,132,134-141, 143-147 Water-soluble fluorescent compounds have been prepared by treating difficultly water-soluble amines, such as 2-(4-aminophenyl)-5-methylbenzothiazole, 5-amino-2-phenylbenzotriazole, 7-amino-4-methylcoumarin, 7-ethylamino-4-methylcoumarin, bis(2-benzimidazolyl)ethylene, or 2-aminopyrene with butanesultone. ^{15a}

Hart and Timmerman¹²³ prepared sulfobetaines of poly(vinylpyridine) by the reaction of 2- or 4-vinylpyridine with *o*-oxathiane 2, 2-dioxide in the presence of a polymerization inhibitor, e.g., *m*-dinitrobenzene, to give the monomer, 4-vinylpyridine butylsulfobetaine, as crystalline needles, which decomposes without melting above 260°; this monomer was polymerized in water in the presence of 0.1% $K_2S_2O_8$ to a polymer having an intrinsic viscosity of 0.72 dl/g (in 0.5 *M* NaCl at 25°).



Helferich and Böllert^{147d} studied the reaction of *o*-oxathiane 2, 2-dioxides with secondary and tertiary alkyl amines and with aromatic amines. They obtained yields of 80% 4-aminobutanesulfonic acids on treating *o*-oxathiane 2, 2-dioxide with amines such as methylamine or diethylamine; with trimethylamine, they obtained a 95% yield of the betaine. On treating *o*-oxathiane 2, 2-dioxide with an aromatic amine, such as aniline or 3, 4-dichloroaniline, and heating the resulting 4-arylamino-butanesulfonic acid with POCl₃, they obtained the sultam or 1, 2-thiazane 1, 1-dioxide (10a). They also carried out this reaction with 3- and 6-ethyl-*o*-oxathiane 2, 2-dioxide.

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Quaedvlieg and Ruhlig,^{243a} in a German patent, claimed the product from the reaction of 4, 6-diphenyl-*o*-oxathiane 2, 2-dioxide and octyl alcohol and also caprylic acid as surfactants. The reaction was carried out in the presence of sodium at 200°C. for two hours.

Hart and Williams^{123a} obtained polymers with internally ionized groups by reacting *o*-oxathiane 2, 2-dioxide with poly(diethylaminoethyl methacrylate), poly(2-vinylpyridine), and poly(4-vinylpyridine). These polymers are useful in photographic layers as complete or partial replacements for gelatin. According to Brunken and co-workers,^{37a} products from the reaction of *o*-oxathiane 2, 2-dioxide with amides are useful in photographic compositions for colored pictures.

2. Dihydro-*o*-oxathiin

Bordwell, Chapman, and Osborne^{32b} prepared 4, 5-dimethyl-3, 6-dihydro-*o*-oxathiin 2, 2-dioxide (11) in 6. 5% yield by the sulfonation of 2, 3-dimethyl-1, 3-butadiene in ethylene chloride with dioxane-sulfur tri-

TABLE 3. Reactions of *o*-Oxathiane 2,2-Dioxide with Various Reagents

Reactant	Conditions	Product	Yield	Ref.
NH ₃	in EtOH, 5 hrs., 60-65°	$\text{H}_3\text{N}^+(\text{CH}_2)_4\text{SO}_3^-$	95	146
RNH ₂	100°	$\text{RNH}_2(\text{CH}_2)_4\text{SO}_3^-$	100	
R = C ₂ H ₅ -				146
= C ₆ H ₅ -				138, 146, 147d
= C ₆ H ₅ -				30, 31, 303
= C ₈ H ₁₇ -				313
<i>p</i> -C ₆ H ₄ (NH ₂) ₂	boiling xylene	<i>p</i> -H ₂ NC ₆ H ₄ NH ⁺ (CH ₂) ₄ SO ₃ ⁻		97
(C ₂ H ₅) ₂ NH		(C ₂ H ₅) ₂ NH ⁺ (CH ₂) ₄ SO ₃ ⁻		159
C ₆ H ₅ N(CH ₃) ₂		(C ₆ H ₅) (CH ₃) ₂ N ⁺ (CH ₂) ₄ SO ₃ ⁻	97	146
-N=		$\text{N}^+(\text{CH}_2)_4\text{SO}_3^-$		
Pyridine			100	7, 123, 146, 304, 313
Isoquinoline				159
Carbazole				159
MX		$\text{C}_{12}\text{H}_8\text{N}^+(\text{CH}_2)_4\text{SO}_3^-$		
KI	Δ, several hrs.	X(CH ₂) ₄ SO ₃ M		
KF	CH ₃ COC ₂ H ₅			139, 146
NaBr				139, 159
KCN			92	139, 159
				146

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KCNS			94	130, 146
NaSH			100	130
RONa	100-150°	RO(CH ₂) ₄ SO ₃ Na		
R = CH ₃ -			98	145, 147
=C ₂ H ₅ -			91	147, 305
=(C ₂ H ₅) ₂ CHCH ₂ -			90	132
=C ₄ H ₉ CH(C ₂ H ₅)CH ₂ -				
=(C ₄ H ₉) ₂ CHCH ₂ -				
=(C ₅ H ₁₁) ₂ CH-				
=CH ₃ O(CH ₂) ₄ -				
=C ₆ H ₁₃ CH(C ₄ H ₉)CH ₂ -				
=(C ₆ H ₁₃) ₂ CH(CH ₃)-				
=C ₄ H ₉ CH(C ₂ H ₅)(CH ₂) ₂ CH(iso-C ₄ H ₉)-				
=C ₆ H ₁₃ CH(CH ₃)CH(C ₅ H ₁₁)CH(CH ₃)-				
=C ₈ H ₁₇ CH(C ₆ H ₁₃)CH ₂ -				
=C ₁₂ H ₂₅ -			90	145, 147
=C ₁₈ H ₃₇ -				147
=castor oil				147
=C ₆ H ₅ -			90	146, 147
=2-naphthyl-			90	146, 147
RSNa	Δ on water bath	RS(CH ₂) ₄ SO ₃ Na		

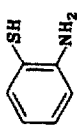
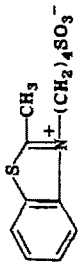
TABLE 3. Reactions of *o*-Oxathiane 2, 2-Dioxide with Various Reagents (contd)

Reactant	Conditions	Product	Yield	Ref.
R = cyclohexyl-				130
= C ₁₂ H ₂₅ -				130
= C ₆ H ₅ -			93	130, 146
RCOONa	80-100°	RCOO(CH ₂) ₄ SO ₃ Na	100	134, 135
R = CH ₃ -				132
= (C ₂ H ₅) ₂ CH-				132
= C ₄ H ₉ CH(C ₂ H ₅)-				132
= C ₆ H ₁₃ CH(C ₄ H ₉)-				132
= C ₁₁ H ₂₃ -			65	134
= C ₁₅ H ₃₁ -				134
= C ₁₇ H ₃₃ -				134
= C ₁₇ H ₃₅ -			60	159
= C ₆ H ₅ CH ₂ -			80	159
= C ₆ H ₅ -			60	159
RCONH ₂	Na ₂ CO ₃ , water-bath	RCONH(CH ₂) ₄ SO ₃ Na		
Acetamide			80	159
Benzamide				140
Phthalimide			97	140, 146

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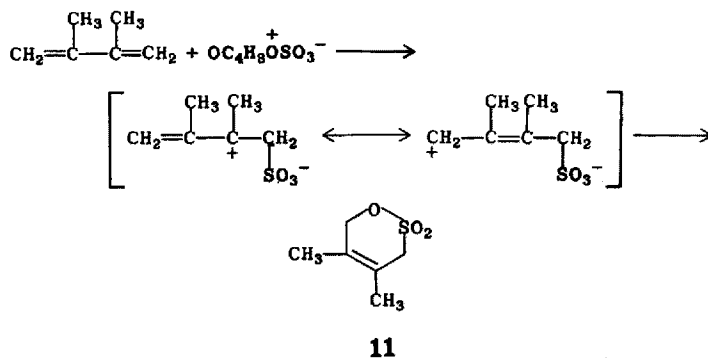
RSO ₂ Na	140°, 2-3 hrs.	RSO ₂ (CH ₂) ₄ SO ₃ Na	
R = C ₂ H ₅ -			141
= C ₃ H ₇ -			141
= C ₄ H ₉ -			141
= C ₆ H ₁₃ -			141
= C ₁₂ H ₂₅ -			141
= C ₆ H ₅ -			53
= <i>p</i> -CH ₃ CONHC ₆ H ₄ -			141, 305
= <i>p</i> -(<i>iso</i> -C ₈ H ₁₇)C ₆ H ₄ -			87
<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ NNa ₂	120°, 4 hrs.	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ N[(CH ₂) ₄ SO ₃ Na] ₂	141
			144
<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ N(C ₁₂ H ₂₅)Na		RSO ₂ N(C ₁₂ H ₂₅)(CH ₂) ₄ SO ₃ Na	144
C ₁₀ H ₁₇ SO ₂ N(CH ₃)Na		RSO ₂ N(CH ₃)(CH ₂) ₄ SO ₃ Na	144
RMgBr		R(CH ₂) ₄ SO ₃ H	
R = C ₂ H ₅ -			135, 313
= C ₆ H ₅ -			90
RNa (or Li)	RH or RCl + Na or Li in xylene and heat	R(CH ₂) ₄ SO ₃ Na	135, 305
R = C ₄ H ₉ -			58
= C ₆ H ₅ C≡C-			85
= fluorenyl			135, 137, 143
= C ₆ H ₅ -			137, 143

TABLE 3. Reactions of *o*-Oxathiane 2, 2-Dioxide with Various Reagents (contd)

Reactant	Conditions	Product	Yield	Ref.
$= \text{C}_6\text{H}_5\text{CH}_2^-$				137, 143
$= \text{C}_{12}\text{H}_{25}^-$				137, 143
$= 9\text{-phenanthrenyl}$				137, 143
$= \text{CH}_3\text{COCHCOOC}_2\text{H}_5$			82	305
$= -\text{CH}(\text{COOC}_2\text{H}_5)_2$			95	305
$= (\text{C}_6\text{H}_5\text{CO})_2\text{CH}-$			54	305
RH	AlCl_3 , excess RH	$\text{R}(\text{CH}_2)_4\text{SO}_3\text{H}$	54-88	303, 304
$\text{R} = \text{C}_6\text{H}_5^-$				
$= p\text{-(CH}_3)_2\text{C}_6\text{H}_3^-$				
$= p\text{-(Cl)}_2\text{C}_6\text{H}_3^-$				
$(\text{CH}_3)_2\text{CHOC-SNa}$ $(\text{H}_2\text{N})_2\text{C=S}$	Δ , water-bath MeOH, reflux 30 min.	$(\text{CH}_3)_2\text{CHOC-S}(\text{CH}_2)_4\text{SO}_3\text{Na}$ $\text{H}_2\text{NC}(\text{:NH})\text{S}(\text{CH}_2)_4\text{SO}_3\text{H}$	81	118 28
	Ac_2O , reflux		37	36a

C₄OS Ring Systems

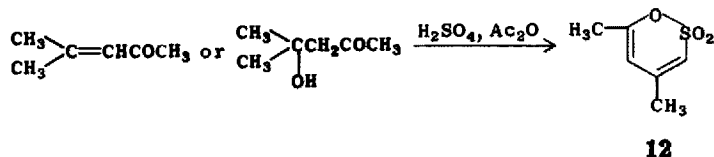
oxide. Using pentane to precipitate the sultone raised the yield to 16%. The course of the reaction was postulated to be:



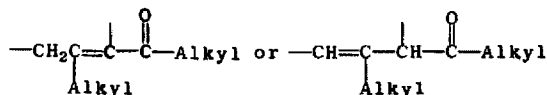
11 melted at 40-41° and boiled at 100° at 3 mm. Its hydrolysis rate was 1000 times that of the saturated sultone.

3. *o*-Oxathiin

An *o*-oxathiin was first prepared in 1948 by Morel and Verkade²¹⁰ by the reaction of α, β -unsaturated ketones with concentrated sulfuric acid and acetic anhydride (molecular ratio of 1:2) at low temperature (below 0°). Thus, with mesityl oxide (or with diacetone alcohol), 4, 6-dimethyl-*o*-oxathiin (**12**) was obtained.



Under the same conditions, however, no sultone was formed from the following α, β -unsaturated ketones: 3-penten-2-one, 3-decen-2-one, and 3-methyl-3-penten-2-one; nor from the corresponding β -ketols. Nor could sultones be prepared from the β, γ -unsaturated ketones, 1-hexen-4-one and 4-hepten-2-one. The compounds which successfully gave the sultone had the following structures:



The formation of sultone proceeded rather slowly, and the reaction mixture was usually kept at -5° for one day and then at room temperature for another day.²¹¹ In general heat was not applied to the reaction as these sultones decompose rather rapidly with evolution of sulfur dioxide, some even at room temperature. Those which decomposed too readily were not kept at room temperature, but were worked up within

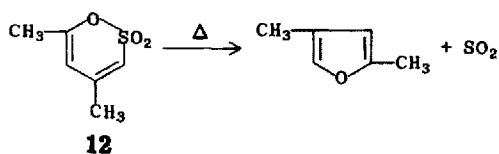
a few hours. The sultones were isolated by pouring the reaction mixture into iced sodium hydroxide solution, the crystalline sultones being filtered and liquid sultones (oil) extracted with ether.

About the same time Morel and Verkade were extending the Treibs reaction so were Eastman and Gallup,⁷⁷ who studied the sulfonation of α, β -unsaturated ketones and aldehydes using both sulfuric acid and chlorosulfonic acid. They were successful only in the treatment of mesityl oxide with acetic anhydride and chlorosulfonic acid, obtaining a 41% yield of sultone.

Fetizon, Fritel, and Baranger⁸⁴ had hoped to prepare an *o*-oxathiin from styrylpyruvic acid, but no subsequent publication has described the preparation of the expected 3-phenyl-*o*-oxathiin-6-carboxylic acid 2, 2-dioxide.

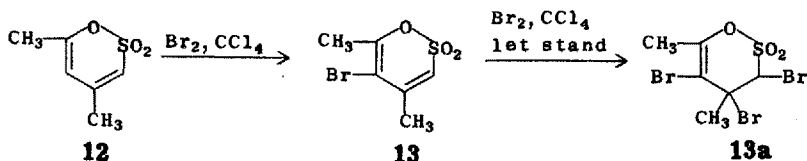
These sultones, listed in Table 4, are colorless, crystalline compounds, although in two cases only viscous liquids could be obtained. They are in general readily soluble in cold ether, acetone, chloroform, and benzene, moderately soluble in methanol and ethanol, and slightly soluble in petroleum ether and cold water. When the sultones were stored at room temperature, there was a tendency towards discoloration; Eastman and Gallup⁷⁷ noted that their sultone from mesityl oxide decomposed with violence to form sulfur dioxide and a black tar on storing for several weeks. The sultones are hydrolyzed by treatment with hot, dilute alkali or mineral acid.

Pyrolysis of these sultones provides a new route to the synthesis of substituted furans in good yields.²¹⁰



Pyrolysis has been carried out in boiling quinoline³¹⁶ and with lime, copper oxide, iron, and diphenylamine to give 76% yields of furans.³²¹ Eastman and Gallup, on the other hand, on pyrolyzing their sultone at atmospheric pressure, reduced pressure, and in an atmosphere of nitrogen could not isolate any furan.

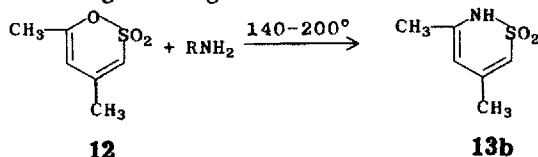
On bromination of their sultone, Eastman and Gallup obtained 5-bromo-4, 6-dimethyl-*o*-oxathiin 2, 2-dioxide (**13**). This compound (**13**) was stated to be a powerful skin irritant. On letting the bromination mixture stand for a day, the 3, 4, 5-tribromo compound precipitated (**13a**).⁷⁷



C₄OS Ring Systems

Gaertner,⁹⁵ on refluxing a mixture of **12** and phenylhydrazine in acetic acid, obtained a 2 : 1 adduct which was said to be a wheat rust erad-
icant.

Helferich and co-workers^{147a} obtained good yields (up to 90%) of the corresponding thiazine (**13b**) on heating *o*-oxathiin 2, 2-dioxides with equivalent amounts of ammonia or various primary amines in an auto-
clave or a high boiling solvent.



R = H, CH₃, C₂H₅, CH₂=CHCH₂—, (CH₃)₂CH—, *m*- and
p-H₂NC₆H₄—, etc.

However, if at least three moles of amine are used per mole of *o*-oxathiin 2, 2-dioxide, the primary product is *N,N'*-dialkylsulfuryldiamide (**13c**).^{147c}

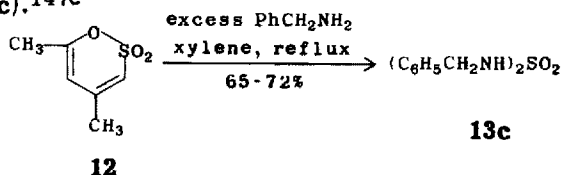
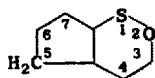


TABLE 4. *o*-Oxathiin 2, 2-Dioxides

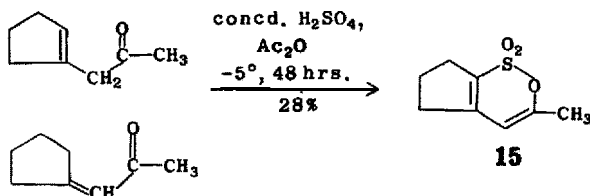
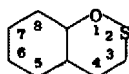


Substituent	Yield	M.p. (°C)	B.p. (°C)	(mm)	Ref.
4, 5-(CH ₃ -) ₂	54	85. 6			211
4, 6-(CH ₃ -) ₂	40	70. 5-71. 0			211
	41	65. 7			77
	45	66			321
4-CH ₃ -6-C ₂ H ₅ -	43		136-138	3. 5	211
4-CH ₃ -6-C ₆ H ₅ -	84	83. 4			211
6-CH ₃ -4-C ₆ H ₅ -	40	89. 5-90. 0			211
3, 4, 6-(CH ₃ -) ₃	41	68. 5-69. 0			211
4-CH ₃ -6-(CH ₃) ₃ C-	60	57-57. 5			211
3, 6-(CH ₃ -) ₂ -4-C ₂ H ₅ -	45		152-156	11	211
3, 5-(CH ₃ -) ₂ -4, 6-(C ₂ H ₅ -) ₂	43	74. 5	135-139	3	211

B. C₄OS-C₅ 5H-CYCLOPENT[c][1,2]OXATHIIN (14)**14**

(RRI 1369)

Only one compound in this system has been reported, 3-methyl-6, 7-dihydro-5H-cyclopent[c][1,2]oxathiin 1, 1-dioxide (15). The compound was indexed by Chemical Abstracts under this name. It was prepared by Morel and Verkade²¹¹ by the treatment of a mixture of cyclopentylidenepropanone and (1-cyclopenten-1-yl)propanone with concentrated sulfuric acid; 15 melts at 88.0-88.5°.

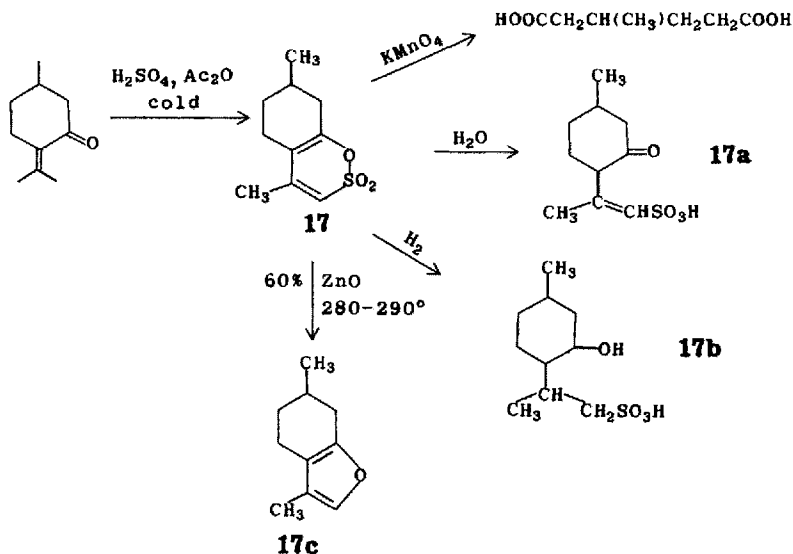
**15**C. C₄OS-C₆1. **1, 2-Benzoxathiin (16)****16**

(RRI 1637)

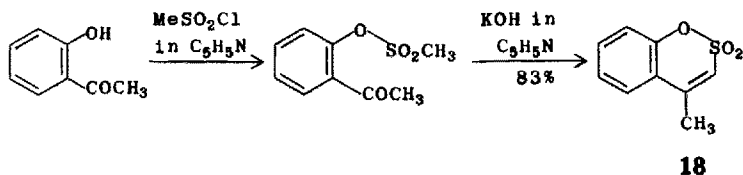
The parent compound is not known. The few derivatives that have been reported in the literature are of the sultone or 2, 2-dioxide form. These compounds are listed in Table 5. Chemical Abstracts has indexed the compounds of this ring system under 1,2-benzoxathiin.

In his studies in the terpene and sesquiterpene series, Treibs³⁰² treated one mole of pulegone with a cold mixture of two moles of acetic anhydride and one mole of sulfuric acid (Reychler's method) and obtained the sultone 17, melting at 85°. Treatment of this sultone (17) with hot alkali, hydrochloric acid, or superheated steam caused hydrolysis to the sulfonic acid (17a). Hydrogenation of 17 in methanol in the presence of palladium saturated the compound and opened the sultone ring. Oxidation with permanganate yielded β-methyladipic acid. On heating 17 with zinc oxide, sulfur dioxide was evolved and menthofuran (17c) was obtained.^{17,302}

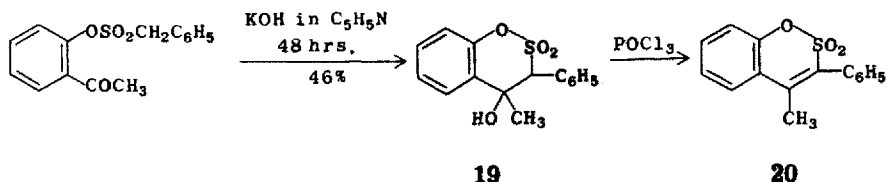
C₄OS Ring Systems



4-Methyl-1, 2-benzoxathiin 2, 2-dioxide (**18**) was prepared in 83% yield by treating *o*-acetylphenyl methanesulfonate with powdered potassium hydroxide in pyridine for 48 hours under agitation.²³⁶

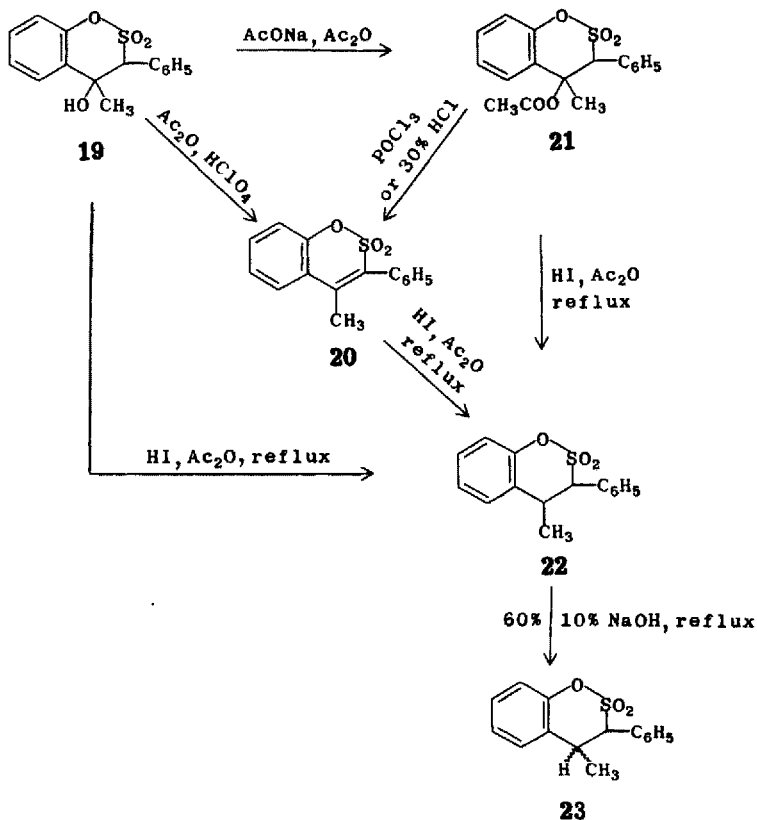


Under the same conditions *o*-acetylphenyl toluene- ω -sulfonate was converted to 4-hydroxy-4-methyl-3-phenyl-3, 4-dihydro-1, 2-benzoxathiin 2, 2-dioxide (**19**) in 46% yield; refluxing **19** with POCl_3 for 2.5 hours gave 4-methyl-3-phenyl-1, 2-benzoxathiin 2, 2-dioxide (**20**) by dehydration.²³⁶



Prolonged treatment of *o*-acetylphenyl toluene- ω -sulfonate with potassium hydroxide in pyridine for 14 days gave a 92% yield of **20**. Infra-red spectra and the following reactions confirm the 1, 2-benzoxathiin 2, 2-dioxide structure:

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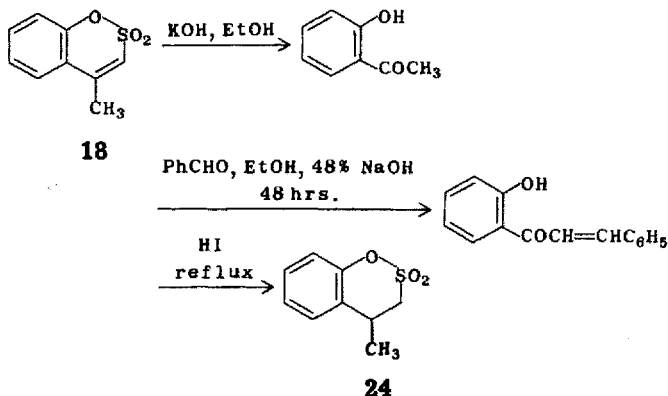


Infrared spectra of the 3-phenyl-1, 2-benzoxathiin 2, 2-dioxides gave bands (cm^{-1}) at 1164, 1348, and 1384 for the 4-hydroxy (19); 1164, 1372, and 1384 for the unsaturated 4-methyl (20); 1173 and 1364 for the 4-methyl-4-acetoxy (21); 1152, 1171, and 1368 for the 4-methyl (22); and 1169 and 1363 for the epimeric 4-methyl (23). The bands for $-\text{OSO}_2-$ are at 1145-1200 and 1330-1420 cm^{-1} .

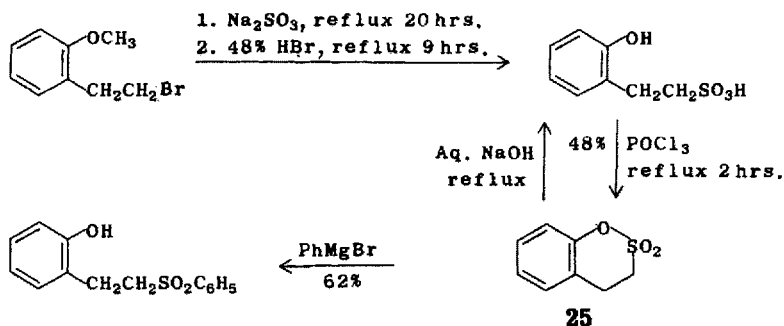
The infrared spectra of the two saturated 4-methyl compounds (22 and 23) differed only slightly. They were characterized by different melting points, 107-108° (22) and 158-160° (23). It appears, therefore, that the epimer (23) occurred through alkaline epimerization of 22.

4-Methyl-1, 2-benzoxathiin 2, 2-dioxide (18) exhibits chemical properties different from the 3-phenyl derivative (20). It is hydrolyzed with ethanolic alkali whereas the 3-phenyl derivative is not affected. Treatment with 35% NaOH under reflux, however, did not cause hydrolysis of 18. 18 reacts with benzaldehyde to give *o*-hydroxyphenyl styryl ketone. Refluxing with hydriodic acid hydrogenates 18 to the 3, 4-dihydro compound (24).²³⁶

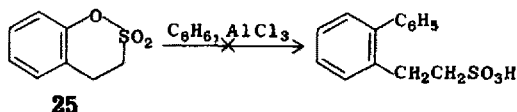
C₄OS Ring Systems



Truce and Hoerger,^{159,303-5} in their studies of sultones and the Friedel-Crafts reaction of sultones, prepared 3, 4-dihydro-1, 2-benzoxathiin 2, 2-dioxide (**25**) through ring closure of 2-(*o*-hydroxyphenyl)ethane-sulfonic acid.



No alkylation occurred when **25** was treated with benzene, anisole, or *m*-xylene in the Friedel-Crafts reaction using AlCl₃ and 68-90% of the 3, 4-dihydro-1, 2-benzoxathiin 2, 2-dioxide was recovered unchanged. As Truce and Hoerger pointed out, carbon atom 8a which holds the oxygen atom of the sultone would have to become positively polarized for the electrophilic substitution of the Friedel-Crafts reaction. This is unlikely in view of the electron richness of the benzene ring.



Hydrolysis of **25** by refluxing with excess alkali for three hours gave a product whose *S*-benzylthiuronium salt melted at 156.5-157.5°. Phenylmagnesium bromide reacts with **25** to give a 62% yield of *o*-(β-phenylsulfonyl)ethylphenol.²⁵² This reaction differs from that of *o*-oxathiane 2, 2-dioxide, which gives 4-phenylbutyl-1-sulfonic acid, for the same reason that **25** does not behave as an alkylating agent in the Friedel-Crafts reaction.

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Helferich and co-workers^{147b} obtained the corresponding benzothiazine (25a) on heating pulegonesultone (17) with aniline (69% yield), benzylamine (22% yield), and isopropylamine (10% yield).

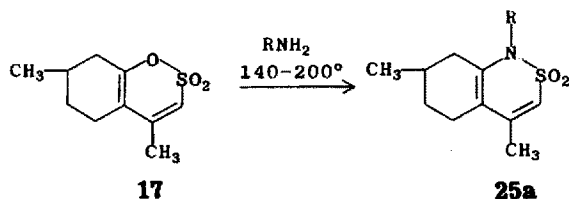
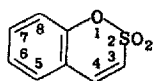
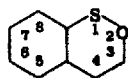


TABLE 5. 1, 2-Benzoxathiin 2, 2-Dioxides



Substituent	Yield	M.p.(°C)	Ref.
3, 4-H ₂	42	109-112	159, 303-5
4-CH ₃ -	83	86-87	236
4-CH ₃ -3-C ₆ H ₅ -		173-174	236
4-CH ₃ -4-OH-3-C ₆ H ₅ -3, 4-H ₂	46	202-203	236
4-CH ₃ -3-CH ₃ CO ₂ -3-C ₆ H ₅ -3, 4-H ₂		148-150	236
4-CH ₃ -3-C ₆ H ₅ -3, 4-H ₂		106-108	236
		158-160	236
4, 7-(CH ₃) ₂ -3, 4, 5, 6, 7, 8-H ₆	35	85	17, 302
	61	85-86	211

2. 2, 1-Benzoxathiin (26)



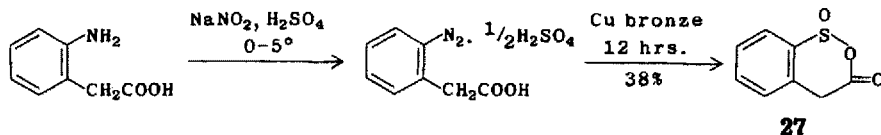
26

(RRI 1638)

The parent compound has not been reported. The few derivatives of the sultone or lactone and anhydride forms comprising this ring system are listed in Table 6. Chemical Abstracts has indexed these compounds under 2, 1-benzoxathiin only since 1947; previously they were indexed under the arylsulfonic or -sulfinic acid.

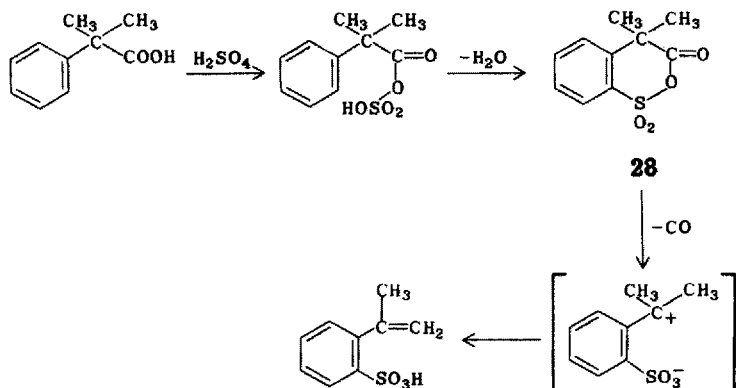
C₄OS Ring Systems

3, 4-Dihydro-2, 1-benzoxathiin-3-one 1-monoxide (**27**) was the first compound in this ring system reported. Neber²²¹ prepared it in 1922 by the diazotization of *o*-aminophenylacetic acid and treatment of the resulting diazo compound with copper bronze.

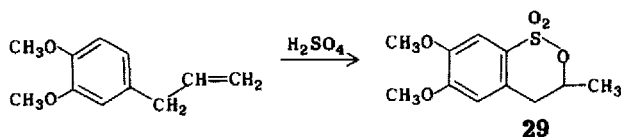


Neber named this compound, which melted at 185° with sintering at 177°, phenylacetic-*o*-sulfinic acid anhydride.

In a study of the action of sulfuric acid on compounds containing a tertiary carboxylic acid, Campaigne and Suter,⁴¹ on letting dimethylphenylacetic acid and concentrated sulfuric acid stand at room temperature for 33 hours and then at 72° for one hour, obtained a 67% yield of *o*-sulfo- α -methylstyrene. They suggested the formation of 4, 4-dimethyl-3, 4-dihydro-2, 1-benzoxathiin-3-one 1, 1-dioxide (**28**), which was not isolated, as an intermediate in the mechanism for this reaction.



Clemons and Turnbull,⁵² in sulfonation studies of eugenol derivatives, reacted *O*-methyleugenol with concentrated sulfuric acid at room temperature for 5 hours and obtained 6, 7-dimethoxy-3-methyl-3, 4-dihydro-2, 1-benzoxathiin 1, 1-dioxide (**29**).



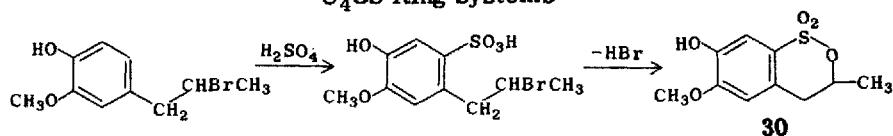
Similarly *O*-acetyleneugenol gave 7-hydroxy-6-methoxy-3-methyl-3, 4-dihydro-2, 1-benzoxathiin 1, 1-dioxide (**30**). Methylation of this gave the 6, 7-dimethoxy compound (**29**). The δ -lactone structure was confirmed by the synthesis of **29** or **30** from the corresponding β -bromodihydro-eugenol.

TABLE 6. 2,1-Benzoxathiins

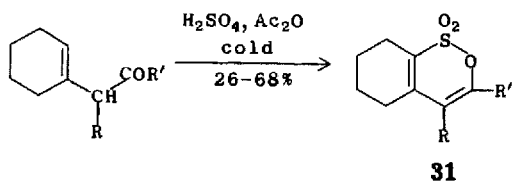


Substituent	Yield (%)	B.p. (°C)	B.p. (mm)	M.p. (°C)	Ref.
3, 4-(H) ₂ -3-(=O) 1-monoxide	38			185 (sinters at 177)	221
3, 4-(H) ₂ -3-CH ₃ -6-CH ₃ O-7-HO- 1, 1-dioxide				166-167	52
3, 4-(H) ₂ -3-CH ₃ -6, 7-(CH ₃ O) ₂ 1, 1-dioxide				141-143	52
5, 6, 7, 8-(H) ₄ -3-CH ₃ - 1, 1-dioxide	50			90.5-91.0	211
5, 6, 7, 8-(H) ₄ -3-C ₂ H ₅ - 1, 1-dioxide	26	150-151	2		211
5, 6, 7, 8-(H) ₄ -3-C ₆ H ₅ - 1, 1-dioxide	68			119.5-120.0	211
5, 6, 7, 8-(H) ₄ -3, 4-(CH ₃) ₂ 1, 1-dioxide	65			142.5-143.0	211

C₄OS Ring Systems

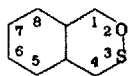


Morel and Verkade²¹¹ prepared several compounds in this ring system by treating cyclic substituted ketones with a mixture of acetic anhydride and sulfuric acid (Reychler's method).



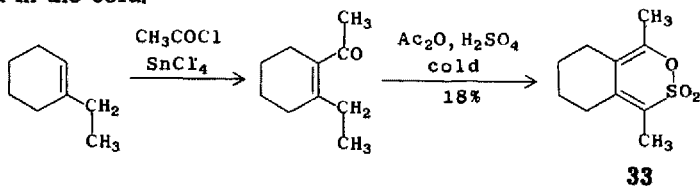
These sultones had no anthelmintic activity; their toxicity to mice was low; they showed no activity against *Streptococci* or against trophozoite-induced *P. gallinaceum* infection in chicks.⁵²

3. 2, 3-Benzoxathiin (32)



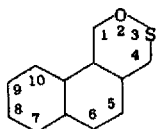
32
(RRI 1641)

In Morel and Verkade's studies of δ -sultones, they obtained 1, 4-dimethyl-5, 6, 7, 8-tetrahydro-2, 3-benzoxathiin 3, 3-dioxide (**33**), m.p. 142.5-143.0°, in 18% yield by treating the reaction mixture obtained from the action of acetyl chloride on 1-ethylcyclohex-1-ene in the presence of stannic chloride with acetic anhydride and concentrated sulfuric acid in the cold.²¹¹



D. C₄OS-C₆-C₆

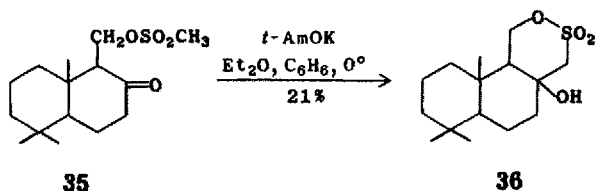
1. 3H-Naphth[1, 2-d]-2, 3-oxathiin (34)



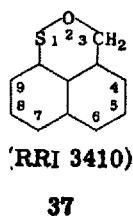
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Only one compound in this ring system has been reported, and this in a footnote in a paper by Romann, Frey, Stadler, and Eschenmoser,²⁴⁷ who described the preparation of 4a-hydroxy-7,7,10a-trimethyl-1,4,5,6,7,8,9,10-octahydronaphth[1,2-d]-2,3-oxathiin 3,3-dioxide (**36**) from the corresponding methyl 2-oxodecalin-1-methylsulfonate (**35**). The structure of **36**, m.p. 157°, was adduced from chemical analysis and infrared spectra.

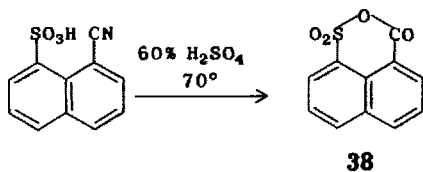


2. 3*H*-Naphth[1,8-*cd*]-[1,2]-oxathiin (**37**)



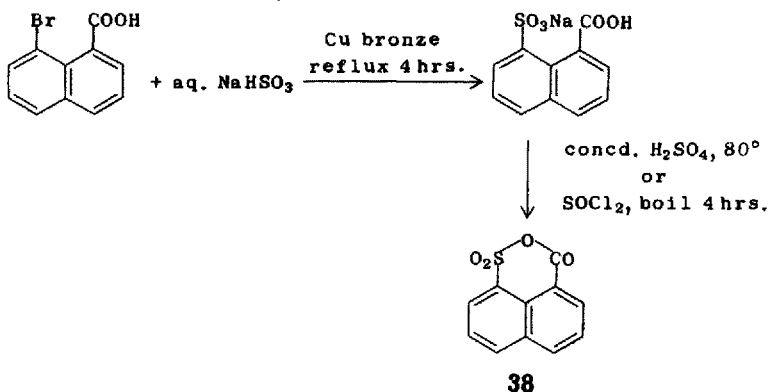
This ring system is represented by only 3*H*-naphtha[1,8-*cd*]-[1,2]-oxathiin-3-one 1,1-dioxide (**38**). Chemical Abstracts indexed this compound under the anhydride of 8-sulfo-1-naphthoic acid.

8-Sulfo-1-naphthoic acid cyclic anhydride, m.p. 151-152°, first reported in 1926,¹⁶⁹ was prepared by hydrolyzing and cyclizing 8-cyanonaphthalene-1-sulfonic acid.⁴⁴

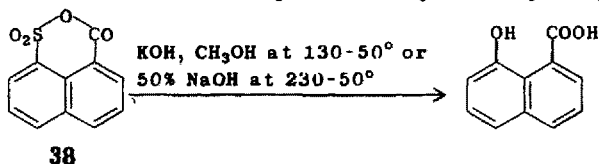


The cyano compound was obtained from 8-aminonaphthalene-1-sulfonic acid; the overall yield was poor because of the preferential cyclization of the diazonium salt to naphthosultone. Rule and Turner²⁵¹ obtained the anhydride in up to 85% yield by the reaction of 8-bromo-1-naphthoic acid with aqueous sodium bisulfite and treating the sulfonaphthoic acid with sulfuric acid or with thionyl chloride.

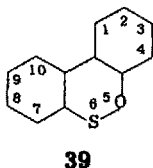
C₄OS Ring Systems



The anhydride (**38**) is soluble in ethyl alcohol and in benzene. It reacts with alkali at elevated temperature to yield 8-hydroxy-1-naphthoic acid.

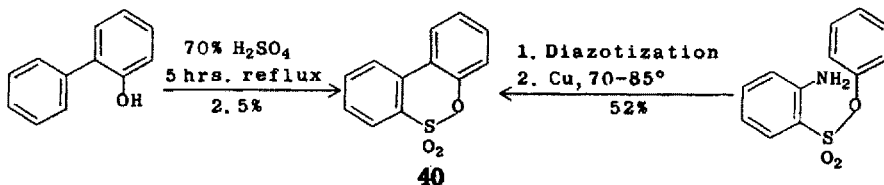


3. Dibenz[ce]-[1,2]-oxathiin (**39**)



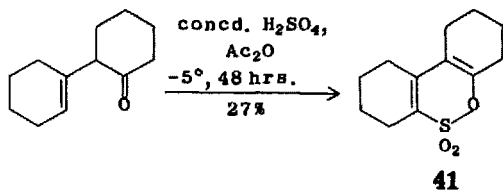
(RRI 3409)

The several derivatives prepared in this system are listed in Table 7. Cullinane, Morgan, and Plummer⁶⁰ first obtained the sultone (**40**) as colorless needles, m.p. 110°, in 1937 by the treatment of *o*-phenylphenol with 70% sulfuric acid under reflux. Schetty²⁵⁴ prepared the sultone in 52% yield by the diazotization of phenyl 2-aminobenzenesulfonate and treatment of the diazo compound with copper powder. Most of the compounds listed in Table 7 were prepared by this method.



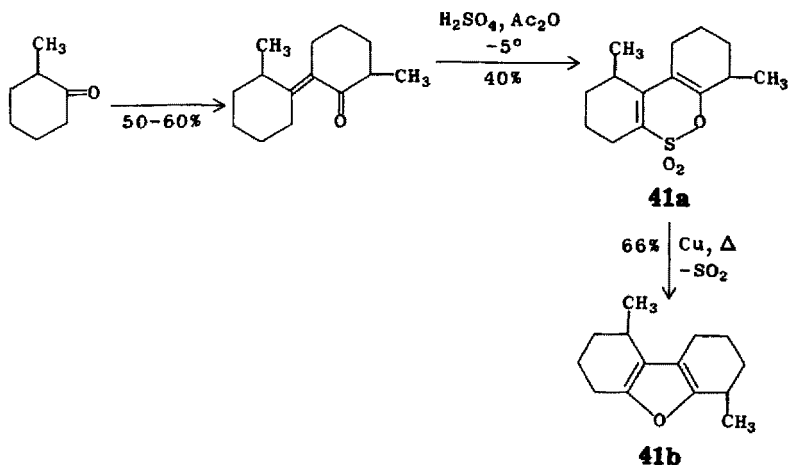
Morel and Verkade²¹¹ prepared the octahydro sultone (**41**) by the treatment of 2-(1-cyclohexen-1-yl)cyclohexanone with concentrated sulfuric acid.

Chapter 11



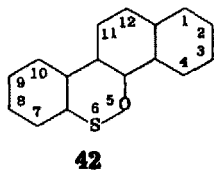
This compound was isolated as a yellow mass which turned brown-red on exposure to air; it could not be obtained crystalline.

Treibs^{302a} prepared 1, 7-dimethyl-1,2,3,4,7,8,9,10-octahydrodibenz-[c, e]-[1, 2]-oxathiin 6, 6-dioxide (**41a**) by the treatment of 2-(2-methyl-1-cyclohexylidene)-6-methylcyclohexanone-1 (from the condensation of 2-methylcyclohexanone) with concentrated sulfuric acid by the Morel and Verkade²¹¹ method. On heating this sultone with copper powder and distilling, Treibs obtained 1, 4-dimethyl-1, 2, 3, 4, 6, 7, 8, 9-octahydrodibenzofuran (**41b**).



E. C₄OS-C₆-C₆-C₆

1. Benzo[c]naphth[2, 1-e]-[1, 2]-oxathiin (**42**)

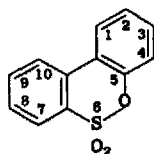


(RRI 5027)

Only the 6, 6-dioxide, or sultone form (**43**), has been reported. Chemical Abstracts indexed this under 5-oxa-6-thiachrysene 6, 6-dioxide.

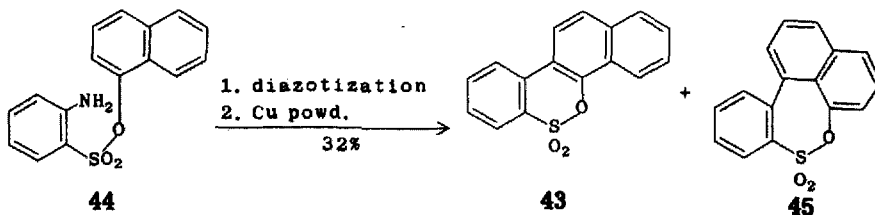
C₄OS Ring Systems

TABLE 7. Dibenz[ce]-[1, 2]-oxathiin 6, 6-Dioxides

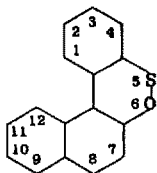


Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Ref.
None	2.5	110			60
	52	108.5-109.5			254
2-CH ₃ -	52	154-155			254
2-C ₂ H ₅ (CH ₃) ₂ C-	23	104.5-105.5			254
2-Cl	15	163-165			254
9-Cl	80	175-176			254
2-CH ₃ -9-Cl	46	220-222			254
2, 9-(Cl) ₂	16	219-220			254
1, 2, 3, 4, 7, 8, 9, 10-H ₈	27		189-192	2	211
4, 10-(CH ₃) ₂ -1, 2, 3, 4, 7, 8, 9, 10-H ₈	40		162-163	0.4	302a

Schetty,²⁵⁴ using the method he developed for the preparation of dibenz[ce]-[1, 2]-oxathiins, diazotized 1-(α -naphthyl)-2-aminobenzenesulfonate (**44**), treated the diazo compound with copper powder and obtained an inseparable mixture of isomers in a yield of 32%. This mixture, m.p. 145-152° and sintering at 130°, was believed to contain, in equal amounts, a seven-membered ring sultone (**45**) and, benzo[*c*]naphth[2, 1-*e*]-[1, 2]-oxathiin 6, 6-dioxide (**43**), which Schetty called 1-hydroxy-2-naphthyl-1'-phenyl-2'-sulfonic acid sultone.

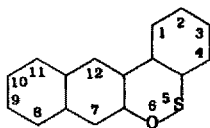


2. Benzo[*c*]naphth[1, 2-*e*]-[1, 2]-oxathiin (46) and
Benzo[*c*]naphth[2, 3-*e*]-[1, 2]-oxathiin (47)



46

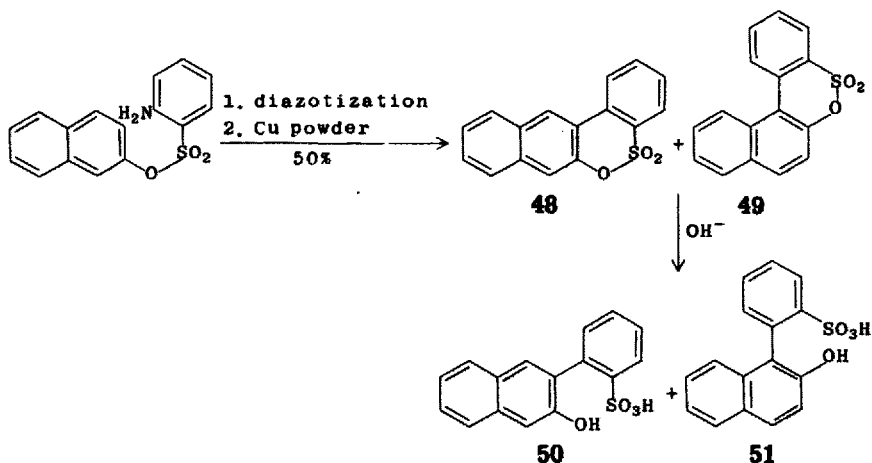
(RRI 5028)



47

(RRI 5025)

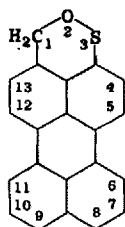
These two ring systems, known only as the sultone or 5, 5-dioxide (48 and 49), were indexed by Chemical Abstracts under the above names. Schetty²⁵⁴ prepared the two sultones as an inseparable mixture, m.p. 184-188° (sintering 170°), by the diazotization of 1-(β-naphthyl)-2-aminobenzenesulfonate and treatment of the diazo compound with copper powder. Schetty named these two compounds 2-hydroxy-1-(or 3) naphthyl-1'-phenyl-2'-sulfonic acid sultone. Alkaline saponification opened the heterocyclic ring.



Treatment of the saponified mixture with phenyldiazonium chloride coupled only 50, from which it was estimated that 23% 48 was present in the sultone mixture.

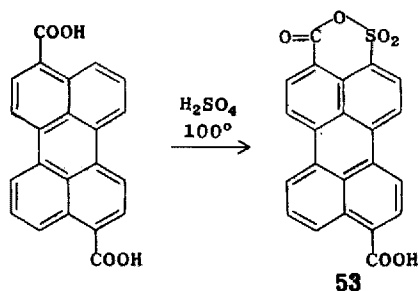
C₄OS Ring Systems

F. C₄OS-C₆-C₆-C₆-C₆-C₆ 1*H*-PERYLO[1, 12-*c, d*]-[1, 2]-OXATHIIN (52)



52

Pontratz²⁴⁰ postulated the following reaction from the treatment of perylene-3, 9-dicarboxylic acid with concentrated sulfuric acid at 100°:

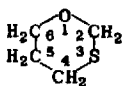


53

He called the product (53) perylene-3, 9-dicarboxylic acid-4-sulfonic anhydride. Chemical Abstracts indexed it as 4-sulfo-3, 9-perylenedicarboxylic acid 3, 4-cyclic anhydride.

II. *m*-OXATHIA COMPOUNDS

A. C₄OS *m*-OXATHIANE (54)



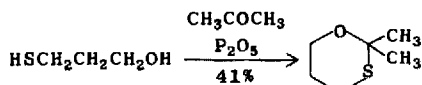
54

(RRI 254)

The parent compound has not been reported, nor has its derivatives been specifically studied. Rather, the few derivatives that have been reported, and which are listed in Table 8, resulted from other research objectives. The derivatives have been given various names: 1, 3-oxathiane and *m*-oxathiane (Chemical Abstracts); the spiro nomenclature based on *m*-oxathiane has been used also.

Apparently, the first *m*-oxathiane was prepared by Sjöberg,²⁶⁵ who heated mercaptopropanol and acetone with P₂O₅ on a sand bath.

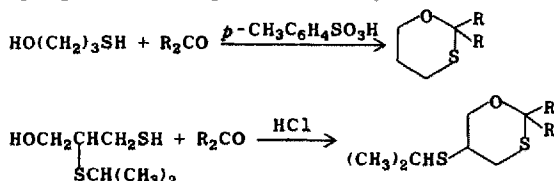
Chapter 11



55

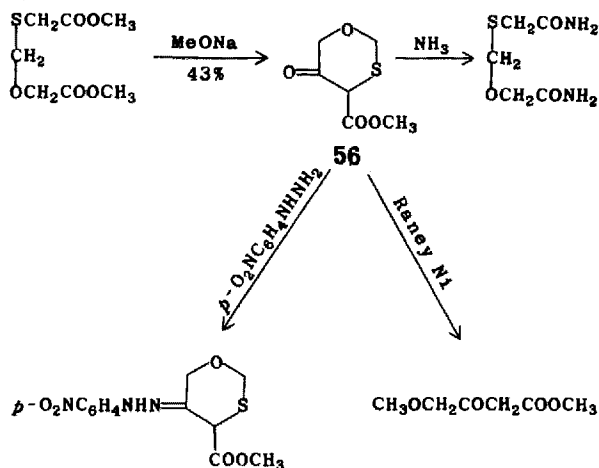
He called this compound acetone- α -hydroxypropylmercaptan, and described it as a colorless oil, difficultly soluble in water, soluble in alcohol, acetone, and ether.

Djerassi and Gorman^{70,72} condensed 3-mercaptopropanol with ketones in benzene solution in the presence of *p*-toluenesulfonic acid, distilling off the water of reaction as the benzene azeotrope. Miles and Owen²⁰⁷ condensed benzaldehyde and also acetone with 2-isopropylthio-3-mercaptopropanol in the presence of hydrochloric acid.



Whereas Djerassi and Gorman^{70,72} were unable to condense benzophenone with 3-mercaptopropanol, Marshall and Stevenson^{198a} did so successfully when they used toluene in place of benzene in the presence of *p*-toluenesulfonic acid. Conducting the condensation in boiling toluene, Marshall and Stevenson were able to prepare several new *m*-oxathianes from ketones.

Brehm and Levenson³⁶ cyclized bis(carbomethoxymethyl) monothioformal by the Dieckmann method, using sodium methoxide at 0° in ether (43% yield) or 80° in toluene (22% yield).

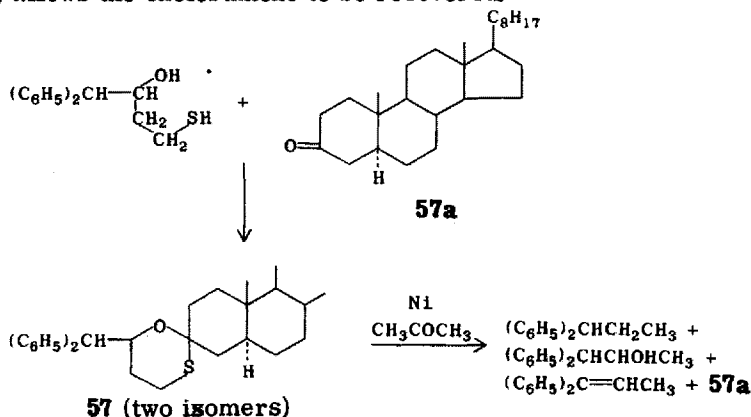


The fact that the 4-carbomethoxy derivative (56) was obtained and no (—) 6-carbomethoxy derivative was attributed to the form C=S— in the mono-

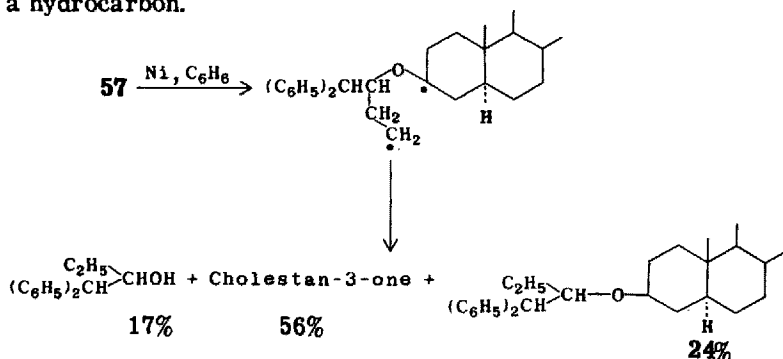
C₄OS Ring System

thioformal which reverses the normal order of electronegativities.^{49a} The product was a white, crystalline solid. It gave an intense color with ferric chloride. The oxidation with ferric chloride or with iodine was used for its quantitative determination. It reacted with ammonia to rupture the ring. The *p*-nitrophenylhydrazone of **56** was obtained in two forms; one melting at 165-166° and the other melting at 214-216°. Desulfurization of **56** with Raney nickel gave methyl 4-methoxy-3-oxo-butyrate.

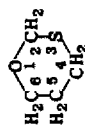
Djerassi, Shamma, and Kan⁷² prepared spiro[6-benzhydryl-1, 3-oxathiane-2,3'-cholestane] (**57**) by reacting cholestane-3-one with 1, 1-diphenyl-4-mercaptobutan-2-ol in dioxane at room temperature for three days with stirring in the presence of anhydrous sodium sulfate and zinc chloride. Raney nickel desulfurization of the spiro compound (**57**) allows the cholestanone to be recovered.



Desulfurization of spiro-1, 3-oxathianes in acetone or ethyl methyl ketone gave results analogous to the oxathiolane analogs (see Chapter 4). Desulfurization in benzene was different, however, as the 1, 4-diradical mechanism is not likely in the oxathiane series. Thus, where the oxathiolane spiro compound desulfurized to the original ketone plus an olefin, the spiro-1, 3-oxathiane of cholestanone and of acetophenone desulfurized to the original ketone (major product) plus an ether, an alcohol, and a hydrocarbon.



[For references, see pp. 939-951.]

TABLE 8. *m*-Oxathianes

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Ref.
2-HCl · HN=		81.5-83.0			492
2-HS-					148
2- <i>p</i> -ClC ₆ H ₄ -n		48-50	133	1.2	198a
2,2-(CH ₃ -) ₂	41		60	12	<i>d</i> ²⁰ 1.0291
	81		49	18	<i>d</i> ²⁴ 1.0216
					<i>n</i> _D ²⁴ 1.4880
2,2-(C ₆ H ₅ CH ₂ -) ₂	65	70-71			70
2,2-(C ₆ H ₅ CH ₂ -) ₂ 3,3-Dioxide	85	108-110			70
2,2-(CH ₃ -) ₂ -5-[(CH ₃) ₂ CHS-]			80	1	<i>n</i> _D ²³ 1.5134
2-C ₆ H ₅ -5-[(CH ₃) ₂ CHS-]	79		125	0.5	<i>n</i> _D ²⁰ 1.5765
4-CH ₃ OOO-5-(O=)	43	70.5-72			36
4-CH ₃ OOO-5-C ₆ H ₅ NHNH-		165-166 and 214-216			36
2-CH ₃ -2-C ₆ H ₅ -6-[(C ₆ H ₅) ₂ CH-]	37	138-139			72
Spiro[1,3-oxathiane-2,1'-cyclohexane]			86-87	2	<i>n</i> _D ²⁴ 1.5212
					198a

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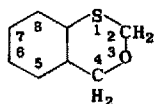
Treatment of 2,2-dibenzyl-*m*-oxathiane with monoperphthalic acid gave the colorless sulfone, m.p. 108–110°, in 85% yield.⁷⁰

m-Oxathian-2-imine hydrochloride was prepared by Wagner-Jauregg and Haring^{306b} from the reaction of trimethylene oxide with thiocyanic acid in the presence of hydrochloric acid at from –10 to 0°. This reaction proceeded similarly to that of epoxides in the preparation of 1,3-oxathiolane-2-imines (see Chapter 4, section II A-2a(5)).

The 2-mercapto and thione derivatives of *m*-oxathiane, among other heterocyclic compounds, was said to be useful as an insecticide.¹⁴⁸

B. C_4OS-C_6

1. 3,1-Benzoxathian (58)

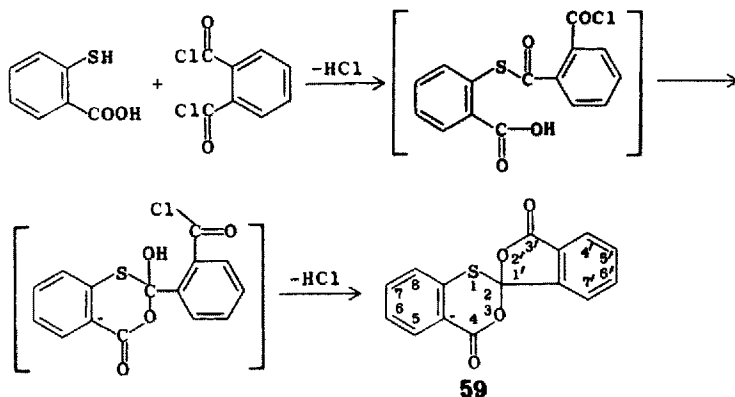


58

(RRI 1639)

The parent compound has not been prepared. A few 4-one, or benzoic acid lactone form, derivatives have been described, but little studied. These are listed in Table 9. Chemical Abstracts has indexed these compounds under the benzoic acid lactone nomenclature as well as under 3,1-benzoxathian.

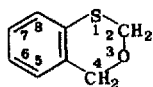
The first member of this ring system was prepared by Kaufmann and Rossbach¹⁷⁴ by reacting *o*-phthalyl chloride with thiosalicylic acid in the presence of dimethylaniline. The reaction probably proceeds as indicated in the equation. They obtained a 76% yield of spiro[3,1,4*H*-benzoxathian-4-one-2,1'(3'*H*)-isobenzofuran] (59) as yellow needles, m.p. 230°.

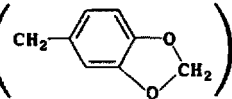
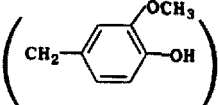
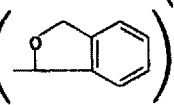


(RRI 4600)

C₄OS Ring System

TABLE 9. 3,1-Benzoxathians

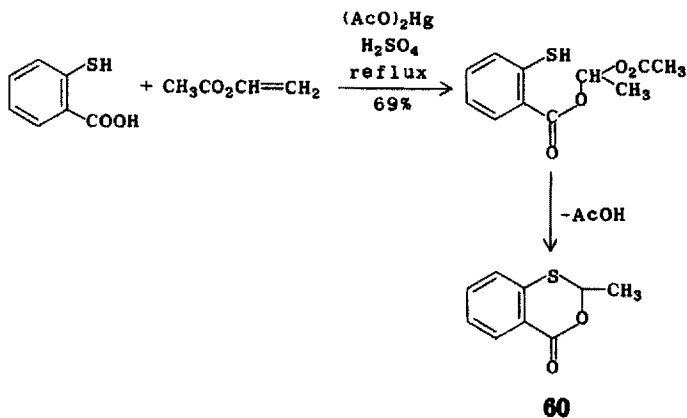


Substituent	Yield (%)	M.p. (°C)	B.p. (°C) (mm)	Ref.
2,4-(O=)	45			175
2-CH ₃ -4-(O=)	69	57	147 5	212
2-CCl ₃ -4-(O=)	69	98		26
2-C ₆ H ₅ -4-(O=)	74	90		213
5,6,7,8-(H ₄)-2-C ₆ H ₅ -4-(O=)		85		46
2-  -4-(O=)	59	129		213
5,6,7,8-(H ₄)-2-  -4-(O=)		124		46
2-  -4-(O=)	76	230		174

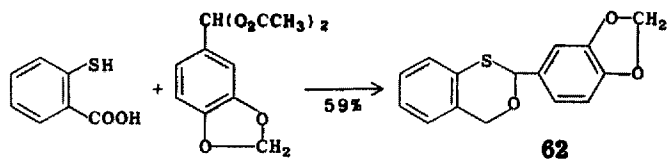
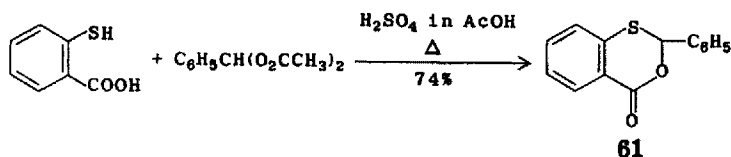
They called this compound thiosalicylic acid phthalidene ether ester, which was also formed by heating a solution of phthalyl chloride in benzene with dry sodium thiosalicylate. Treatment of this compound with sodium carbonate or sodium hydroxide solution did not open the ring. Heating with alcoholic sodium hydroxide did open the ring.

Mowry, Yanko, and Ringwald²¹² prepared 2-methyl-3,1-benzoxathian-4-one (60), m.p. 57°, b.p. 147° at 5 mm, by reacting thiosalicylic acid with a 100% excess of vinyl acetate in the presence of mercuric acetate as an ester interchange catalyst. Presumably this reaction occurs in two steps: first the formation of α -acetoxyethyl thiosalicylate, and second the cyclization of this intermediate with elimination of acetic acid.

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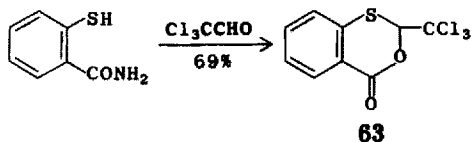


Mowry²¹³ condensed benzal diacetate and piperonal diacetate with thiosalicylic acid in the presence of a trace of sulfuric acid to give good yields of the corresponding 3,1-benzoxathian-4-one.



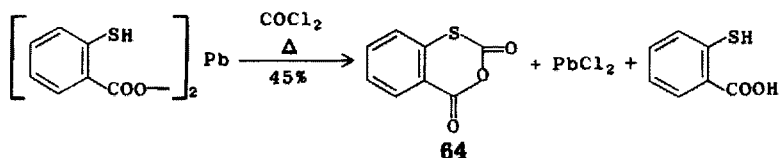
These two methods of preparation described by Mowry and co-workers are also the subject of several patents^{209,216,217} in which the benzoxathians are cited as useful insecticides. The 2-methyl- (60) and 2-phenyl- (61)-3,1-benzoxathian-4-one were tested against *Plasmodium lophurae* in white Pekin duck, but were found to be lacking in antimalarial activity.¹⁶

Böhme and Schmidt²⁶ obtained a 69% yield of 2-trichloromethyl-3,1-benzoxathian-4-one (63) as colorless leaflets, on condensing *o*-thiosalicylamide with chloral in ethanol under a carbon dioxide blanket at 50°.

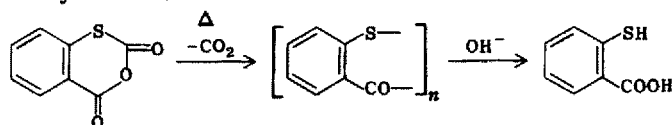


3,1-Benzoxathian-2,4-dione (64) has been prepared¹⁷⁵ by the reaction of lead thiosalicylate with phosgene in benzene solution with vigorous shaking for a day.

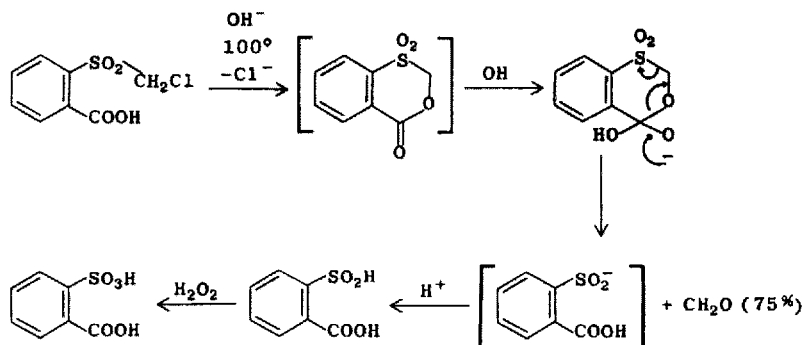
C₄OS Ring System



The dione begins to decompose at 100°, and on continued heating the decomposition is violent at 120°. It is insoluble in water, easily soluble in benzene and toluene and difficultly soluble in ethanol. It is not as sensitive to acids as is the oxygen analog. On heating with water, decomposition occurs. The product obtained by thermal decomposition is a yellow polythiosalicylide resin which when treated with 2 *N* NaOH gives thiosalicylic acid.

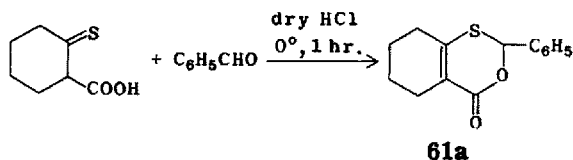


3, 1-Benzoxathian-4-one 1, 1-dioxide is postulated to be an intermediate in the mild oxidation of *o*-(chloromethylsulfonyl)benzoic acid to *o*-sulfobenzoic acid.³²



The reaction with hydroxide ion proceeds about six times faster with *o*-(chloromethylsulfonyl)benzoic acid than with the *p*-isomer. The release of chloride ion in the first step is about twice as fast in 2 *N* NaOH as in neutral solution; the effect of hydroxide ion on the rate is relatively minor, as an increase of roughly 10⁷ in hydroxide ion (from neutral to 2 *N*) caused only this twofold increase.

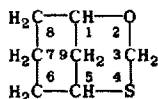
2-Phenyl-5, 6, 7, 8-tetrahydro-3, 1-benzoxathian-4-one (**61a**) was prepared by Chandra, Chakrabarty, and Mitra⁴⁶ by the following condensation:



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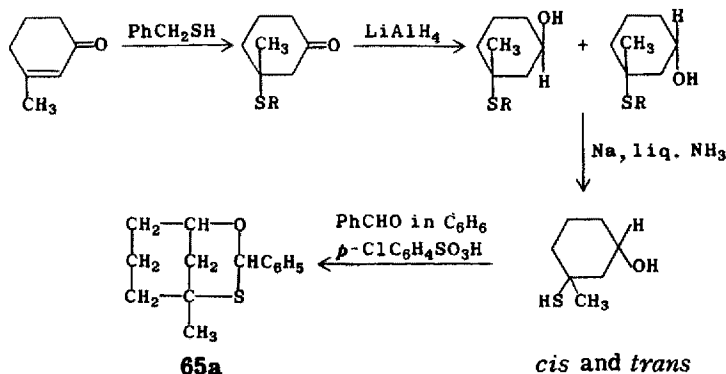
Similarly prepared was 2-(3'-methoxy-4'-hydroxyphenyl)-5, 6, 7, 8-tetrahydro-3, 1-benzoxathian-4-one, m.p. 178°, from vanillin, and 2-(*p*-methoxyphenyl)-5, 6, 7, 8-tetrahydro-3, 1-benzoxathian-4-one from anisaldehyde.

2. 2-Oxa-4-thiabicyclo[3. 3. 1]nonane (65)



65

In a study of the stereochemistry of Raney nickel desulfurization, van Tamelen and Grant^{306a} prepared 5-methyl-3-phenyl-2-oxa-4-thiabicyclo[3. 3. 1]nonane in a 29% yield by the following series of reactions:

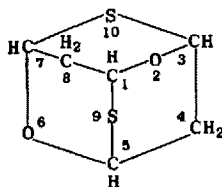


b.p. 130-131. 5° at 0.03 mm.

n_D^{30} 1.5684

Only *cis*-3-methyl-3-mercaptocyclohexanol reacted to give 65a. 65a hydrolyzes very easily on treatment with aqueous mineral acid but with destruction of the mercaptan group. Treating 65a with phenylhydrazine hydrochloride on a steam bath for 30 minutes gives the phenylhydrazone of benzaldehyde and an 80% yield of *cis*-3-methyl-3-mercaptocyclohexanol.

C. C₄OS-C₄OS-C₄OS 2, 6-DIOXA-9, 10-DITHIAADAMANTANE (66)



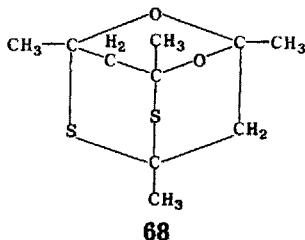
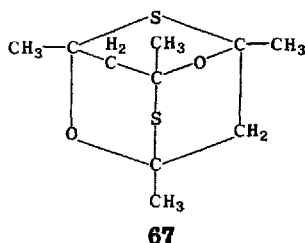
66

C₄OS Ring System

Stetter²⁸⁶ named this heterocyclic class after the parent hydrocarbon, adamantane: 2, 6-dioxa-9, 10-dithiaadamantane (**66**). Chemical Abstracts also uses this nomenclature.

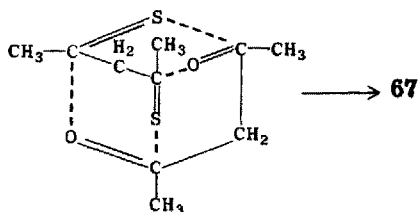
This heterocyclic class was first prepared by Brandström,³⁵ who slowly passed a stream of hydrogen sulfide into a 20% solution of acetylacetone in concentrated hydrochloric acid at room temperature; on steam distilling the product he obtained two isomers, one melting at 131. 2-131. 4° and the other melting at 138. 2-138. 4°; the molecular formula was found to be C₁₀H₁₆O₂S₂.

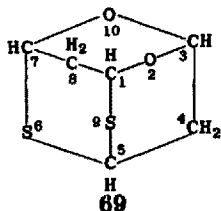
Because the ultraviolet spectra were similar to that of the tetrathia analog (see Chapter 12, section II I) the following two structures were proposed:



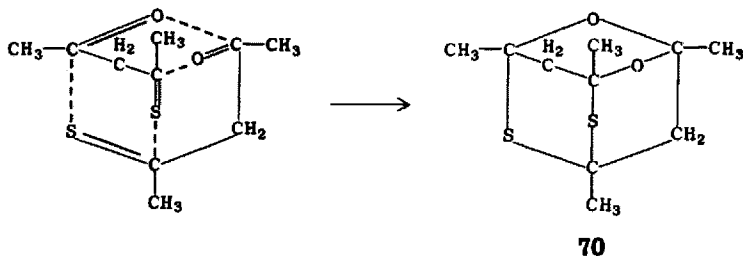
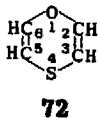
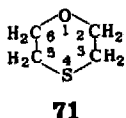
On oxidation with permanganate, the lower melting isomer yielded a disulfone, melting at 250° with decomposition, whereas the higher melting isomer evolved carbon dioxide. The action of the higher melting analog was similar to that of the tetrathia analog. This similarity was also shown in the reaction with mercuric chloride, in that the higher melting isomer and the tetrathia analog gave crystalline precipitates; the lower melting isomer gave none. It was, therefore, concluded that the higher melting isomer contained two sulfur atoms in the same ring and that its structure was **68**. The formation of a stable disulfone from the lower melting isomer indicated that the two sulfur atoms were in different rings and that its structure was **67**.

It was proposed, therefore, that the preparation of **67** occurred through the condensation of acetylacetone with its dithione.



D. $C_4OS-C_4O_2-C_4S_2$ 2, 10-DIOXA-6, 9-DITHIAADAMANTANE (69)

Stetter²⁸⁶ named this heterocyclic class after adamantane, the parent hydrocarbon. The preparation of the only member of this class, the 3, 5, 7-trimethyl derivative (70),³⁵ and its reactions were discussed under section C. It has been proposed that its preparation occurs through the dimerization of 4-thio-2-pentanone.²⁸⁶

III. *p*-OXATHIA COMPOUNDSA. C_4OS *p*-OXATHIANE (71) AND *p*-OXATHIIN (72)

(RRI 255)

p-Oxathiane (71) and its derivatives, listed in Table 10, have been known for some time. The parent compound was first prepared by Clarke⁵¹ in 1912; the anhydride form, *p*-oxathiane-2, 6-dione, was first described by Baumann and Walter¹⁴ in 1893. The lactone form, *p*-oxathiane-2-one, has been reported only once, and that incidentally.⁸

Except for the dihydro form, *p*-oxathiin (72) is unknown. 2, 3-Dihydro-*p*-oxathiin was first prepared in 1952 by Parham, Gordon, and Swalen,²³² although the first member of this series, 2, 5-di(*t*-butyl)-5-hydroxy-2, 3-dihydro-*p*-oxathiin 4, 4-dioxide, was prepared by Backer and Strating⁸ in 1937.

The most popular name for *p*-oxathiane throughout the literature has been *p*-thioxane. It has also been called 1-oxa-4-thiatetramethylene,¹¹⁷

C₄OS Ring System

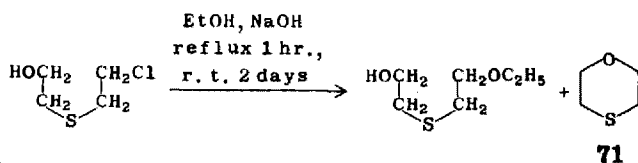
diethylene oxide sulfone for the 4,4-dioxide,⁵⁰ tetrahydro-1,4-thioxin,⁹¹ 1,4-sulfathioxane¹⁸⁰ for the 4,4-dioxide, and thiodiglycolic acid and thiodiacetic acid anhydride^{6,13} for the anhydride form. Chemical Abstracts indexes **71** and its derivatives under *p*-oxathiane and the known derivatives of **72** under *p*-oxathiin. Dihydro-*p*-oxathiin has been called *p*-oxathiene²³² and *p*-thioxene¹²⁵ and Chemical Abstracts, in the fourth decennial index, indexed the Backer and Strating compound under butyric acid as α -(2-hydroxy-3,3-dimethyl-1-butenylsulfonyl)- β , β -dimethylbutyric acid lactone.

1. *p*-Oxathiane

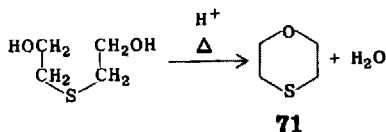
a. Preparation

p-Oxathiane was first prepared by Clarke⁵¹ in 1912 by warming bis(2-iodoethyl) ether with alcoholic potassium sulfide for 2 hours. Meadow and Reid²⁰⁴ reported a 30% yield on warming bis(2-chloroethyl) ether with alcoholic potassium acid sulfide. Whisenhunt^{310a} reported yields of 80-86% of *p*-oxathiane from the reaction of bis(2-chloroethyl) ether and Na₂S·9H₂O under prolonged refluxing (28-34 hours) at 105° using a 30-70% aqueous glycol as solvent; the glycols used included diethylene and triethylene glycols and propylene glycol; using diethylene glycol-ethanol as solvent, the yield was only 50%.

Fuson and Ziegler⁹⁴ obtained *p*-oxathiane in low yield on refluxing 2-chloroethyl 2-hydroxyethyl sulfide with a slight excess of sodium hydroxide in ethanol.



One of the more convenient methods of preparing *p*-oxathiane in good to quantitative yields is by the acid catalyzed dehydration of bis(hydroxyethyl) sulfide.



p-Oxathiane has been prepared by heating bis(hydroxyethyl) sulfide with concentrated sulfuric acid at 160°^{5a} and at 180°.¹⁵⁰ Dehydration of bis(hydroxyethyl) sulfide with an equal weight of potassium bisulfate gives *p*-oxathiane and a small amount of *p*-dithiane;^{93,320} similar results were obtained using sulfuric acid. Catalytic dehydration in the presence of alumina at 225° yields only a small amount of *p*-oxathiane; the major product being *p*-dithiane. Dehydration in the presence of aluminum silicate gives a 66.5% yield of *p*-oxathiane and 14.5% *p*-dithiane. It appears



TABLE 10. *p*-Oxathianes

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	n_D^{20}	d_4^{20}	Ref.
None			145.5-146.4	740	1.5072/20	1.1176	2
			147	75.5		1.1177	51
	100						55
			147				93
			148			1.1174	150
		-17	69.9	47	1.5081/20		172
			100.0	165			172
			137.7	549			172
	30						204
	60		147.5				205
	10		147-149				246
					1.5025/20	1.1070	309
			144.5-146.5	740	1.5072/20	1.1176	317, 318, 319
	5-10		45-55	22			94
	7-8		67	44	1.5080/20	1.105	96a

C₄OS Ring System

HgCl ₂ complex	86	149-150	760	310a
	60	148-149	760	5a
CuCl ₂ complex				147a
				51
AsCl ₃ complex				317
				147a
PtCl ₂ complex				308
				147a
4-Monoxide				4
				43
				55
				252
				284
				93
4, 4-Dioxide				4
				14
				43
				55
				91
				180
				181

TABLE 10. *p*-Oxathianes (contd.)

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	n_D^{20}	d_4^{20}	Ref.
	100						181
	96	132					230
	85						62
		129-130	130-140	1			241
		130					285
		130					93
	85						62
2-Cl							128, 234
	30						125
3-Cl							125
2-CH ₃ O-	87		57	5	1.4911/23		232
			85	20			232
	37		85	23			234
2-C ₂ H ₅ O-	90		81-82	4	1.4840/20		231
2-CH ₃ (CH ₂) ₃ O-	72		109	13			231
2-SP(=S)(OC ₂ H ₅) ₂							125, 128
3-SP(=S)(OC ₂ H ₅) ₂	85						125, 128

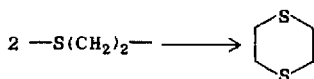
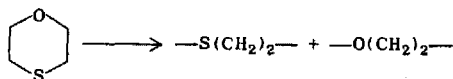
C ₄ OS Ring System					
2, 3-Cl ₂	29	40.5-41.0	115-117	19	124, 128
2, 6-(OH) ₂	100	73			53
2, 6-(C ₂ H ₅ O-) ₂	99	101			50
	100				53
	52	97			259
2, 6-(C ₂ H ₅ O-) ₂ 4-monoxide	11		120-130	10	259
2, 6-(OC ₂ H ₅) ₂ : C ₂ H ₅ I . HgI ₂ complex		95-97			50
2-C ₂ H ₅ O-6-CH ₃ -	93		88	14	231
3, 5-(CH ₃ -) ₂	43		113-114	160	121, 122
2, 6-(CH ₃ -) ₂	7		162		167
			162		166
			160-161	1.4733/20	199
2, 6-(CH ₃ -) ₂ 4, 4-dioxide	24	107			9
		103-104			91
		102			167
	94	104.5-105.5	}		
		92.5-93			
2, 3-(C ₆ H ₅ -) ₂	45	95.0-95.5			128
2, 3-(CH ₃ CO ₂ -) ₂	70	73.4			128
3-[-(CHOH) ₃ CH ₂ OH]-5-CH ₂ SH	low				120

TABLE 10. *p*-Oxathianes (contd.)

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	n_D /°C	d^{20}	Ref.
2-CH ₃ CO ₂ -3-[2, 4-(O ₂ N) ₂ C ₆ H ₃ S-]	75	148-149					232
2, 3-[-SP(=S)(OCH ₃) ₂] ₂	48						124
2, 3-[-SP(=S)(OC ₂ H ₅) ₂] ₂	85						124, 128
3-Cl-2, 6-(CH ₃) ₂	65		95-96	15			128
2-C ₂ H ₅ O-6, 6-(CH ₃) ₂	90		87	12	1.4732/20		231
2-[CH ₃ (CH ₂) ₃ O-]-6, 6-(CH ₃) ₂	73		119	13	1.4700/20		231
2, 5-(<i>l</i> -C ₄ H ₉) ₂ -6-(=O) 4, 4-dioxide		106					8
2, 3, 5, 6-Cl ₄							126
3, 3, 5, 5-(CH ₃) ₄	22		130-132	190	1.4748/20		121, 122
2, 3, 5, 6-(C ₆ H ₅) ₄	84	159-160					45
2, 3-(Cl) ₂ -2, 6-(CH ₃) ₂	11		61-63	0.4			128
2, 3-Cl ₂ -5, 6-[-SP(=S)(OC ₂ H ₅) ₂] ₂	73						126
2, 3- <i>x</i> -Cl ₃ - <i>y</i> -[-SP(=S)(OC ₂ H ₅) ₂]							126
2, 6-(CH ₃) ₂ -2, 3-[-SP(=S)(OC ₂ H ₅) ₂] ₂	72						128
2, 6-(CH ₃) ₂ -3-[-SP(=SO)(OC ₂ H ₅) ₂]	71						128
2, 2, 3, 3, 4, 4, 4, 4, 5, 5, 6, 6-F ₁₂	8		80-80.5		1.3015/20	1.859/25	160
							260

C₄OS Ring System

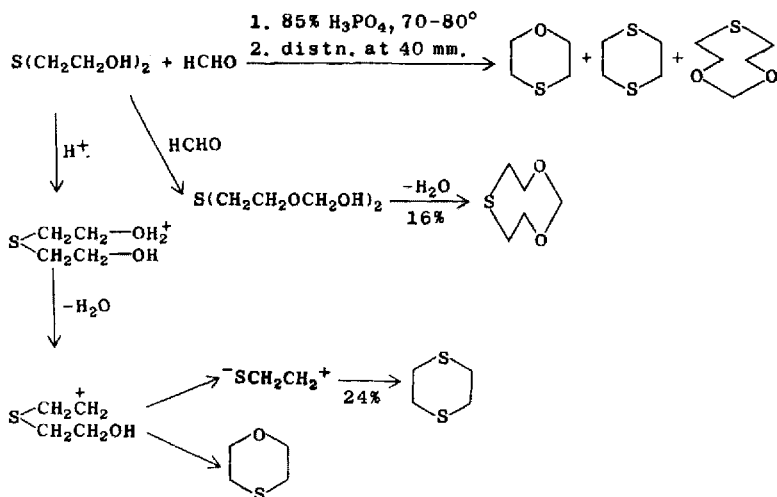
that alumina at temperatures above 200° favors a partial disproportionation of *p*-oxathiane with formation of acetaldehyde and *p*-dithiane.



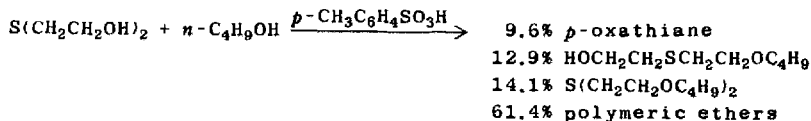
At 250°, hydrogen sulfide is also produced.

In the preparation of divinyl sulfide, Georgieff and Dupré^{96a} dehydrated thiodiglycol at 195–230° with potassium hydroxide and obtained a 36% yield of the desired divinyl sulfide, 9–10% of 2-methyl-1,3-oxathiolane, 7–8% of *p*-oxathiane, and 3.5% of vinyl 2-hydroxyethyl sulfide.

On condensing bis(hydroxyethyl) sulfide with formaldehyde, Laurent and Taste^{184a} obtained 11% *p*-oxathiane, 24% *p*-dithiane, and 16% 1,3-dioxo-6-thiocane. They accounted for the three products by the following reactions:



In the condensation of bis(hydroxyethyl) sulfide with alcohols, phenols, and glycols, some *p*-oxathiane was similarly formed. Thus, in the acid-catalyzed reaction of bis(hydroxyethyl) sulfide with *n*-butanol, 9.6% of *p*-oxathiane was isolated.²⁴⁶



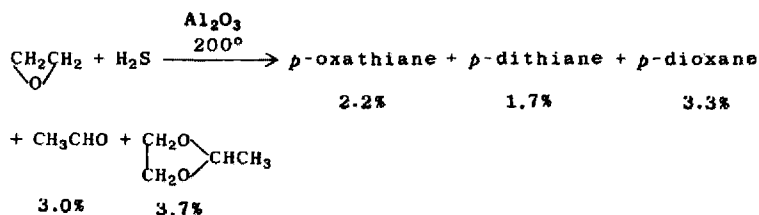
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The condensation with glycols proceeds even more slowly than with butanol. The reaction requires a higher temperature and leads also to the formation of *p*-dithiane. The most important side reaction is intermolecular condensation leading to linear polymeric ethers. A less important reaction is the intermolecular condensation of *p*-oxathiane.

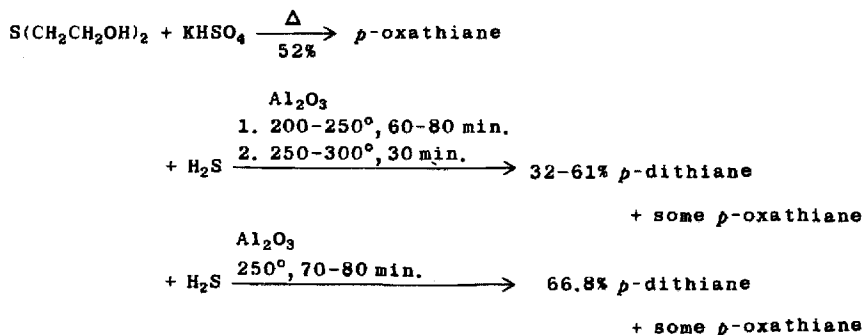
Correll and Mittaush,⁵⁵ on treating bis(hydroxyethyl) sulfide with 8% *p*-toluenesulfonic acid at 130–140° under a pressure of 0.6 mm obtained a hexamer, m.p. 34°. On heating this at 190°, a quantitative yield of *p*-oxathiane was obtained. Ballard and Morris^{11,12} also cyclized the polymeric material they obtained from bis(hydroxyethyl) sulfide at about 200° and atmospheric pressure to *p*-oxathiane.

Woodward and co-workers^{1,315a} showed that the autocondensation of bis(hydroxyethyl) sulfide to its dimer, trimer, and higher polymers, as high as eleven monomer units, in yields of up to 67% occurs when the dehydration is carried out in the presence of 0.5-3.0% HCl, H₂SO₄, or ZnCl₂ at 50-200° for 4-12 hours. Under these conditions only a small amount of *p*-oxathiane is obtained.

The following mixture was obtained on passing ethylene oxide at 10 g/hr and hydrogen sulfide at 18-20 l/hr over alumina at 200°:³¹⁷

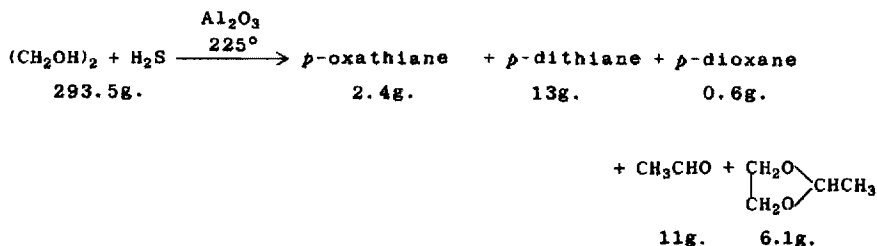


That *p*-oxathiane and *p*-dithiane were formed through dehydration of the intermediate bis(2-hydroxyethyl) sulfide was shown by the following reactions:³¹⁸



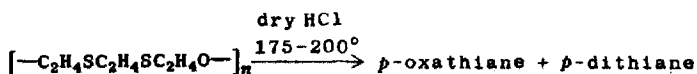
C₄OS Ring System

On passing ethylene glycol at 10 g/hr in a hydrogen sulfide stream over alumina at 225°, the following was obtained:³¹⁹



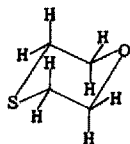
The reaction presumably proceeds through the formation of ethylene oxide. As the temperature of the reaction of ethylene oxide with hydrogen sulfide is increased, the yield of thiophene increases³²² and that of *p*-oxathiane decreases.

Meadow and Reid²⁰⁴ reported a mixture of 15-20% *p*-oxathiane and 5-10% *p*-dithiane from the decomposition of a sulfide polymer.



b. Properties and Uses

p-Oxathiane is a colorless liquid. It is soluble in dilute ethanol and insoluble in water. It has an odor like that of *p*-dithiane and *p*-dioxane.^{117,150} Although its structure has not been determined, it undoubtedly exists in the staggered chair form.^{60a}



The following properties of *p*-oxathiane are recorded in the literature:

melting point -17° ¹⁷²

boiling point $45-55^\circ$ at 22 mm⁹⁴

67° at 44 mm^{96a}

69.9° at 47 mm¹⁷²

100.0° at 165 mm¹⁷²

$144.5-146.5^\circ$ at 740 mm^{2,317,318,319}

$147-150^\circ$ at 760 mm^{5a,93,150,205,246,310a}

n_D^{20} 1.5025³⁰⁹, 1.5072², 1.5081^{96a,172}

d_4^{20} 1.105,^{96a} 1.1070,³⁰⁹ 1.1174-1.1177^{2,50,150}

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compressibility $44.8 \times 10^{-12} \text{ cm}^2/\text{dyne}^{309}$

sound velocity at 30° 1419.8 m/sec³⁰⁹

irreversible oxidation potential + 0.346¹⁹⁴

specific volume^{60a}

parachor¹⁸

dipole moment^{60a}

mutual solubilities *p*-oxathiane-liquid CO₂ binary⁹²

p-oxathiane-liquid CO₂-pyridine ternary⁹²

Raman spectra^{2,3,205}

Sulfur *para* to sulfur, as in *p*-dithiane, has a higher activity than sulfur *para* to oxygen, as in *p*-oxathiane.⁵⁰ Thus, *p*-dithiane's velocity of combination with bromoacetophenone is not only considerably greater than that of *p*-oxathiane, but *p*-oxathiane does not react beyond 4.5% sulfonium bromide. The order of reactivity is the same as the ultraviolet absorption.^{100a, 164} The absorption is in the order *p*-dithiane > tetrahydrothiapyran > *p*-oxathiane. The absorption is anomalous relative to that of open-chain analogs.

Fehnel and Carmack^{83a} observed little difference in the effect of sulfur and oxygen when either of these is separated from a sulfide function by two carbon atoms. This is in marked contrast to the unique behaviour observed when only a single carbon atom separates two sulfide functions.

Cumper and Vogel^{60a} determined the dielectric constants, specific volumes, and refractive indices to sodium light of *p*-oxathiane, its sulfide, and sulfone in benzene solution. The dipole moments are, respectively, 0.42, 2.92, and 3.29 D.

In a study of solvents for Grignard reactions, Hepworth¹⁵⁰ observed that *p*-oxathiane was almost as active as *p*-dioxane and more active than *p*-dithiane, tetrahydrothiapyran or oxide, but less active than ethyl propyl sulfide or oxide.

In tests on the toxicity and repellency of compounds to larvae of *Lucilia Sericata*, *p*-oxathiane was listed as both repellent and toxic to the fly.¹⁹² Inhalation of 4000 parts per million of *p*-oxathiane for four hours killed up to 4-6 rats.⁴² The single dose, oral LD₅₀ in rats is 2.83 g *p*-oxathiane per kilogram of body weight.²⁸⁰

c. Reactions

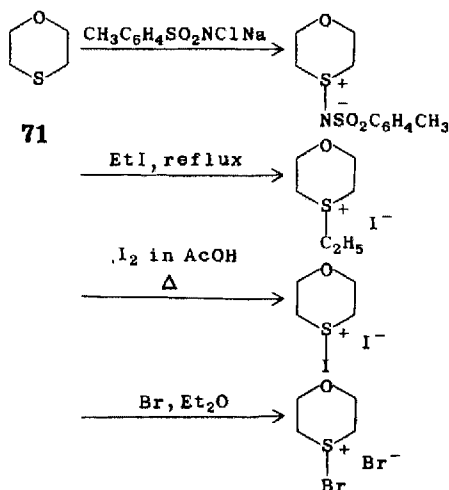
p-Oxathiane forms a crystalline chloromercurate, m.p. 171° , which has been used to isolate and purify *p*-oxathiane.^{50, 117, 147a, 150} *p*-Oxathiane forms a complex with sulfur trioxide.¹¹⁷ The sulfur trioxide complex has been described in patents as a reactant in the preparation of sulfonates from secondary alcohols and unsaturated compounds^{218, 219, 220} and in the sulfonation of polystyrene to an alkali-soluble polymer.²⁶⁴

C₄OS Ring System

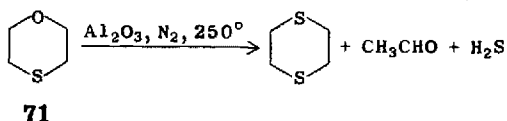
The sulfur trioxide complex is prepared by the action of fuming sulfuric acid, sulfur trioxide, methylsulfonic acid, chlorosulfonic acid, or fluorosulfonic acid on *p*-oxathiane.²¹⁸ *p*-Oxathiane also forms a complex, m.p. 70–72°, with arsenic trichloride, which is almost completely dissociated in solution.³⁰⁸ It also forms a complex with cupric chloride and with platinous chloride.^{147a} Hendra and Powell^{147a} found that the infrared spectra of *p*-oxathiane complexes with mercuric, cupric, and platinous chlorides were similar to that of *p*-oxathiane, suggesting that the structure of the six-membered ring is similar for all. The mercuric and cupric complexes were prepared by merely adding an alcoholic solution of the salt to an alcoholic solution of *p*-oxathiane; the platinous chloride complex was prepared by addition of *p*-oxathiane to an aqueous solution of potassium chloroplatinate.

p-Oxathiane imparts a lemon-yellow color to tetranitromethane. The color reaction was studied spectroscopically by Macbeth¹⁹⁶ and compared with that of tetrahydrothiapyran and *p*-dithiane in tetranitromethane. The reaction is greater with the other two than with *p*-oxathiane, which is in harmony with Clarke's⁵¹ conclusion that oxygen *para* to sulfur decreases the reactivity of sulfur compared to sulfur *para* to sulfur.

p-Oxathiane is readily converted to an oxathianium compound.^{93,94,172a}

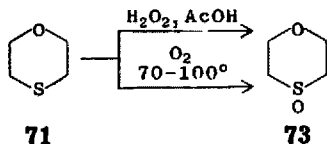


In the reaction of ethylene oxide with hydrogen sulfide over alumina at 200° and above, *p*-dithiane is always formed with the *p*-oxathiane. As the temperature is increased, more *p*-dithiane is formed. One of the reactions that takes place in this system is the conversion of oxathiane to dithiane, the optimum temperature being 250°. ^{318,320}

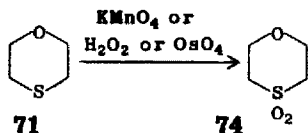


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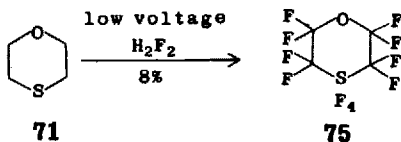
The sulfur in *p*-oxathiane is easily oxidized to the monoxide (**73**) and to the dioxide (**74**). The monoxide has been prepared by treating *p*-oxathiane with hydrogen peroxide in acetic acid^{55, 93} and by treating *p*-oxathiane with oxygenated water:²⁸⁴



The dioxide has been prepared by oxidation of *p*-oxathiane with permanganate,⁵⁵ peroxide,⁹³ and osmium tetroxide.^{61, 62}



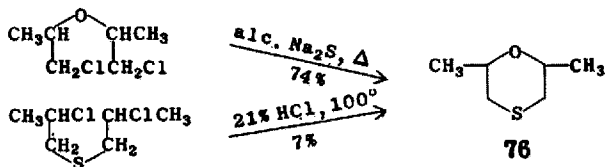
Treatment of *p*-oxathiane with chlorine at from 0° to -10° yields 3-chloro-*p*-oxathiane;¹²⁵ chlorination at higher temperatures yields 2, 3-dichloro- and 2, 3, 5, 6-tetrachloro-*p*-oxathiane.^{124, 126} The positions of the chlorines were undoubtedly assigned by analogy with the chlorination of *p*-dioxane. Electrofluorination of *p*-oxathiane in anhydrous hydrogen fluoride yields a perfluorinated oxathiane (**75**).^{74, 160, 260}



2. Substituted *p*-Oxathianes

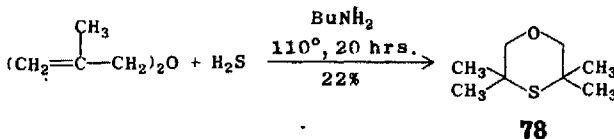
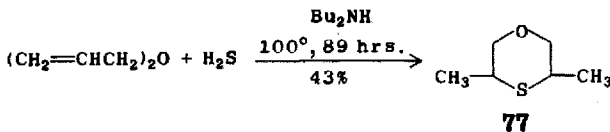
a. Preparation

Hunt and Marvel¹⁶⁷ obtained a 74% yield of 2, 6-dimethyl-*p*-oxathiane (**76**) from the reaction of bis(1-chloro-2-propyl) ether with alcoholic sodium sulfide under reflux. Hughes and Veatch¹⁶⁶ obtained a 7% yield of **76** from the hydrolysis and ring closure of bis(2-chloropropyl) sulfide. The major product in this reaction was the condensation product.



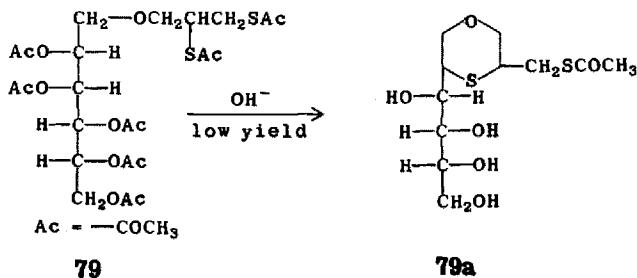
Olefins undergo normal addition on treatment with hydrogen sulfide in the presence of amines. Harman and Vaughn^{121, 122} observed the formation of *p*-oxathianes on reacting hydrogen sulfide with allylic ethers in the presence of butyl amine or dibutyl amine.

C₄OS Ring System



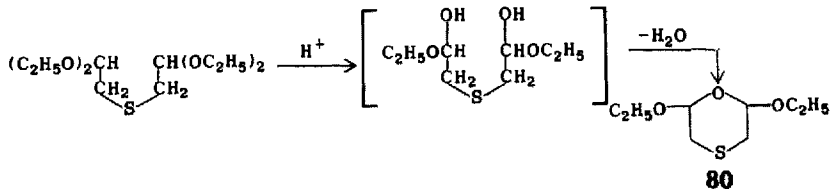
Ballard and Morris^{11,12} obtained polymeric products from the treatment of vinyl ethers with hydrogen sulfide; these were cyclized to *p*-oxathianes on heating at about 200° and atmospheric pressure.

An interesting reaction reported by Harding and Owen¹²⁰ is the alkaline deacetylation of the acetylated mannitol ether of 2, 3-dimercaptopropanol (79) in which the *p*-oxathiane structure (79a) was postulated as being formed with inversion of C-2 in the hexitol:



The simple analog, 2-acetoxyethyl 2, 3-bisacetylthiopropyl ether, on alkaline hydrolysis reached a thiol value equivalent to 1.9 groups corresponding to 10% cyclization. However, attempts to isolate the *p*-oxathiane were unsuccessful.

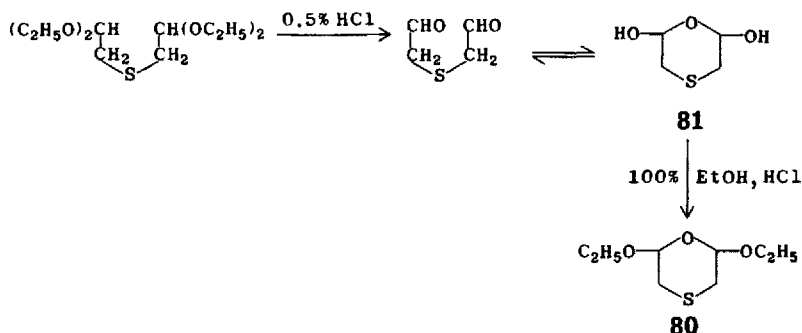
Clarke and Smiles,⁵⁰ in 1909, obtained a 99% yield of 2, 6-diethoxy-*p*-oxathiane (**80**) by treating thiodiacetal in absolute ethanol or dry ether with dry hydrogen chloride. In the presence of cold mineral acids, thiodiacetal was presumed to go to the *p*-oxathiane through the hemiacetal.



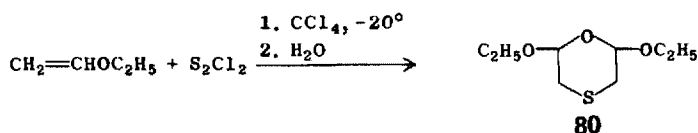
According to Coghill,⁵³ dilute hydrochloric acid (0.5%) hydrolyzes the diacetal to the diacetaldehyde, which could not be isolated as such. It was believed to exist in equilibrium with 1,4-oxathiane-2,6-diol (81)

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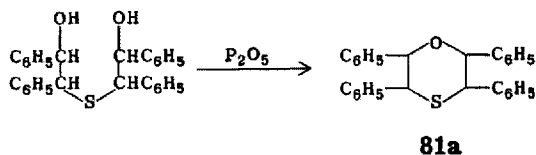
which could be isolated in nearly theoretical yield by concentrating the solution.



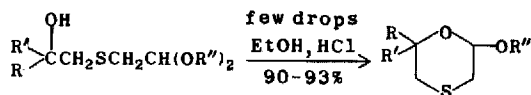
Seefelder and Pasedach²⁵⁹ prepared 2,6-diethoxy-*p*-oxathiane (**80**) by mixing vinyl ethyl ether and sulfur monochloride in carbon tetrachloride at -20° followed by addition of water.



Cattaneo⁴⁵ prepared 2,3,5,6-tetraphenyl-*p*-oxathiane (**81a**) by heating bis(2-hydroxy-1,2-diphenylethyl) sulfide with phosphorus pentoxide at $125-30^\circ$ for 2 hours.



Parham²³¹ prepared several *p*-oxathianes by the following general reaction:



$\text{R} = \text{H, H, CH}_3$

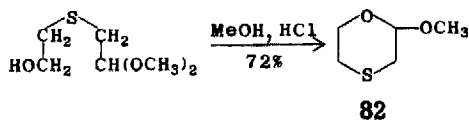
$\text{R}' = \text{H, CH}_3, \text{CH}_3$

$\text{R}'' = \text{C}_2\text{H}_5, \text{C}_2\text{H}_5, \text{C}_2\text{H}_5$

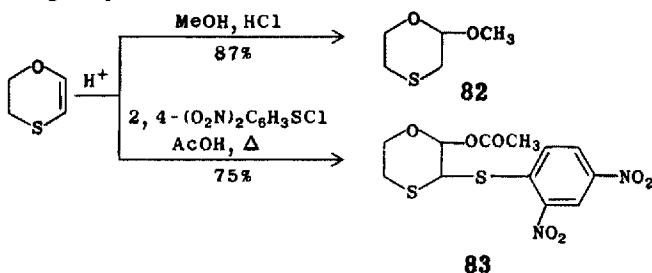
It was not possible to reverse the ring closure to get the acetals by the action of ethanolic HCl. Heating the *p*-oxathianes with dilute hydrochloric acid for 80 minutes did reverse the reaction to give 62% aldehyde.

Treatment of 2-hydroxyethylthioacetaldehyde methyl acetal with methanolic HCl gave a 72% yield of 2-methoxy-*p*-oxathiane (**82**).²³²

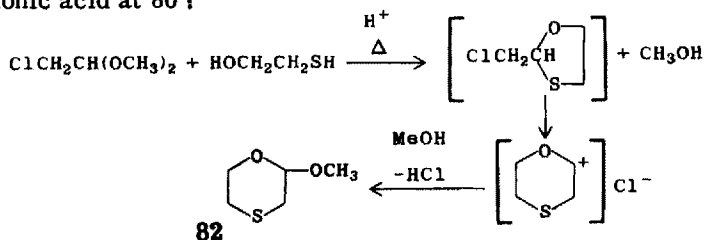
C₄OS Ring System



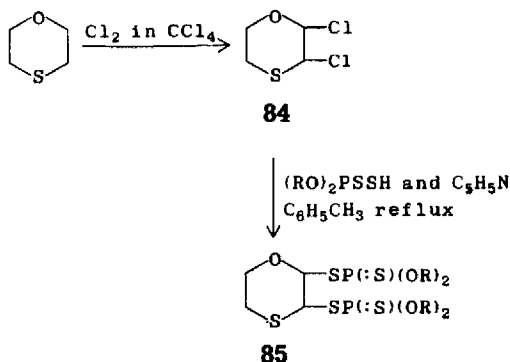
Dihydro-*p*-oxathiin undergoes acid-catalyzed addition at the double bond to give *p*-oxathiane derivatives.²³²



Parham, Heberling, and Wynberg²³⁴ postulated the following mechanism on obtaining a 37% yield of 2-methoxy-*p*-oxathiane (**82**) from the vigorous and somewhat uncontrolled reaction that occurred on heating a mixture of chloroacetal and monothioglycol in the presence of *p*-toluenesulfonic acid at 80°:



Perfluoro-*p*-oxathiane-4-tetrafluoride is reduced to the ether $\text{HC}_2\text{F}_4\text{OC}_2\text{F}_4\text{H}$ in 45% yield by heating with alcoholic potassium hydroxide at 125° in an autoclave for 6 hours.²⁶⁰ Chlorinated *p*-oxathianes, on reaction with diethyl dithiophosphate and pyridine under toluene reflux, are converted to the corresponding or chlorinated diethyl dithiophosphates of 1,4-oxathianethiol (**85**).¹²⁴⁻¹²⁸



The alkyl radical was varied from ethyl to butyl.

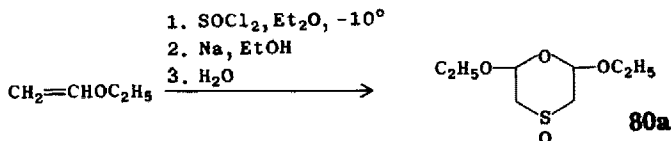
b. Properties, Reactions and Uses

Substituted *p*-oxathianes are high boiling, colorless liquids. 2-Butoxy-*p*-oxathiane has been characterized as having a sweet odor.²³¹ 2, 6-Dihydroxy-*p*-oxathiane (**81**) is soluble in water at room temperature; it stains skin a deep brown, the stain being impossible to remove; and it has a characteristic odor.⁵³ 2, 6-Diethoxy-*p*-oxathiane (**80**) is soluble in hot water and organic solvents.⁵⁰ Perfluoro-*p*-oxathiane is thermally stable at 400°;²⁶⁰ its NMR spectrum has been reported.²¹⁴ 2, 3, 5, 6-Tetraphenyl-*p*-oxathiane is stable in light and air; its ultraviolet absorption spectrum shows a band at 316 mμ and a very intense band below 220 mμ; it shows distinct bathochromatism and hyperchromatism relative to the dioxane analog.⁴⁵

It has been pointed out in the discussion of the properties of *p*-oxathiane that it undoubtedly exists in the staggered chair form. When we consider the substituted *p*-oxathianes, such as 2, 3-dichloro-*p*-oxathiane (**84**) and its derivatives or tetraphenyl-*p*-oxathiane (**81a**), in particular, it is reasonable to expect that they would be isolated as geometrical isomers. The only *cis-trans* isomers reported is that of 2, 6-dimethyl-*p*-oxathiane 4, 4-dioxide with melting points of 104. 5-105. 5° and 92. 5-93. 0°. ¹⁹⁹ That no other cases have been reported is surprising. The sharpness of the melting points and the good yields revealed in Table 9 leads one to raise the question whether these compounds could have a preferred conformation.

The sulfur in alkoxy-*p*-oxathiane, according to Clarke and Smiles,⁵⁰ has a depressed activity in comparison with that of an open chain sulfide in the reaction with mercuric chloride or iodide in acetone, hydrogen peroxide (three days at room temperature), and ethyl iodide-mercuric iodide mixture (Table 10a).

2, 6-Diethoxy-*p*-oxathiane monoxide (**80a**) was prepared by Seefelder and Pasedach²⁹⁵ by the reaction of vinyl ethyl ether with thionyl chloride in ethyl ether at -10° followed by treatment with sodium and ethanol.

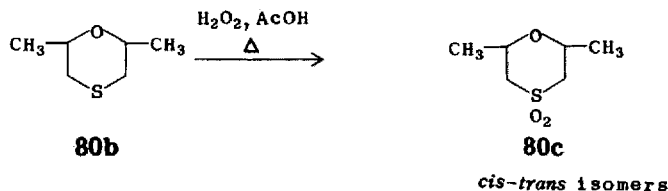


Treatment of 2, 6-dimethyl-*p*-oxathiane with hydrogen peroxide in acetic acid with warming gave two 4, 4-dioxides, presumably *cis-trans* isomers, one melting at 104. 5-105. 5° and the other at 92. 5-93°. ¹⁹⁹ That the two geometrical isomers (**80c**) were obtained directly from 2, 6-dimethyl-*p*-oxathiane (**80b**) indicates that it also was a mixture of the *cis-trans* isomers. Using chromic oxide in acetic acid, only low yields of the 4, 4-dioxide (m.p. 102°) were obtained.

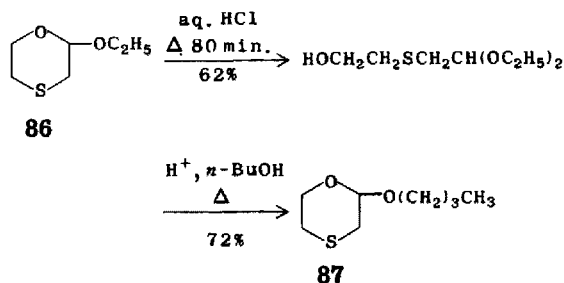
TABLE 10a. Reactivity of *p*-Oxathiane

Reactant	Sulfide: (C ₆ H ₅ CH ₂) ₂ S	((C ₂ H ₅ O) ₂ CHCH ₂) ₂ S	2, 6-Diethoxy- <i>p</i> -Oxathiane
HgCl ₂ or HgI ₂ in acetone	complex	complex	no reaction
H ₂ O ₂	sulfoxide	sulfoxide	no reaction
C ₂ H ₅ I + HgI ₂	sulfonium (0.5 hr)	sulfonium (5 hr)	slight reaction in 8 hrs.

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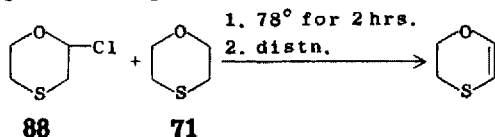


2, 6-Dihydroxy-*p*-oxathiane polymerizes when its solutions are treated with saturated salt solution, a trace of alkali, or when the solid compound is kept in the dry state. It reacts readily with ethanol in the presence of acid to give 2, 6-diethoxy-*p*-oxathiane (**80**) quantitatively.⁵³ 2, 6-Diethoxy-*p*-oxathiane (**80**) decomposes on treatment with concentrated hydrochloric acid; concentrated sulfuric acid solutions of 2, 6-diethoxy-*p*-oxathiane are red; treatment with ethyl iodide and mercuric iodide for 24 hours gives a complex, m.p. 95. 7°. ⁵⁰ Treatment of 2-ethoxy-*p*-oxathiane (**86**) with dilute hydrochloric acid causes ring opening.²³¹ 2-Ethoxy-*p*-oxathiane (**86**) and (2-hydroxyethylmercapto)-acetaldehyde diethyl acetal give the same 2, 4-dinitrophenylhydrazone, m.p. 74-5°. 2-Ethoxy-*p*-oxathiane undergoes transesterification with butanol in the presence of a few drops of alcoholic hydrochloric acid under reflux for 5 minutes.²³¹



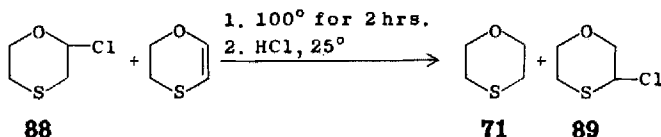
6-Ethoxy-2, 2-dimethyl-*p*-oxathiane similarly undergoes transesterification with butanol in a 73% yield. The alkoxy-*p*-oxathianes, in the absence of alcohol, however, do not undergo ring opening by this catalytic amount of alcoholic hydrochloric acid. The ether interchange fails when the entering alcohol is tertiary.

2-Chloro-*p*-oxathiane (**88**) reacts with *p*-oxathiane under a nitrogen sparge at 78° to give dihydro-*p*-oxathiin.¹²⁵



The 2-chloro compound (**88**) and dihydro-*p*-oxathiin held at 100° under pressure for two hours and then sparged at 25° with hydrogen chloride gas give a mixture of *p*-oxathiane (**71**) and 3-chloro-*p*-oxathiane (**89**).¹²⁵

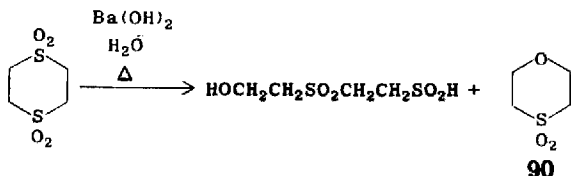
C₄OS Ring System



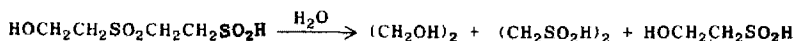
The reaction product of the chloro-*p*-oxathianes with dialkyl dithiophosphates exhibit insecticidal activity against pea aphids, two-spotted mites, Mexican bean beetles, and flies in concentration of 1% and less.¹²⁴⁻¹²⁶ 2, 6-Diethoxy-*p*-oxathiane (**80**) and its sulfoxide (**80a**) were said to be useful as pharmaceutical intermediates and as insecticides.²⁵⁹ Nevers and Fettes^{222a} patented the use of dimethyl-*p*-oxathiane as a fuel gas odorant.

3. *p*-Oxathiane 4-Oxides

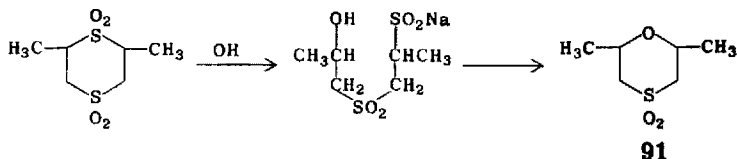
The first reported preparation of *p*-oxathiane 4, 4-dioxide (**90**) was that of Baumann and Walter¹⁴ by the hydrolysis of *p*-dithiane 1, 1, 4, 4-tetroxide with barium hydroxide solution:



The *p*-oxathiane presumably arises from hydroxyethyl sulfoethyl sulfone or from ethylene glycol and hydroxyethylsulfonic acid which are decomposition products of the *p*-dithiane sulfone.



Marvel and Weill¹⁹⁹ postulated that the alkaline cleavage of 2, 6-dimethyl-*p*-dithiane disulfone leads to a β -hydroxysulfonyl compound which then undergoes base-catalyzed etherification. The mechanism of the ring closure is still not elucidated.

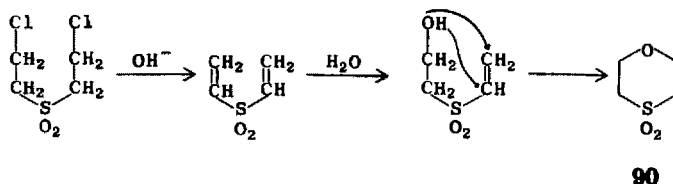


Kretov¹⁸¹ obtained *p*-oxathiane 4, 4-dioxide (**90**) on refluxing bis(hydroxyethyl) sulfone in alkali. Price and Bullitt²⁴¹ also obtained the 4, 4-dioxide (**90**) in good yield, instead of the expected bis(hydroxyethyl) sulfone, on treating bis(hydroxyethyl) sulfide with hydrogen peroxide in acetic acid or with chlorine.

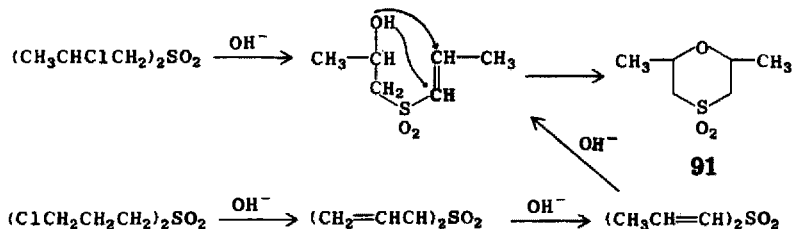
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In preparing divinyl sulfone by refluxing bis(hydroxyethyl) sulfide with 2% P_2O_5 and 27-35% H_2O_2 two to four hours and then heating the mixture with 85% phosphoric acid at 280° , the end of the fractionation of divinyl sulfone from the products is indicated by the appearance of the 4, 4-dioxide (90).²³⁰ When the reaction is carried out in glacial acetic acid, the 4, 4-dioxide (90) is obtained in 80% yield. The dioxide (90) is also obtained by starting with bis(acetoxyethyl) sulfide; using potassium permanganate in aqueous acetic acid, bis(acetoxyethyl) sulfide gave 62% 4, 4-dioxide (90). Treatment of the bis(acetoxyethyl) sulfone with sodium ethylate in ethanol gave 96% dioxide (90); the benzoate gave an 81% yield.

Cashmore⁴³ observed that the treatment of bis(2-chloroethyl) sulfoxide or sulfone with alcoholic or aqueous sodium hydroxide under reflux gave *p*-oxathiane 4-monoxide and the 4, 4-dioxide (90), respectively. This was unexpected, as bis(2-chloroethyl) sulfide or bis(2-hydroxyethyl) sulfide under similar conditions did not give *p*-oxathiane. The strong activating effect of a sulfoxide or sulfone group on a halogen, however, is well known and it is reasonable to assume the ready dehydrohalogenation of the bis(chloroethyl) sulfone to divinyl sulfone. This should hydrate readily and rearrange to *p*-oxathiane 4, 4-dioxide.



Bis(2-chloroethyl) sulfone, on treatment with aqueous sodium carbonate gave a low yield of *p*-oxathiane 4, 4-dioxide (90), most of the product being bis(2-hydroxyethyl) sulfone,⁹¹ whereas dilute sodium hydroxide gave an 80% yield of *p*-oxathiane 4, 4-dioxide. In the aqueous sodium carbonate reaction, if, after refluxing for one hour, additional aqueous sodium carbonate is added and the mixture heated for another hour, the yield of *p*-oxathiane 4, 4-dioxide is increased seven-fold. According to Ford-Moore, hot alkaline reaction of bis(2-chloroethyl) sulfone goes through divinyl sulfone formation as an intermediate step. It is more likely, however, that the intermediate is hydroxyethyl vinyl sulfone as discussed above. Hot aqueous sodium hydroxide similarly converts bis(2- or 3-chloropropyl) sulfone to 2, 6-dimethyl-*p*-oxathiane 4, 4-dioxide (91).^{91,199}



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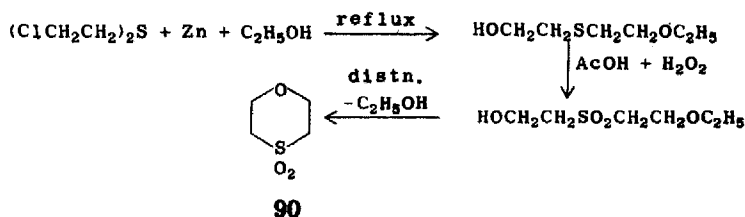
The dehydrochlorination of bis(2-chloroethyl) sulfone to *p*-oxathiane 4, 4-dioxide (**90**) occurs at a relatively low pH; at pH 8 and 38°, 96% of the chlorine is ionic after 2 hours and 99% after 3 hours; at pH 7.35 and 38°, the reaction is 58% complete after 2 hours and 75% after 3 hours. The dehydrochlorination of bis(2-chloroethyl) sulfoxide is much slower; at pH 8 and 38°, it is less than 2% complete in 2 and about 12% in 5 hours.⁹¹

Alexander and McCombie⁴ obtained *p*-oxathiane 4-monoxide and 4, 4-dioxide, respectively, on heating divinyl sulfoxide and sulfone with 5% sodium hydroxide. Divinyl sulfide, on treatment with sodium hydroxide yielded only polymeric products. Ford-Moore⁹¹ obtained a 97% yield of dioxide (**90**) on refluxing divinyl sulfone with dilute sodium carbonate solution.

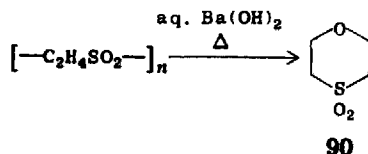
Davis and Sorensen⁶² disproportionated the sulfoxide to the dioxide (**90**) by heating with nitrogen dioxide and osmium tetroxide for two hours at 130° in the presence of oxygen.

Backer and van der Ley⁹ reported a 24% yield of 2, 6-dimethyl-*p*-oxathiane 4, 4-dioxide (**91**) on refluxing diallyl sulfone with aqueous sodium carbonate. The same product was obtained by Hunt and Marvel¹⁶⁷ on refluxing for a long time poly(propylene sulfone) with aqueous sodium carbonate. The mechanism of the diallyl sulfone reaction probably involves first isomerization and then a hydration.

Kretov¹⁸⁰ prepared *p*-oxathiane 4, 4-dioxide by the following series of reactions:



Staudinger and Ritzenthaler²⁸⁵ reported the preparation of *p*-oxathiane 4, 4-dioxide by the heating of poly(ethylene sulfone) with aqueous barium hydroxide:



On the other hand, poly(propylene sulfone) treated similarly gave only the dithiane derivative. Hunt and Marvel,¹⁶⁷ however, on treating 25 g poly(propylene sulfone) with hot 5% sodium carbonate solution obtained a mixture of 3 g 2, 6-dimethyl-*p*-oxathiane 4, 4-dioxide (**91**) and 2 g 2, 5-dimethyl-*p*-dithiane disulfone.

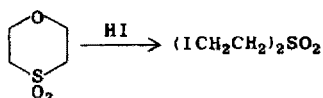
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The oxides also have been prepared by oxidation of the corresponding *p*-oxathianes. These have been discussed in the previous sections.

p-Oxathiane 4-oxide is a hygroscopic solid, melting at 44.5–45.0°; above its melting point it is a pale yellow, viscous liquid with an unpleasant odor much like that of a mercaptan; the liquid boils at 150° at 23 mm; it is soluble in ethanol, ethyl ether, and chloroform and insoluble in water.^{43,55} *p*-Oxathiane 4, 4-dioxide is a solid, melting at 130° and boiling at 130–140° at 1 mm;²⁴¹ it is soluble in ethanol, water, and chloroform, but sparingly soluble in light petroleum.⁴³

The dipole moment of *p*-oxathiane 4-monoxide is 2.92 D; that of the 4, 4-dioxide is 3.29 D.^{60a}

p-Oxathiane 4, 4-dioxide is converted to bis(iodoethyl) sulfone on treatment with hydrogen iodide.⁹³

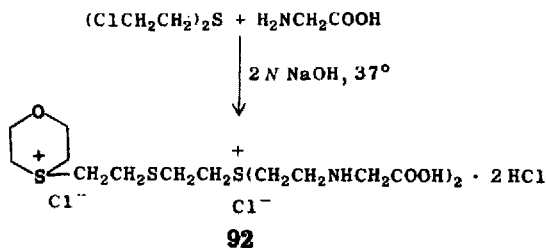


p-Oxathiane 4, 4-dioxide is a powerful solvent when used with acetone, benzene, or alcohol. It has been suggested for use as a solvent in cosmetics, varnishes, and for dissolving aspirin, mercuric iodide, quinine, and other medicinals; also for spinning thread, for dye solvents, and as a softener for polyvinyl alcohol or acetal.²⁸⁴ It has a separation factor of 17/1 at 42° for acetylene mixtures and has been suggested as a gas absorbent.²⁵² A mixture of 40% *p*-oxathiane 4, 4-dioxide and dimethyl sulfoxide forms an eutectic, m.p. –2°, which has a separation factor of 30/1 at 0–30°.

Pollitzer^{239a} used *p*-oxathiane 4-monoxide containing 10% water as an extracting solvent for the separation of aromatics and cyclic hydrocarbons, *e.g.*, benzene and methylcyclopentane.

4. *p*-Oxathianium Compounds

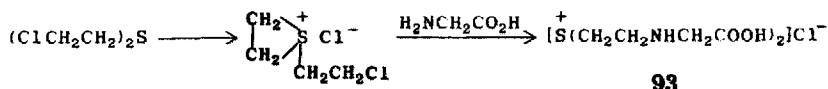
A *p*-oxathianium compound (**92**) was characterized by Douglas and Heard⁷³ from the reaction of bis(2-chloroethyl) sulfide with glycine at pH 7.5.



This *p*-oxathianium compound is a solid, melting at 161° to a viscous liquid. The chloride ion is titratable with mercuric nitrate. Treatment

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with very dilute cupric ion gives a greenish-blue color. It was postulated that the reaction proceeded by the following mechanism:



This intermediate, by virtue of its labile structure, is a strong alkylating agent and, thus, alkylates the amino group of glycine; the remaining chlorine atom becomes ionic and a second cyclic structure is formed which alkylates a second molecule of glycine to give the alkylated glycine (**93**). This undergoes further alkylation by bis(2-chloroethyl) sulfide to form a sulfonium chloride which reacts with another molecule of bis(2-chloroethyl) sulfide or with *p*-oxathiane.

Other *p*-oxathianium compounds which were prepared directly from *p*-oxathianes are discussed in the previous sections. The *p*-oxathianium compounds prepared and their properties are listed in Table 11.

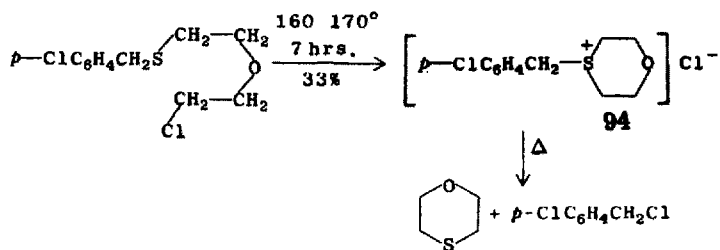
TABLE 11. *p*-Oxathianium Compounds

X ⁻	R	B.p. (°C)	M.p. (°C)	<i>n</i> _D ²²	Ref.
I	I		66-67		93
Br	Br		75-80		93
Br	C ₂ H ₅ -		85		93
Br	C ₆ H ₅ COCH ₂ -				51
Cl	<i>p</i> -ClC ₆ H ₄ CH ₂ -	147-150*		1.5070	183
Cl	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ NH-		147.5-148.5		94
Cl	-[-CH ₂ CH ₂ SCH ₂ CH ₂ S ⁺ (CH ₂ CH ₂ NHCH ₂ COOH) ₂ ·2HCl]Cl ⁻		161		73
Br	HC≡CCH ₂ -		140-141		172a

* It is difficult to reconcile this boiling point with the melting points of the other compounds.

The ease with which *p*-oxathianium compounds are formed was the basis for Clarke's⁵¹ conclusion that oxygen para to sulfur decreases the reactivity of the sulfur.

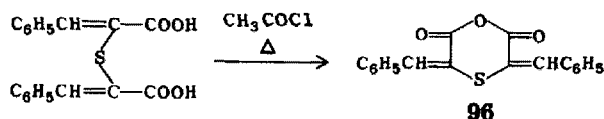
Kulka,¹⁸³ on heating β -*p*-chlorobenzylmercaptoethyl 2-chloroethyl ether (94a), obtained the oxathianium compound (94), a malodorous liquid; on dry distillation, the oxathianium compound decomposed to *p*-oxathiane and *p*-chlorobenzyl chloride:



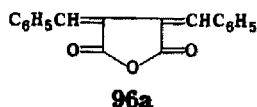
S-Propynyl-*p*-oxathianium bromide, which Johnston^{172a} prepared by letting a mixture of *p*-oxathiane and 2-propynyl bromide stand for ten days at room temperature, was found to possess cholinergic activity analogous to that of acetyl choline.

5. *p*-Oxathiane-2,6-diones (Anhydride Form)

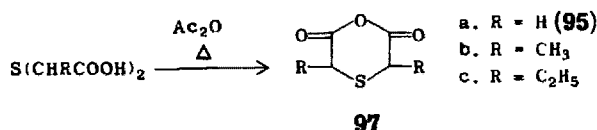
One of the earliest preparations of *p*-oxathianes was that of Anschütz and Biernaux in which thiodiacetic acid and acetyl chloride were heated to give *p*-oxathiane-2, 6-dione (95) as needles from chloroform.⁶ The same mixture on standing in the cold did not react. Stobbe, Ljungren, and Freyberg²⁸⁸ prepared 3, 5-dibenzal-*p*-oxathiane-2, 6-dione (96) by heating the corresponding thiodiacetic acid and acetyl chloride for 6-8 hours.



In comparison to this, they point out that diphenylfulgide (96a) (the corresponding furan derivative) is prepared by mere treatment of dibenzylsuccinic acid with cold acetyl chloride.

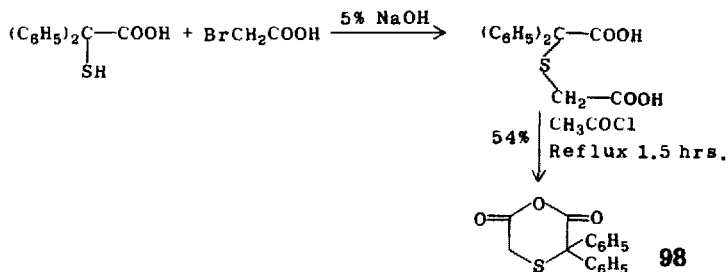


Lappas and Jenkins¹⁸⁴ prepared the unsubstituted, the 3, 5-dimethyl-, and 3, 5-diethyl-*p*-oxathiane-2, 6-diones (97) in yields of 71-96% by heating the thiodiacetic acid and acetic anhydride three hours.



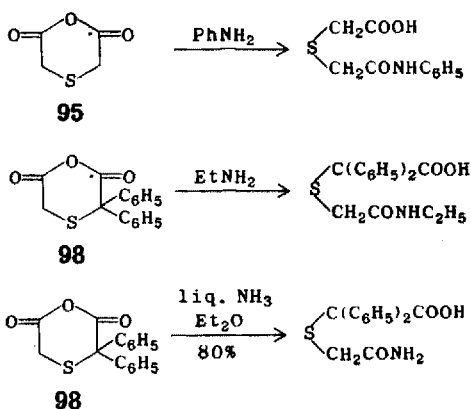
C₄OS Ring System

Skinner and Bicking²⁶⁶ prepared unsymmetrical anhydrides by the following series of reactions:

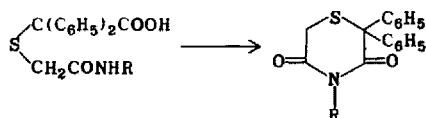


The anhydride form and its substitution derivatives, listed in Table 12, are colorless solids with relatively high boiling points. *p*-Oxathiane-2, 6-dione is soluble in water, difficultly soluble in chloroform in the cold, and soluble in hot chloroform or warm ether.⁶ It is easily hydrolyzed to thiodiglycolic acid. 3, 5-Dibenzal-*p*-oxathiane-2, 6-dione²⁸⁸ is soluble in chloroform and acetone, difficultly soluble in carbon disulfide, acetic acid, ethanol, and benzene, and insoluble in benzene and petroleum ether. It is bright-yellow and stable to air. The thioglycolic anhydride (96) hydrolyzes much more readily than does the fulgide (96a). The sulfur atom does not function as a chromophore. The halochromism disappears when either compound is hydrolyzed.

The anhydride form reacts readily with liquid ammonia or with amines to open the ring and to form amides,^{6,13,184,266-7}



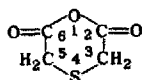
The half amides undergo ring closure to give the corresponding 3, 5-thiamorpholinedione; ^{13,266}



Chapter 11

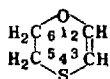
p-Oxathiane-2, 6-dione has been used as a solvent and gelatinizing agent for polyacrylonitrile.^{21a}

TABLE 12. *p*-Oxathiane-2, 6-diones



Substituent	Yield (%)	M.p. (°C)	(B.p.) (°C)	(B.p.) (mm)	n_D^{20}	Ref.
None	71	101	158-159	12		184
		102	158	10		6
3-C ₆ H ₅ -						13
3, 5-(CH ₃ -) ₂	81.5		133-137	14	1.5010	184
3, 5-(C ₂ H ₅ -) ₂	96.2	14-15	149-150	15	1.4942	184
3, 3-(C ₂ H ₅ -) ₂			149-151	15		267
3, 5-(C ₆ H ₅ -) ₂						13
3, 3-(C ₆ H ₅ -) ₂	54	108-109				266
						13
3, 3, 5-(C ₆ H ₅ -) ₃						13
3, 5-(C ₆ H ₅ CH=) ₂		110				288

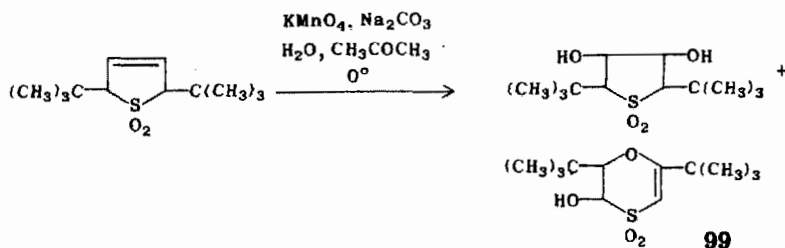
6. Dihydro-*p*-Oxathiin (100)



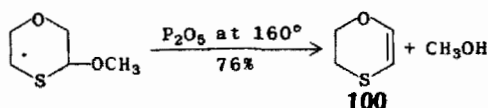
100

Relatively little preparative work has been done on dihydro-*p*-oxathiin and its derivatives. Those which have been reported are listed in Table 13. The first member of this series prepared was apparently 2, 6-di-(*t*-butyl)-5-hydroxy-5, 6-dihydro-*p*-oxathiin 4, 4-dioxide (**99**) which Backer and Strating⁸ obtained as a secondary product from the hydration of 2, 5-di-*t*-butyl-2, 5-dihydrothiophene 1, 1-dioxide with potassium permanganate in aqueous acetone.

C₄OS Ring System

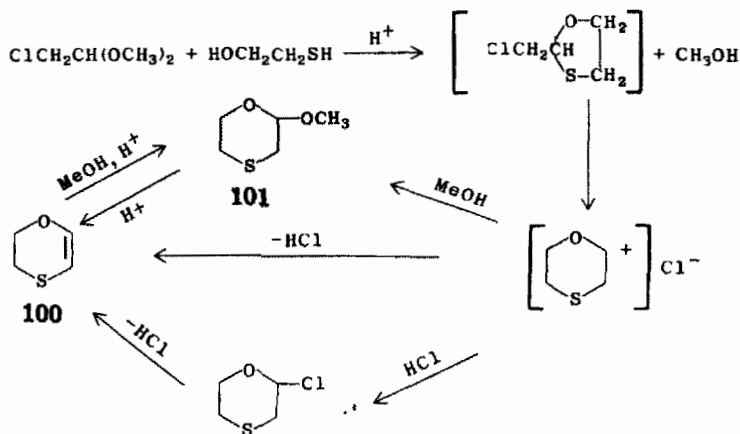


Parham, Gordon, and Swalen,²³² on heating 3-methoxy-*p*-oxathiane with phosphorus pentoxide at 160°, obtained a 76% yield of dihydro-*p*-oxathiin (**100**), which they called *p*-oxathiene.



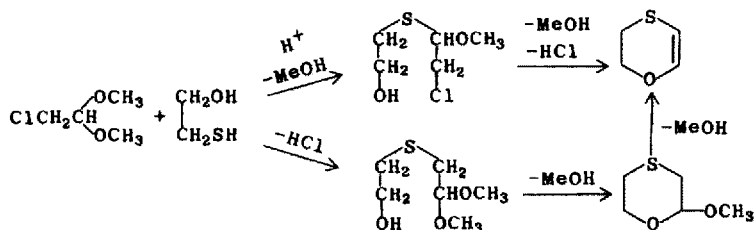
Haubein,^{125,128} in preparing a series of *p*-oxathiane derivatives for insecticidal studies, heated a solution of *p*-oxathiane and its monochlorination derivative, 2-chloro-*p*-oxathiane, at 78° for two hours under a nitrogen sparge and obtained dihydro-*p*-oxathiin, which he called thioxene.

Parham, Heberling, and Wynberg²³⁴ reported that on heating a mixture of chloroacetal and mercaptoethanol in the presence of *p*-toluenesulfonic acid to 80° in the absence of solvent, a vigorous reaction took place with evolution of methanol and hydrogen chloride. The first fraction obtained on distillation was dihydro-*p*-oxathiin (minor amount), and the second (major) was 2-methoxy-*p*-oxathiane (**101**). The course of the reaction was postulated as follows:

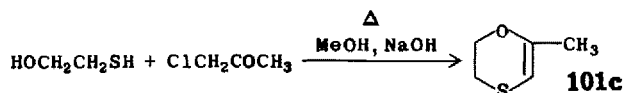
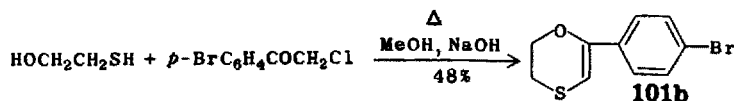
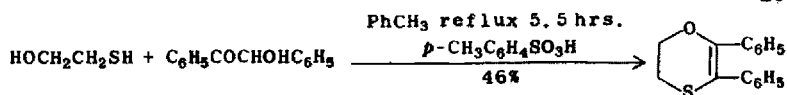
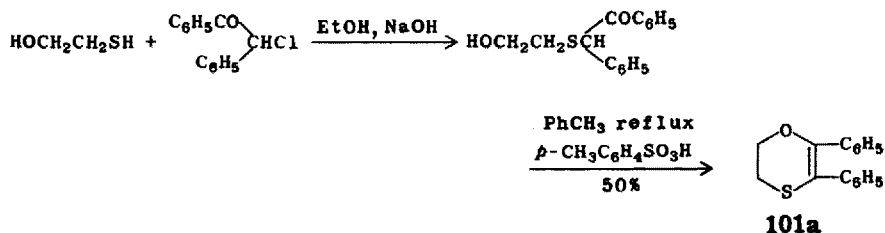


Although this is a likely mechanism, other equally reasonable mech-

anisms can be postulated, such as the following:



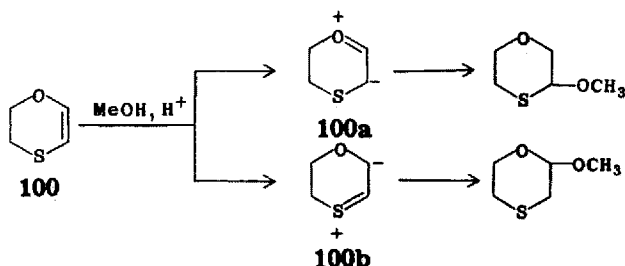
Marshall and Stevenson^{198a} described a general method for the preparation of dihydro-*p*-oxathiins in good yields by the reaction of 1, 2-mercaptoalcohols with 1, 2-ketoalcohols, acid chlorides, or α -chloro-ketones. Thus, they obtained a 50% yield of 2, 3-diphenyl-5, 6-dihydro-*p*-oxathiin (101a) on reacting mercaptoethanol with desyl chloride and dehydrating the resulting α -(2-hydroxyethylthio)desoxybenzoin with refluxing toluene in the presence of *p*-toluenesulfonic acid. 2, 3-Diphenyl-5, 6-dihydro-*p*-oxathiin was obtained in 46% yield by refluxing a mixture of mercaptoethanol and benzoin in toluene in the presence of *p*-toluenesulfonic acid. 2-*p*-Bromophenyl-5, 6-dihydro-*p*-oxathiin (101b) was prepared in 48% yield by reacting *p*-bromophenacyl chloride with mercaptoethanol in aqueous methanolic solution; 2-methyl-5, 6-dihydro-*p*-oxathiin (101c) was prepared similarly from mercaptoethanol and chloroacetone.



Dihydro-*p*-oxathiin slowly polymerizes to a colorless product which melts at 200–220°. It is quite stable, however, if kept free of acids or peroxides. It polymerizes immediately on the addition of boron trifluoride. It reacts readily with methanolic hydrochloric acid to give 2-methoxy-*p*-oxathiane (101). This reaction, as well as hydration, was

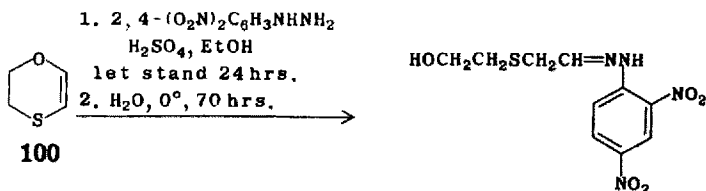
C₄OS Ring System

studied²³² in order to determine the relative tendencies of the hetero oxygen and sulfur to release electrons, or, in other words, which of the two structures was favored, **100a** or **100b**.

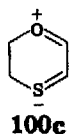


The fact that only 2-methoxy-*p*-oxathiane was obtained favors the thianium structure (**100b**).

Treatment of dihydro-*p*-oxathiin in methanol with 2, 4-dinitrophenylhydrazine in the presence of sulfuric acid gives the hydrazone of hydroxyethylthioacetaldehyde.



The alternative product from this reaction would be the hydrazone of mercaptoethylglycolaldehyde; however, none was found. This result and that of the acid catalyzed addition of methanol were cited as evidence that oxygen releases electrons more readily in the direction of its covalent bond than does sulfur. In addition, the ultraviolet spectra of dihydrothiapyran and of dihydropyran showed no maximum above 227 mμ whereas dihydro-*p*-oxathiin had a distinct maximum at 229 mμ (ε = 3820). It was therefore suggested that the following resonance hybrid appears to be indicated:²³²

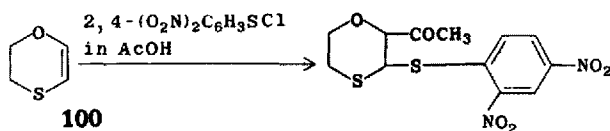


Hydrogen peroxide in acetone does not convert dihydro-*p*-oxathiin to the sulfoxide or sulfone. Treatment with 2, 4-dinitrobenzenesulfonyl chloride in glacial acetic acid gives 75% 2-acetoxy-3-(2, 4-dinitrobenzenesulfonyl)-*p*-oxathiane.

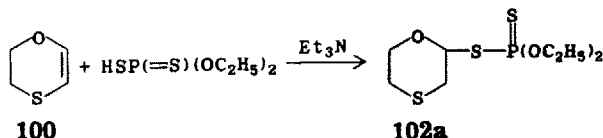
TABLE 13. Dihydro-*p*-oxathiins

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	n_D^{20}	Ref.
None	35		47-48	19	1.5209/20°	125, 128
2-CH ₃ -	76		54	20	1.5357/23°	232
			54	22	1.5337/22°	234
			56	10	1.5288/16°	198a
2-C ₆ H ₅ -			126	0.7	1.6491/16°	198a
2- <i>p</i> -BrC ₆ H ₄ -	48	97				198a
2-[-SP(=S)(OC ₂ H ₅) ₂]	65					68
2, 3-(C ₆ H ₅) ₂	50	63-65				198a
2, 6-[-C(CH ₃) ₃] ₂ -5-OH 4, 4-dioxide		157.5				8
2, 6-[-C(CH ₃) ₃] ₂ -5-OCOCH ₃ 4, 4-dioxide		101				8
2, 6-[-C(CH ₃) ₃] ₂ -5-(=O) 4, 4-dioxide		106				8

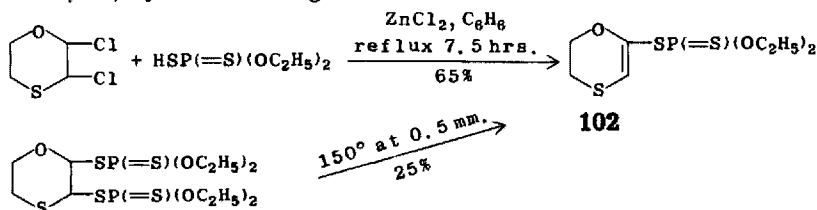
C₄OS Ring System



Haubein,^{125,128} on treating a mixture of *p*-oxathiane and dihydro-*p*-oxathiin in benzene with *O, O*-diethylphosphorodithioate in the presence of triethylamine, obtained the *S*-(*O, O*-diethylphosphorodithioate) derivative of *p*-oxathiane-2-thiol (**102a**). This product, which exhibited insecticidal activity against two-spotted mites and pea aphids, was also prepared from 2-chloro-*p*-oxathiane, which, in turn was prepared by heating dihydro-*p*-oxathiin under pressure at 100° for 2 hours and then passing in hydrogen chloride as the mixture cooled to 25°.



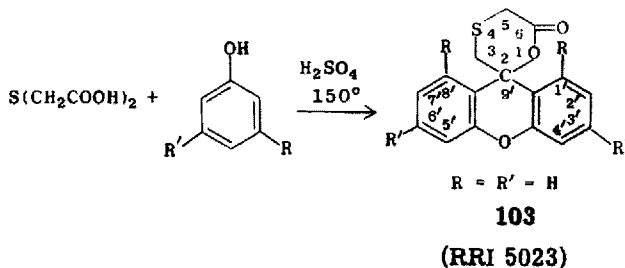
Diveley⁶⁸ prepared 2-(*O, O*-diethylphosphorodithioate)-dihydro-*p*-oxathiin (**102**) by the following two methods:



102 was found to be toxic to mites.

7. Spiro-*p*-oxathianes

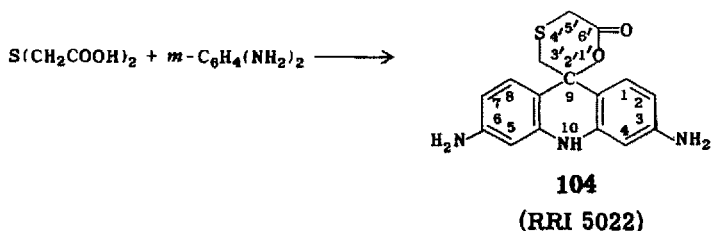
In a study on the effect of replacing carbon with sulfur in certain dyes, Dey and Dutt⁶⁵ reacted thiodiglycolic acid with phenols. The condensation of thiodiglycolic acid with phenol at 150° in the presence of sulfuric acid yielded spiro[6-oxo-*p*-oxathiane-2, 9'-xanthene] (**103**).



Chapter 11

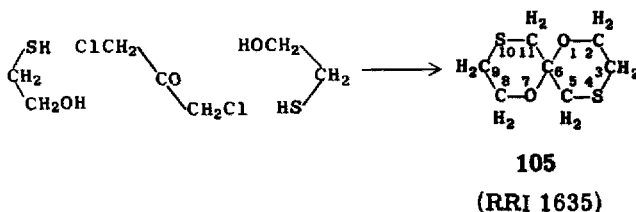
Using resorcinol the product ($R = H, R' = OH$) did not melt below 310° and was soluble in alkali, the solution having a yellow color and green fluorescence. Using phloroglucinol, the product ($R = R' = OH$) was not crystalline; its alkaline solution was orange. Using *m*-hydroxydiethylaniline, the product ($R = H, R' = C_2H_5NH-$) was a red powder, m.p. $172-173^\circ$.

Similarly, the reaction of thiodiglycolic acid with *m*-phenylenediamine yielded the spiro[acridan-9, 2'-*p*-oxathiane] (104).⁶⁵

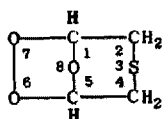


Dey and Dutt called these compounds thiodiglycoleins.

Backer and Wiggerink¹⁰ prepared 1, 7-dioxa-4, 10-dithiaspiro[5. 5] hendecane (105), m.p. $127-127.5^\circ$, by passing gaseous hydrogen chloride into a cooled anhydrous ethyl ether solution of dichloroacetone and mercaptoethanol:

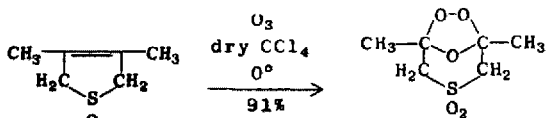


B. $C_2O_3-C_4OS$ 6, 7, 8-TRIOXA-3-THIABICYCLO[3. 2. 1]OCTANE (106)



This ring system, indexed by Chemical Abstracts under the above name, was relatively recently reported by Criegee and Lohaus⁵⁶ from studies on the ozonization of unsaturated cyclic sulfones. A 91% yield of 2,3-dimethylbutadiene sulfone ozonide (107) was obtained by the ozonization with 6% O_3 of the butadiene sulfone.

C₄OS Ring System



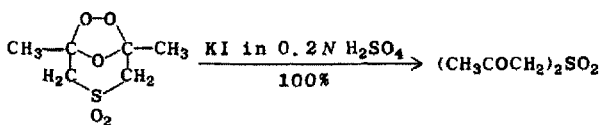
91%

107

The appearance of a blue color indicated the completion of the ozonization. The ozonide (**107**) melted at 154-155° with decomposition. The ozonide was described as being unusually stable and not affected by heating with water, aqueous acids, pyridine, or ethanol; it decomposed on treatment with alkalis in the cold; it exploded in the free flame; it was not affected by treatment with lead tetraacetate or benzoyl chloride in pyridine.

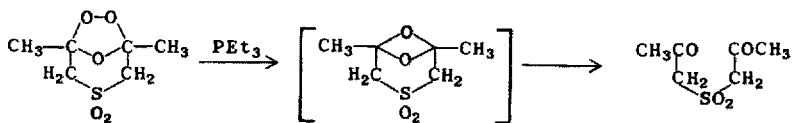
Ozonolysis of the butadiene sulfone in wet carbon tetrachloride (80 cc CCl₄ and 10 cc H₂O) gave a 59% yield of the ozonide and by-products consisting of a peroxide-containing sirup, sulfur acids, and volatile fatty acids.

Treatment of the ozonide (**107**) with potassium iodide reduced it to diacetylsulfone.



107

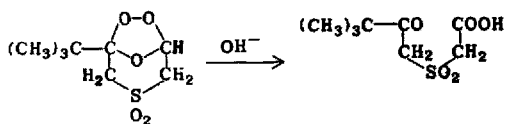
Treatment of the ozonide (**107**) with triethylphosphine¹⁶² also yielded diacetylsulfone. The reaction was carried out with the hope of obtaining the dioxathia heterocycle (**107a**).



107

107a

The ozonolysis of *t*-butylbutadiene sulfone was also rather thoroughly investigated. The heterocyclic ozonide (**108**) forms in both dry and wet carbon tetrachloride, and, as above, the higher yield is obtained by use of the dry solvent, 85% as against 70%. The ozonide melts at 148-149° with decomposition. It dissolves slowly in cold aqueous sodium hydroxide with formation of the expected keto-acid.



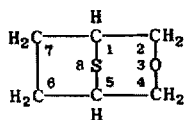
108

[For references, see pp. 939-951.]

Pyridine similarly attacks the ozonide to yield the keto-acid. Heating the ozonide with water for several hours also yields the keto-acid quantitatively. Treatment of the ozonide with potassium iodide in acetic acid yields the keto-aldehyde.

Ozonolysis of 2-phenylbutadiene sulfone yields the expected phenyl ozonide in 45-47% yield. Its melting point is affected by the heating and apparently is between 127 and 143°. The ozonolysis has been carried out in chloroform, methylene chloride, and methanol.

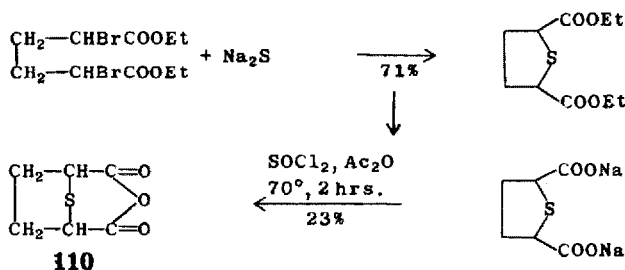
C. C_4S-C_4OS 3-OXA-8-THIABICYCLO[3.2.1]OCTANE (109)



109

(RRI 1342)

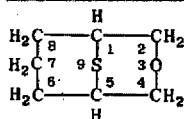
This ring system, indexed in Chemical Abstracts as a 2,5-thiophene-dicarboxylic anhydride, is known only as the 2,4-dione. Turner and Hill³⁰⁶ prepared the anhydride (110), which they called the anhydride of thiophane-2,5-dicarboxylic acid, from diethyl *meso*-2,5-dibromoadipate by the following series of reactions:



The anhydride was obtained as transparent rods and plates, m.p. 141-142°.

Horak¹⁶¹ prepared the anhydride in 82% yield from *meso*-2,5-dibromoadipic acid and Na_2S and cyclization of the thiophanedicarboxylic acid with acetyl chloride in refluxing benzene. He reported a melting point of 149-150°.

D. C_4OS-C_5S 3-OXA-9-THIABICYCLO[3.3.1]NONANE (111)

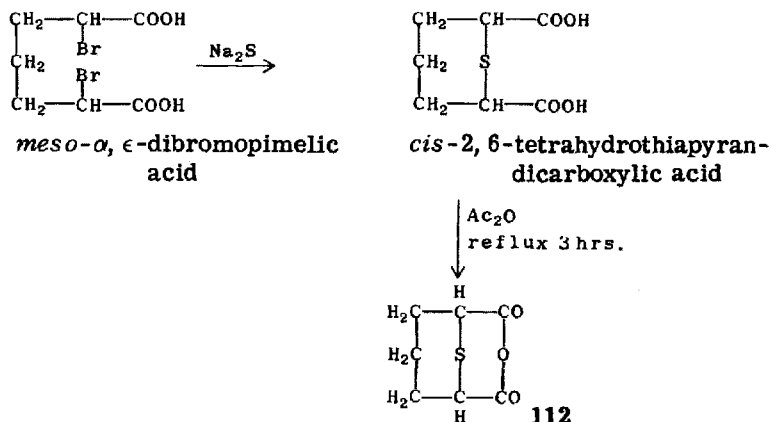


111

(RRI 1636)

C₄OS Ring System

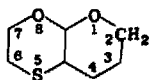
This ring system, indexed in Chemical Abstracts under the above name, is known only as its 2, 4-dione or as the anhydride of 2, 6-tetrahydrothiapyrandicarboxylic acid. Fehnel and Oppenlander⁸³ prepared the *cis*-2, 4-dione (**112**), melting at 168-169° with a slight sintering, in 70% yield through the following reactions:



The *cis*-2, 4-dione on hydrolysis with hot water gave the *cis*-dicarboxylic acid.

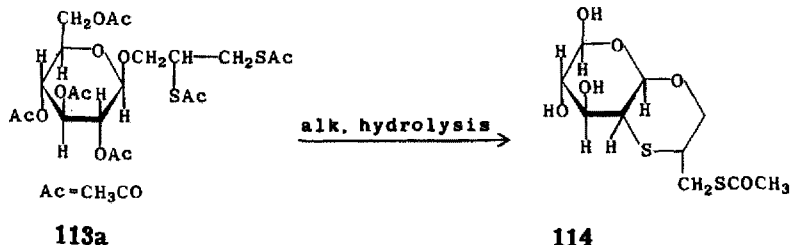
As the cyclic anhydride can only have the *cis* configuration, Schotte²⁵⁶ investigated the action of dehydrating agents on *trans*-2, 6-tetrahydrothiapyrandicarboxylic acid (obtained from racemic- α, ϵ -dibromopimelic acid). Refluxing propionic anhydride gave the *cis* anhydride in 60% yield; refluxing acetyl chloride gave no anhydride, except at higher temperatures under pressure and then in only 30% yield.

E. C₄OS-C₅O 2H-PYRANO[2, 3-*b*]-*p*-OXATHIIN (**113**)



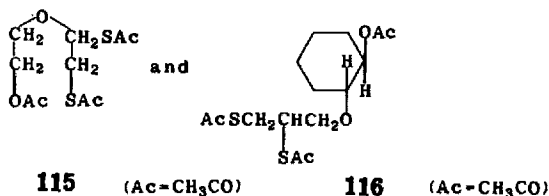
113

The only member of this heterocyclic class is **114**, which Harding and Owen¹²⁰ prepared by the deacetylation of the acetylated β -glucoside (**113a**) with inversion at C-2:



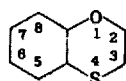
Chapter 11

114 was not characterized. The cyclization reaction was further studied through the synthesis and deacetylation of the following two analogs:



On quantitative alkaline hydrolysis of 2-acetoxyethyl 2,3-bis(acetylthio)propyl ether (115), the thiol value reached a maximum of 1.9 groups when deacetylation was complete. This corresponded to a 10% cyclization, but the cyclic product could not be isolated. On quantitative alkaline hydrolysis of *trans*-2-acetoxycyclohexyl 2,3-bis(acetylthio)propyl ether (116), the thiol value rose to a constant maximum of 1.6 groups on completion of the deacetylation. This corresponds to a 40% cyclization, but the cyclic product was not isolated. In the deacetylation of the above glucoside, the thiol sulfur in the product was 60-70% of the total.

F. C₄OS-C₆ 1,4-BENZOXATHIIN (117)



117

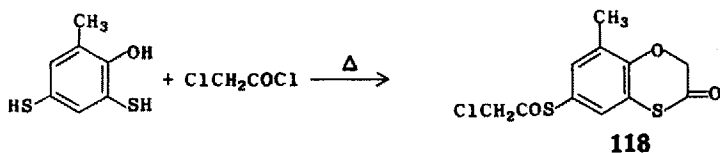
(RRI 1640)

The parent compound, the dihydro form, and various derivatives which have been described are listed in Table 14.

Chemical Abstracts indexes this ring system under 1,4-benzoxathiin. The parent compound has been called benzo-1,4-oxathiadiene and the dihydro form benzo-1,4-oxathiene.^{173,233,239} The lactone nomenclature has been used for the 2-one derivative.

1. Preparation

Pollak, Riesz, and Riesz²³⁹ first prepared a 2,3-dihydro-1,4-benzoxathiin by the condensation of 4,6-dimercapto-*o*-cresol with excess chloroacetyl chloride.

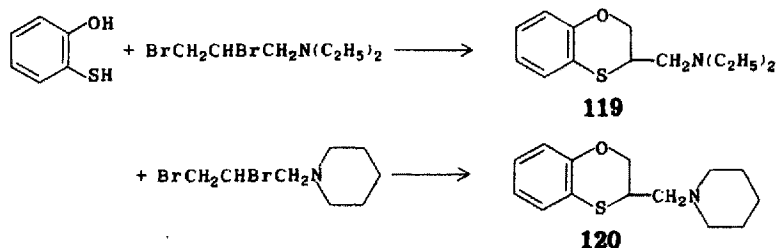


6-Chloroacetylmercapto-8-methyl-2,3-dihydro-1,4-benzoxathiin-3-one

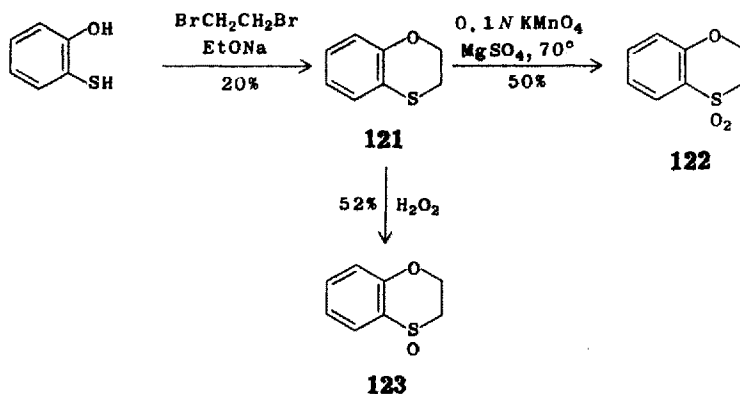
C₄OS Ring System

(118) was isolated as a light yellow powder; it is soluble in benzene, chloroform, ether, and ethanol.

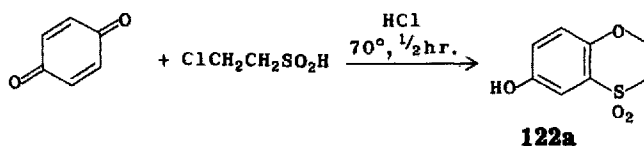
o-Hydroxythiophenol has been condensed with 2,3-dibromopropylamines to give 2,3-dihydro-1,4-benzoxathiins.²⁰



Unsubstituted 2, 3-dihydro-1, 4-benzoxathiin (121) was first prepared by Greenwood and Stevenson¹¹⁶ in 20% yield by refluxing *o*-hydroxythiophenol and ethylene bromide in ethanol with sodium alcoholate for 24 hours. On treating 2, 3-dihydro-1, 4-benzoxathiin with potassium permanganate the 4, 4-dioxide (122) was obtained. The 4-monoxide (123) compound was obtained by treating 2, 3-dihydro-1, 4-benzoxathiin with hydrogen peroxide in acetic acid at room temperature for five days.



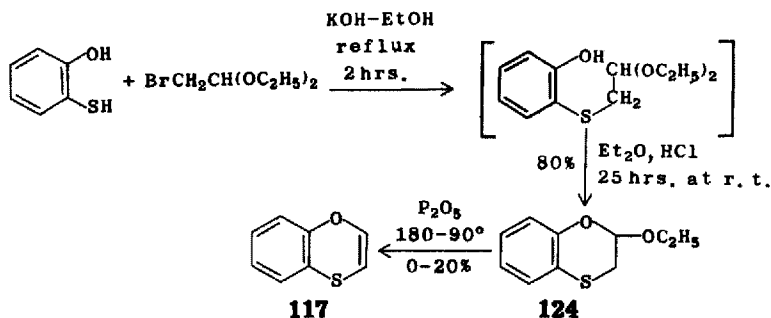
6-Hydroxy-2, 3-dihydro-1, 4-benzoxathiin 4, 4-dioxide (**122a**) was prepared by Pütter and Suckfüll^{242a} by the reaction of *p*-benzoquinone with 2-chloroethylsulfonic acid.



1, 4-Benzoxathiin, the parent compound, was first prepared by Parham and Jones^{173,233} by the elimination of ethanol from 2-ethoxy-2, 3-

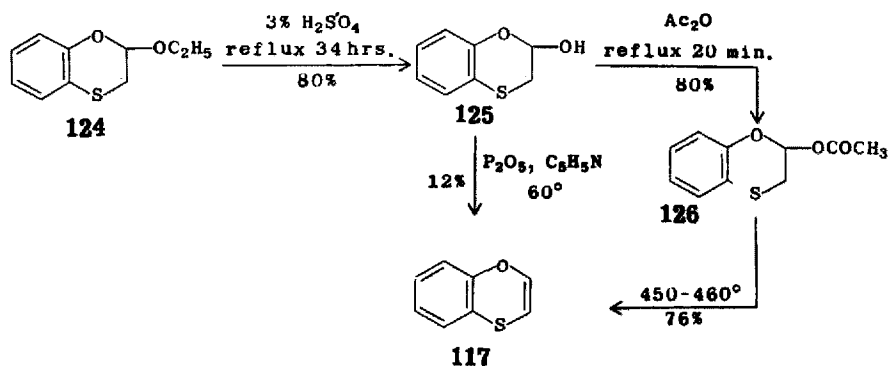
Chapter 11

dihydro-1, 4-benzoxathiin (**124**), which they had prepared from the reaction of *o*-hydroxythiophenol with ethyl bromoacetal.



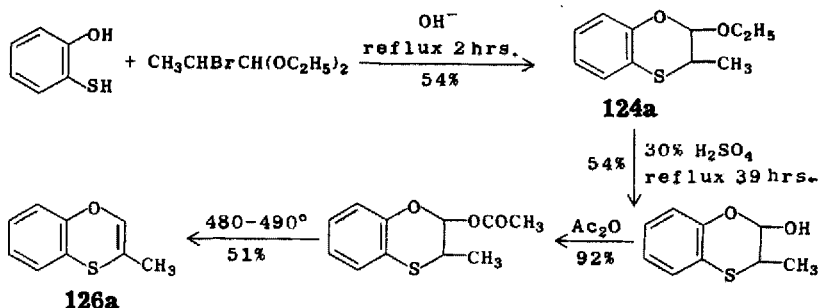
This preparation of 1, 4-benzoxathiin in low yields is in sharp contrast to the analogous preparation of 1, 4-benzodithiin in 72% yield. The relative stability towards dealkoxylation of 2-ethoxy-2, 3-dihydro-1, 4-benzoxathiin (**124**) was further shown by its failure to lose ethanol when its vapor was passed over alumina in an inert atmosphere (2-ethoxy-2, 3-dihydro-1, 4-benzodithiin gives a 58% yield of 1, 4-benzodithiin at 250°). Other attempts, such as reaction with *p*-toluenesulfonic acid or with aluminum *t*-butoxide, also failed to convert the ethoxy compound to 1, 4-benzoxathiin.

A more satisfactory method for the preparation of 1, 4-benzoxathiin is the pyrolysis of 2-acetoxy-2, 3-dihydro-1, 4-benzoxathiin (**126**).²³³

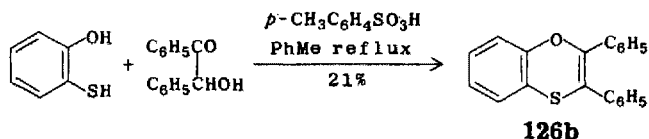


Parham and Willette^{234a} similarly prepared 3-methyl-1, 4-benzoxathiin (**126a**) by the elimination of acetic acid from 2-acetoxy-3-methyl-2, 3-dihydro-1, 4-benzoxathiin, which they prepared from the reaction of *o*-hydroxythiophenol with the ethyl acetal of 2-bromopropionaldehyde.

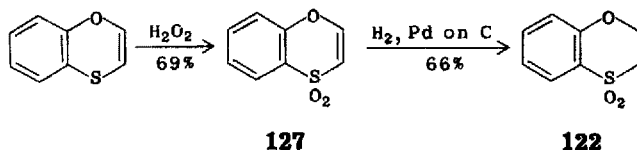
C₄OS Ring System



Marshall and Stevenson^{198a} prepared 2,3-diphenyl-1,4-benzoxathiin (126b) by the reaction of *o*-hydroxythiophenol with benzoin under dehydrating conditions.



1,4-Benzoxathiin 4,4-dioxide (127) is obtained by treating 1,4-benzoxathiin with hydrogen peroxide under glacial acetic acid reflux. This is reduced by hydrogenation over 10% palladium on charcoal to 2,3-dihydro-1,4-benzoxathiin 4,4-dioxide (122).²³³



Snell and Weissberger²⁸¹ prepared the lactone form (128) of this ring system by mixing mercaptoacetic acid in water with benzoquinone in 95% ethanol (the solution became colorless in a few minutes), removing the solvents *in vacuo*, and heating the residue at 150° for 3 hours. It is likely that the initial reaction is a 1,4-addition followed by hydrogen shift and dehydration. This mechanism is supported by the preparation of the lactone (128) by treating a mixture of benzoquinone and 2-mercaptoacetic acid in glacial acetic acid with zinc dust.

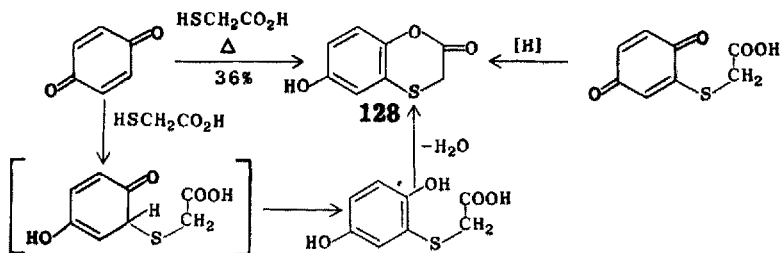
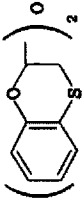


TABLE 14. 1, 4-Benzoxathins



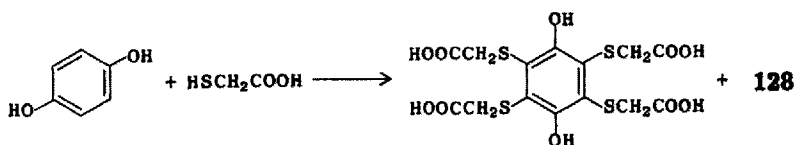
Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	n_D^{20}	Ref.
None	20-76		49	0.08	1.6129/25°	173, 233
4, 4-Dioxide	69	154-155				233
2-CH ₃ -	27					234a
2-CH ₃ - 4, 4-dioxide		162-163				234a
3-CH ₃ -	51		77	1	1.5965/27°	234a
2-CH ₃ -3-CHO	27	66-68				198a
2, 3-(C ₆ H ₅) ₂	21	108-109				198a
2, 3-(H ₂)	20		90	2		116
2, 3-(H ₂) 4-monoxide	52	85				116
2, 3-(H ₂) 4, 4-dioxide	50	82				116
	66	78.5-80				233
2, 3-(H ₂)-2-(=O)	28		128	3		116
2, 3-(H ₂)-2-CH ₃ -	40	67-69				234a
2, 3-(H ₂)-2-OH	80	62-62.5				233
2, 3-(H ₂)-6-OH 4, 4-dioxide		174				242a
2, 3-(H ₂)-2-OC ₂ H ₅	80		129-136	9	1.5713/25°	233

C₄OS Ring System

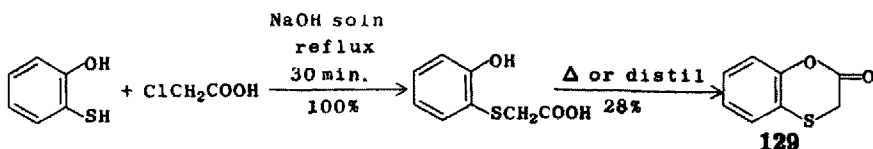
2, 3-(H ₂)-2-OCOCH ₃	80	55-55.5			233
2, 3-(H ₂)-2-O(CH ₂) ₃ CH ₃	79		95-96	0.25	1.5498/23°
2, 3-(H ₂)-2-CH ₃ -4, 4-dioxide	60	119.0-120.5			234a
2, 3-(H ₂)-2-CHO	54	127-128			233
2, 3-(H ₂)-2-(p-O ₂ NC ₆ H ₄ NHN=CH-)	5	217-219			233
2, 3-(H ₂)-2-[2, 4-(O ₂ N) ₂ C ₆ H ₃ NHN=CH-]		246-247			233
2, 3-(H ₂)-2-[(C ₂ H ₅) ₂ NCH ₂ -]			200-203	30	20
2, 3-(H ₂)-2-(C ₅ H ₁₀ NCH ₂ -)		108	185-190	27	20
	31	119-120			233
2, 3-(H ₂)-2, 3-(Br ₂)	89	105-106			233
2, 3-(H ₂)-2-(=O)-6-OH	36	169-171			281
2, 3-(H ₂)-3-(=O)-6-SC ₂ H ₄ Cl		195			239
2, 3-(H ₂)-2-(=O)-8-OH-5, 6-(CH ₃) ₂	24	154-155			163
2, 3-(H ₂)-2-(=O)-6-OH-7-CH ₃ -	82	163-164			115a
2, 3-(H ₂)-2-(=O)-6-OCH ₃ -7-CH ₃ -		83-84			203a
2, 3-(H ₂)-2-OC ₂ H ₅ -3-CH ₃ -	54		125-130	2	234a
2, 3-(H ₂)-2-OH-3-CH ₃ -	54	64.0-64.5			234a
2, 3-(H ₂)-2-OH-3-CH ₃ -4, 4-dioxide	32		122-125	1.0	234a
2, 3-(H ₂)-2-O ₂ CCH ₃ -3-CH ₃ -	92		105-115	0.7	234a
2, 3-(H ₂)-2-CH ₃ -3-CHO	5	140-141			234a

Chapter 11

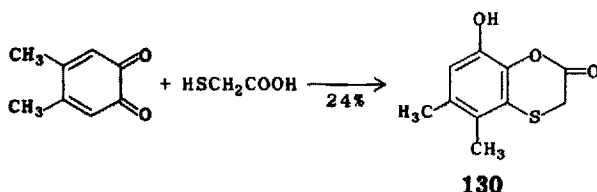
The lactone is also obtained as a by-product in the reaction of hydroquinone with mercaptoacetic acid.²⁵⁷



The parent lactone was prepared as follows:¹¹⁶



The lactone (130) also has been prepared by the reaction of an *o*-quinone with mercaptoacetic acid.¹⁶³

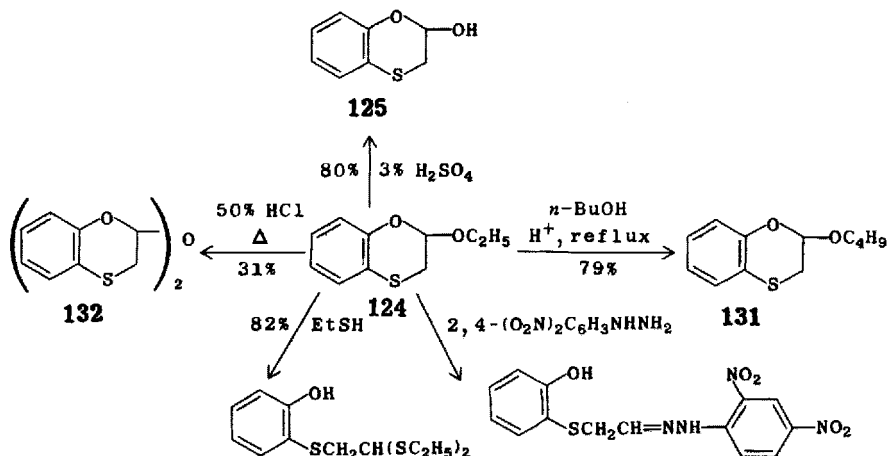


130 gives no enol reaction; it is soluble in 2 *N* NaOH but not in NaHCO₃ solution.

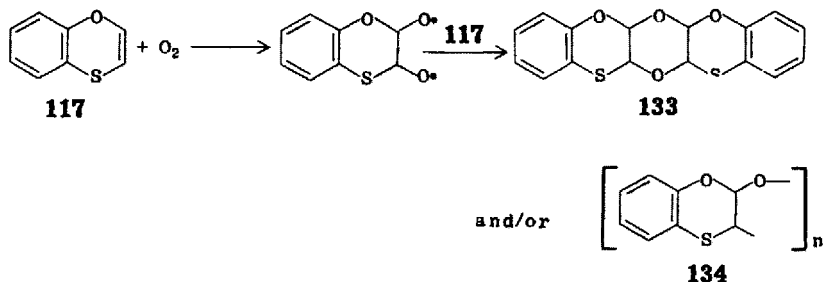
2. Reactions

2-Ethoxy-2, 3-dihydro-1, 4-benzoxathiin (124) is easily converted into 2-hydroxyphenylthioacetaldehyde 2, 4-dinitrophenylhydrazone, thus reacting as an acetal.²³³ It undergoes alcoholysis with excess butyl alcohol containing hydrogen chloride. Reaction with excess ethyl mercaptan in acid medium gives an 82% yield of the diethylmercaptal of 2-hydroxyphenylthioacetaldehyde. Treatment with 50% hydrochloric acid gives bis-2-(2, 3-dihydro-1, 4-benzoxathiinyl) ether (132). This is in contrast to its treatment with 3% sulfuric acid which leads to 2-hydroxy-2, 3-dihydro-1, 4-benzoxathiin (125).

C₄OS Ring System

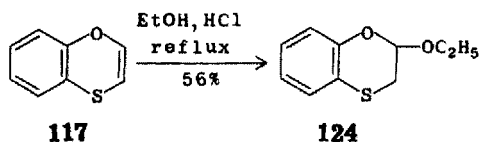


1, 4-Benzoxathiin (**117**) is sensitive to air at room temperature.²³³ It can be stored indefinitely in an atmosphere of nitrogen; on exposure to air, however, it is slowly oxidized to a gelatin-like material (gel formation sometimes occurs immediately, other times after several days exposure to air). The white solid polymer which can be isolated from the gel has been formulated as **134**.



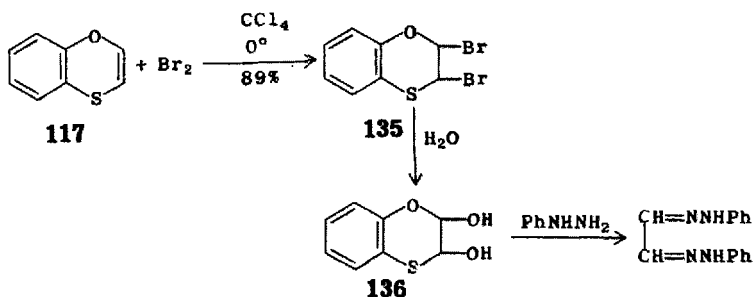
1, 4-Benzoxathiin is polymerized slowly by reaction with benzoyl peroxide and rapidly with boron trifluoride, as is typical of vinyl ethers.

In its reaction with ethanol containing a trace of hydrogen chloride, 1, 4-benzoxathiin is an atypical vinyl ether as ethanolysis does not occur. Ethanolysis is accomplished by refluxing a solution of 1, 4-benzoxathiin in ethanol and 0. 47 *N* hydrogen chloride for 85 hours.

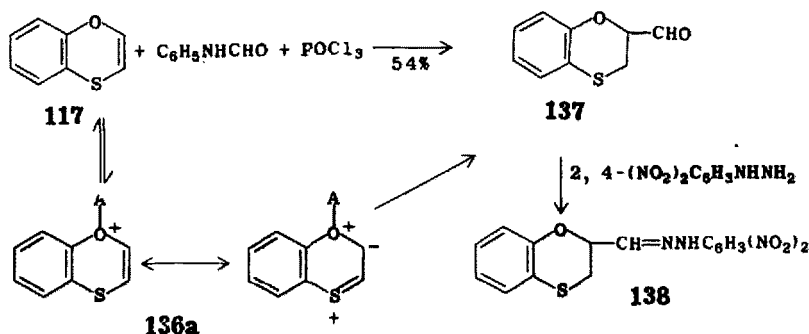


1, 4-Benzoxathiin is easily brominated, giving a stable dibromide (**135**),

which can be hydrolyzed easily in aqueous ethanol to 2, 3-dihydroxy-2, 3-dihydro-1, 4-benzoxathiin (**136**).



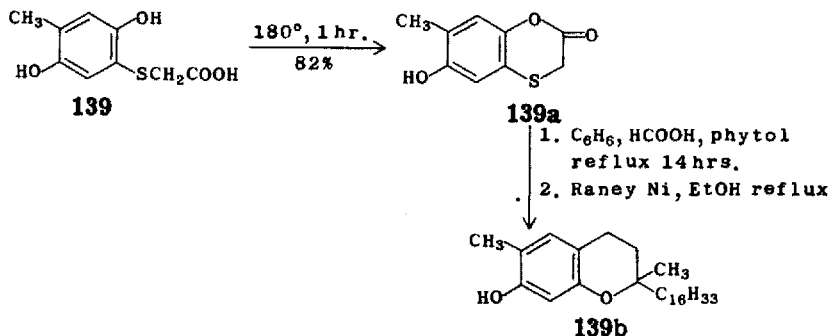
1, 4-Benzoxathiin reacts with nitric acid, but the products have not been characterized. The Vilsmeier reaction yielded 2-formyl-2, 3-dihydro-1, 4-benzoxathiin (**137**).



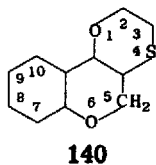
Parham and Willette^{234a} pointed out that the Vilsmeier reaction involves an electrophilic substitution and that the species undergoing substitution is a conjugate acid of 1, 4-benzoxathiin involving the oxygen as illustrated in **136a**. Reduction of the aldehyde (**137**) with hydrazine and alkali (Wolff-Kishner reduction) yielded 2-methyl-1, 4-benzoxathiin, which was characterized by conversion to 2-methyl-1, 4-benzoxathiin 4, 4-dioxide on treatment with hydrogen peroxide.

Green, and co-workers^{115a, 203a} obtained 6-hydroxy-7-methyl-2, 3-dihydro-1, 4-benzoxathiin-2-one (**139a**) on heating 5-(carboxymethylthio)toluquinol (**139**). Reacting this benzoxathiin (**139a**) with phytol, followed by desulfurization, yielded racemic 8-methyltolcol (**139b**).

C₄OS Ring System

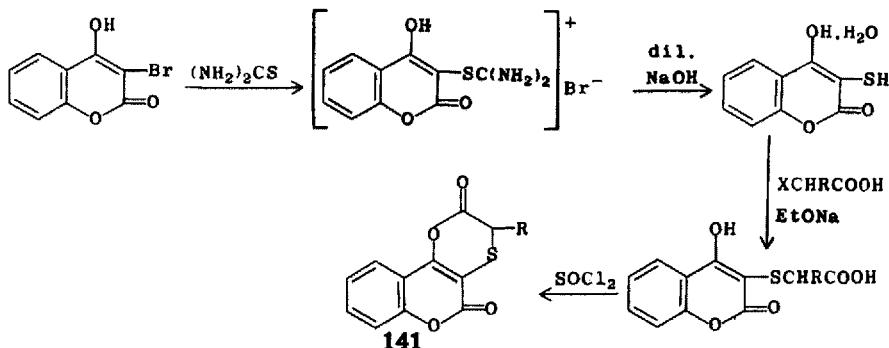


G. C₄OS-C₅O-C₆ 5*H*-1, 4-OXATHINO[3, 2-*c*][1]-BENZOPYRAN (140)



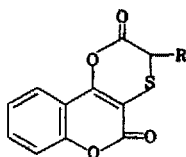
(RRI 3407)

The parent compound is not known. Eisenhauer and Link⁷⁹ prepared the 2, 3-dihydro-5*H*-1, 4-oxathiino[3, 2-*c*][1]-benzopyran-2, 5(3*H*)-diones listed in Table 15 by the reaction of 3-mercapto-4-hydroxycoumarin monohydrate and α -halo acids and cyclization of the resulting 3-(4-hydroxycoumarin)- α -thiocarboxylic acids in benzene solution with thionyl chloride.



These compounds were recrystallized from aqueous ethyl alcohol or from benzene-Skellysolve B. The ethyl-, propyl-, and butyl-derivatives were isolated as the ethyl alcohol complex, which could not be desolvated by heating at 60° and 3 mm pressure over P₂O₅ for 24 hours. This stability is unusual and, as the diones were not characterized, it is conceivable that the products might have been esters.

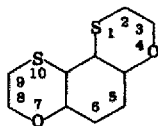
Chapter 11

TABLE 15. 2, 3-Dihydro-5*H*-*p*-oxathiino[3, 2-*c*][1]benzopyran-2, 5(3*H*)-diones

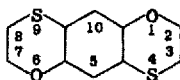
R	Yield (%)	M.p.(°C)	Ref.
H	72		79
CH ₃ -	85	165-167	79
CH ₃ CH ₂ -	76	117-118	79
CH ₃ (CH ₂) ₂ -	93	120-122	79
CH ₃ (CH ₂) ₃ -	97	119-121	79

H. C₄OS-C₄OS-C₆

1. Benzo[1, 2-*b*: 4, 3-*b'*]bis-1, 4-oxathiin (**142**) and Benzo[1, 2-*b*: 4, 5-*b'*]bis-1, 4-oxathiin (**143**)

**142**

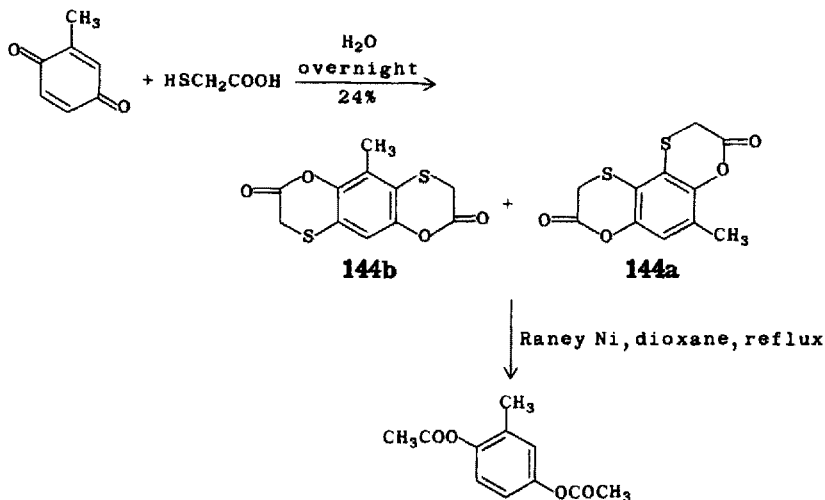
(RRI 3405)

**143**

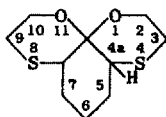
(RRI 3404)

The above two compounds are not known. Blackhall and Thomson,²² on adding thioglycolic acid to toluquinone, obtained an oil from which they were not able to isolate solid derivatives under mild conditions. After removing the toluquinone at 190° and 1 mm pressure, they obtained a solid residue from which two compounds, m.p. 205-206° and 235-236°, were isolated in equal amount for a total yield of 24%. Neither compound reacted with diazomethane or acetyl chloride. Desulfurization with Raney nickel yielded toluquinol diacetate. It was therefore concluded that the two compounds were the isomeric dilactones, 5-methylbenzo[1, 2-*b*: 4, 3-*b'*]bis-1, 4-oxathiin-3, 8(2*H*, 9*H*)-dione (**144a**) and 10-methylbenzo[1, 2-*b*: 4, 5-*b'*]bis-1, 4-oxathiin-2, 7(3*H*, 8*H*)-dione (**144b**).

C₄OS Ring Systems



2. 4a*H*-Benzo[2, 1-*b*: 2, 3-*b'*]bis-1, 4-oxathiin (**145**)

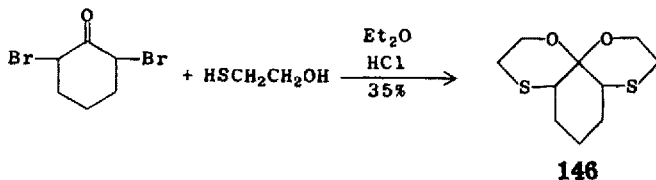


145

(RRI 3406)

Backer and Wiggerink¹⁰ prepared 2, 3, 5, 6, 7, 7a, 9, 10-octahydro-4a*H*-benzo[2, 1-*b*: 2, 3-*b'*]bis-1, 4-oxathiin (**146**), the only member of this ring system reported. Chemical Abstracts indexed it under the above name. Backer and Wiggerink named it 5, 7-trimethylene-1, 11-dioxo-4, 8-dithia-6-spirohendecane.

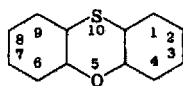
146 was prepared by reacting 2, 6-dibromocyclohexanone with mercaptoethanol in ether in the presence of dry hydrogen chloride.



146, melting at 133. 5-134. 5°, was obtained as monoclinic plates. A quantitative yield of **146** was obtained from the reaction of 2, 6-dibromocyclohexanone with the monosodium salt of mercaptoethanol on heating for 8 hours on a water bath.

I. $C_4OS-C_6-C_6$

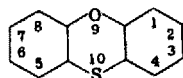
1. Phenoxathiin (148)



148

(RRI 3408)

Phenoxathiin was first prepared in 1906 by Mauthner,²⁰² who a year earlier had first synthesized 2,4-dinitrophenoxathiin and assigned the name "phenoxthin" to this heterocyclic class. Beilstein used this name as well as di-*o*-phenylene-oxide-sulfide and dibenzo-1,4-oxathiin. Mauthner used the following numbering:



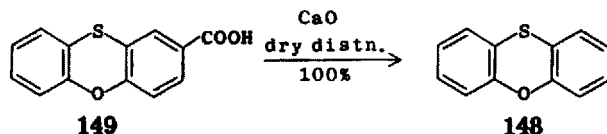
Phenothioxin has been a rather popular name throughout the literature. Other names used have been dibenzo(2-3) (5-6)cyclo(1-oxa-4-thiatetramethylene),¹¹⁷ phenoxthionine,^{19,75} and isophenoxthin.¹⁵⁸

Chemical Abstracts used the name phenothioxin with the same numbering as Mauthner until the fourth decennial index when the name phenoxathiin was used with the numbering cited in Patterson. The reader must approach the literature with caution, as consistency has not been exercised in naming and numbering these compounds. This book uses the present Chemical Abstracts name and numbering.

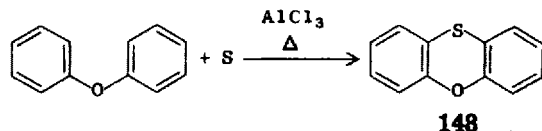
a. Phenoxathiin

(1) Preparation

Phenoxathiin was first prepared by Mauthner²⁰² in 1906 by the decarboxylation of phenoxathiin-2-carboxylic acid (149).

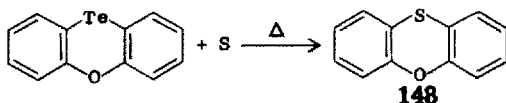


Ackerman, in 1910, patented the preparation of phenoxathiin by the reaction of diphenyl ether with sulphur in the presence of aluminum chloride.^{1a}



Ferrario,⁸² who used magnesium chloride as well as aluminum chloride in the condensation, claimed almost quantitative yields in this process. Suter, McKenzie, and Maxwell,²⁸⁹ on repeating Ferrario's method, obtained mostly tarry products. When they used an excess of diphenyl ether, they obtained yields of up to 72% of pure phenoxathiin. The best results were obtained on using 1.3 moles diphenyl ether, 1 atom sulfur, and 0.5 mole aluminum chloride. With carbon disulfide as solvent, no appreciable reaction occurred; with 1,1,2,2-tetrachloroethane as solvent at steam bath temperature, the yield of phenoxathiin was 48%. Bennett, Leslie, and Turner¹⁹ reported a yield of 88% from the reaction of 2 moles diphenyl ether and 2 atoms sulfur using aluminum chloride at 80-90° and then at 100°.

Drew⁷⁵ reported a quantitative yield of phenoxathiin from the following reaction:

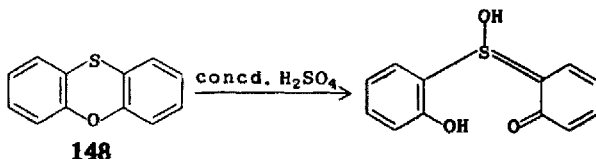


Gilman and Eidt¹⁰⁸ reported a 24.5% yield of phenoxathiin among various products in their cleavage studies of phenoxathiin 10-monoxide with *n*-butyllithium.

(2) Properties and Structure

Phenoxathiin is obtained as colorless needles when crystallized from ethyl alcohol. It has a geraniol odor. It is soluble in the usual organic solvents. Its melting point and boiling point from various preparations are listed in Table 16. It distils at 311° and 745 mm with slight decomposition.²⁹⁰

Phenoxathiin exhibits halochromism in concentrated sulfuric acid,²⁰⁸ and the color of these solutions have been noted variously as violet,²⁰² blue,^{1,82,117} and intense violet.⁷⁵ According to Mauthner,²⁰² dilution of its solution in concentrated sulfuric acid yields a sulfonic acid. According to Hilditch and Smiles,¹⁵⁴ the color in concentrated sulfuric acid is due to the presence of a thionium intermediate.



Drew⁷⁵ ascribed the color to the formation of thionylum compounds of unlikely structures. It is highly probable that the reason for the halochromism of phenoxathiin in sulfuric acid is that discussed for thianthrene (Chapter 12, section III K-1d).

Phenoxathiin and thianthrene form an eutectic.⁵⁹ Phenoxathiin and diphenylamine form an eutectic melting at 26.4°, containing 49.5% phenoxathiin.²²²

Chapter 11

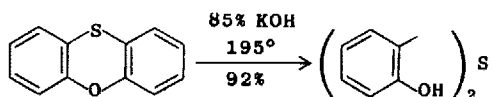
Phenoxathiin has a weak intensity effect in delayed luminescence in infrared absorption, but shows normal visible phosphorescence.¹⁹¹ Crystallographic and optical investigations reveal that phenoxathiin crystals are of the orthorhombic, halohedral class, and X-ray studies show that phenoxathiin is enantiomorphic and isomorphous with phenothiazine, phenoxaselenin, and phenoxatellurin. There are four molecules in each unit cell of these four compounds and phenoxathiin, phenoxaselenin, and phenoxatellurin are folded about the line joining the heterocyclic atoms.³¹⁵

Higasi reported the dipole moment of phenoxathiin as 1.09 D in benzene and in hexane.¹⁵¹⁻² By analogy with diphenylene oxide, the two benzene rings were considered to be folded along the oxygen-sulfur axis. No optical isomerism was expected in phenoxathiin, thianthrene, or phenoxaselenin because the activation energy for racemization is at most only a few kilocalories. According to Leonard and Sutton,¹⁸⁵ the dipole moment of phenoxathiin in benzene at 25° is 1.00 ($A^P=0$) and 0.92 ($A^P=5\% E^P$). This agrees with an angle of $155 \pm 5^\circ$ between the planes of the benzene rings, the molecule being folded along the oxygen-sulfur axis. The low energy of activation explains the failure of Bennett, Leslie, and Turner¹⁹ to resolve phenoxathiin-2-carboxylic acid or 8-methyl-3-nitrophenoxathiin-1-carboxylic acid.

According to Capitán-Garcia and Parellada-Bellod,^{41a} the absorption spectrum of phenoxathiin shows two maxima at 237 and 294 m μ and a minimum at 260 m μ . They reported a solubility of 9×10^{-4} g/l of phenoxathiin in water.

(3) Ring Opening Reactions

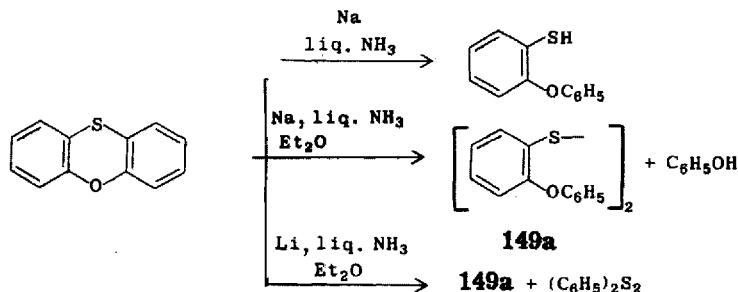
Phenoxathiin in methanol, treated with 85% potassium hydroxide solution and the mixture heated at 195°, is converted in 92% yield to bis(*o*-hydroxyphenyl) sulfide, which is stated to be useful as a bactericide and fungicide, as a stopping agent in emulsion polymerization of styrene-butadiene, and as a rubber stabilizer.¹⁶⁵



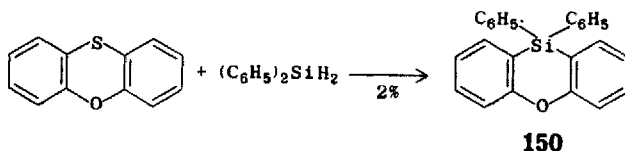
Ferrario⁸² reported that phenoxathiin, on heating with copper powder at 250°, is converted to dibenzofuran. This reaction could not be confirmed by others,^{101,193,289} using copper powder, copper bronze, silver powder, iron powder, zinc dust, etc., at temperatures up to 245°.

A good yield of *o*-mercaptophenyl phenyl ether was obtained on treating phenoxathiin with sodium in liquid ammonia.³⁰⁰ On the other hand, Tomita and Ujiie^{301a} obtained the disulfide (149a) on treating phenoxathiin with sodium or lithium and liquid ammonia in ethyl ether.

C₄OS Ring Systems



On refluxing phenoxathiin and diphenylsilane six days, Gilman and Wittenberg^{112,314} obtained a 2% yield of 10, 10-diphenylphenosilin (150).



(4) Uses

Many uses have been cited for phenoxathiin. It is toxic to a variety of microorganisms, and has been tested against *M. tuberculosis*, *Staph. aureus*, and *E. coli*.³⁰¹ It has a bacteriostatic action on *Streptococcus hemolyticus* and on *Streptococcus hemolyticus epidemicus* and shows considerable inhibition of *Streptococcus viridans* at a level of 100 parts phenoxathiin per million parts of peptone broth.⁸⁰ Phenoxathiin has some anthelmintic activity,¹⁹⁷⁻⁸ but much less than phenothiazine.¹⁴⁴ It has been found to have an inhibiting effect on poliomyelitis virus.^{160a}

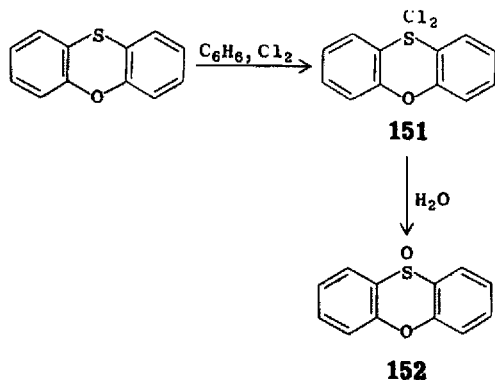
Phenoxathiin kills 50% of mosquito larvae in 16 hours at a concentration of two parts per million.⁸⁵ It is more toxic than lead arsenate to the larvae of *Phlyctaenia rubigalis*.²⁰⁶ Phenoxathiin is active at 0.025 M in killing horse strongyle larvae in feces.¹⁸⁹

Phenoxathiin is effective against the cabbage aphid, termite, American cockroach, codling moth larvae, Hawaiian beet webworm, southern beet webworm, diamond back moth, screwworm, housefly, and rice weevil.^{40,57,263,275-9} Louse powders containing phenoxathiin are highly effective but slow in action.²⁹³ Phenoxathiin mixed with wettable sulfur effectively controls sheep tick.²⁵⁸ Wearing apparel impregnated with phenoxathiin is effective against chiggers.²⁸³ Phenoxathiin is somewhat repellent and toxic to the housefly.¹⁹² It is less effective than is Toxaphene against chiggers.^{176a}

Phenoxathiin inhibits odors in alkylaryl sulfonates stored at 85° for 144 hours.⁸⁶ Phenoxathiin in a concentration of 0.1 g per l. did not inhibit hydrochloric acid corrosion of iron.¹⁹⁵ In the absence of gold, which gives a ruby red color, as little as 0.01 γ of palladium can be detected at a dilution of 1:100,000 with a 10% solution of phenoxathiin in methyl ether.¹⁷⁹

b. Phenoxathiin 10-Monoxide and 10,10-Dioxide

The 10-monoxides and -dioxides of phenoxathiin derivatives were first prepared by Mauthner²⁰¹⁻² by the use of nitric acid for the monoxide and chromic acid for the dioxide; Hilditch and Smiles used hydrogen peroxide for the monoxide and permanganate for the dioxide preparations.¹⁵³ Phenoxathiin monoxide and dioxide, however, were first described by Drew,⁷⁵ who prepared the monoxide by treating phenoxathiin with hydrogen peroxide in glacial acetic acid and the dioxide by prolonged action of hydrogen peroxide or by the use of chromic oxide or permanganate. Tomita and Ikeda²⁹⁶ obtained a yield of 86% of sulfoxide on treating phenoxathiin in glacial acetic acid at 30-40° with nitric acid (density = 1.45); they obtained the sulfone by oxidizing phenoxathiin with chromic oxide. Irie¹⁷¹ oxidized phenoxathiin in glacial acetic acid with fuming nitric acid at 80° to the sulfone; higher temperatures, such as steam bath temperature, led to ring nitration also. Using acetyl nitrate in carbon tetrachloride, Irie obtained the sulfoxide. He also prepared the sulfoxide by the following series of reactions:



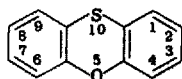
Nobis, Blardinelli, and Blaney²²⁴ on treating phenoxathiin in glacial acetic acid with chlorine obtained an 81% yield of the sulfoxide. They were not able to oxidize the sulfoxide to the sulfone by treatment with fuming nitric acid; on treating phenoxathiin with fuming nitric acid in glacial acetic acid, they obtained a 91% yield of the sulfoxide. Gilman and Eidt¹⁰⁷ obtained a 61.5% yield of sulfoxide on using dilute nitric acid in glacial acetic acid, and Eidt⁷⁸ reported a yield of 93-95% sulfoxide on using concentrated nitric acid in glacial acetic acid.

Gilman and Esmay¹⁰⁵ compared the ease of oxidation of dibenzothio-*phene* and phenoxathiin and studied the optimum conditions for the preparation of sulfoxides and sulfones. The extent of oxidation depends on the oxidizing agent, the solvent, the reaction time and temperature, and on stirring (whether mechanical or by refluxing). They established that optimum yields of both sulfoxide and sulfone are obtained when the refluxing mixture is also stirred mechanically. The oxidation is stepwise and the oxidation rate to the sulfoxide is much faster than that of sulfoxide to sulfone.

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The recommended preparation of the sulfoxide (98.1% yield) is by refluxing phenoxathiin with 30% hydrogen peroxide in ethyl alcohol for twelve hours. The sulfone is best prepared (97% yield) by refluxing phenoxathiin and 30% hydrogen peroxide in glacial acetic acid for one hour and then letting the mixture stand overnight at room temperature.¹⁰⁵ Phenoxathiin is more easily oxidized to the sulfoxide and sulfone than is dibenzothiophene.

TABLE 16. Phenoxathiin, Phenoxathiin 10-Monoxide, and Phenoxathiin 10,10-Dioxide

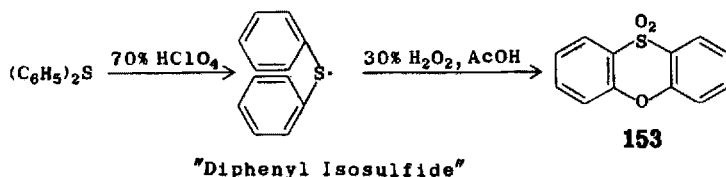


Substituent	Yield (%)	M.p. (°C)	(°C)	B.p. (mm)	Ref.
None	87	57.5-58.0			291
		60-61	183-184	12	1a
	100	60-61			202
	good	60-61			82
		55.3-55.5			222
	100	58			75
	24.5		120-121	1	108
	74	57.5-58.0	185-187	23	289
	88	57-58	183-184	12	19
10-Monoxide	98.1	152-153			105
		158-159			75
	95				78
	61.5	171-173			107
	91	154-156			224
		144			296
		153.5			171
10,10-Dioxide	35	140-141			202
		147-148			105
	97	225			158
		147-148			75
		151-154			296
	86	144-145			171

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Whereas thianthrene is oxidized to the 5-monoxide in good yield by treatment with negatively substituted benzenediazonium salts in glacial acetic acid, Gilman and Swayampati¹¹⁰ reported that phenoxathiin could not be oxidized under the same conditions.

Hinsberg¹⁵⁸ reported in 1929 the preparation of what he called "isophenoxathiin sulfone" in 0.5% yield by the following set of reactions:



The water of crystallization could not be driven off by heating. The melting point of 225° Hinsberg reported for the sulfone makes it doubtful whether the product was phenoxathiin 10, 10-dioxide.

The reported melting points of phenoxathiin 10-monoxide from various preparations are listed in Table 16. It is described as colorless crystals when crystallized from acetic acid or benzene. It is only sparingly soluble in water and may be distilled unchanged. It does not catalytically decompose hydrogen peroxide nor is it reduced by sodium bisulfite. Treatment of phenoxathiin 10-monoxide with zinc dust reduces it to phenoxathiin. It forms mixed crystals with the selenium and tellurium analogs. Its concentrated sulfuric acid solution has a violet color which turns blue on warming.⁷⁵ Moir²⁰⁸ studied the halochromism of phenoxathiin, the monoxide, and the dioxide.

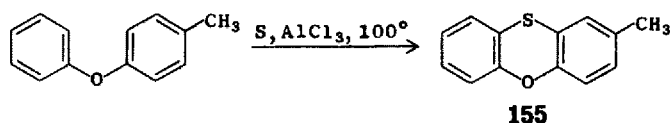
Phenoxathiin 10, 10-dioxide is obtained as colorless needles after recrystallization from dilute acetic acid.⁷⁵ Its reported melting points are given in Table 16. The dioxide is not halochromic in concentrated sulfuric acid.^{75,208} It is resistant to reducing agents.

The sulfone is effective against fall web worm larvae, Colorado potato beetle larvae, and walnut worm; the sulfoxide is effective against Colorado potato beetle larvae, web worm larvae, walnut worm, and southern army worm.²⁷² The sulfone is inactive against horse strongyle larvae.¹⁸⁹

c. Hydrocarbon-Substituted Phenoxathiins

(1) Alkylphenoxathiins

Ackerman^{1a} prepared 2-methylphenoxathiin (155) by the condensation of *p*-tolylphenyl ether with sulfur and aluminum chloride at 100° .

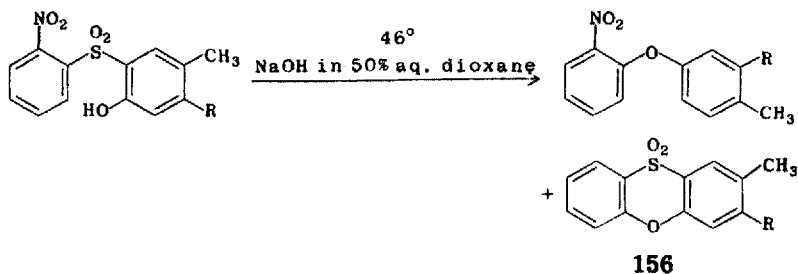


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This compound is colorless, soluble in the usual organic liquids, and its concentrated sulfuric acid solution is blue.

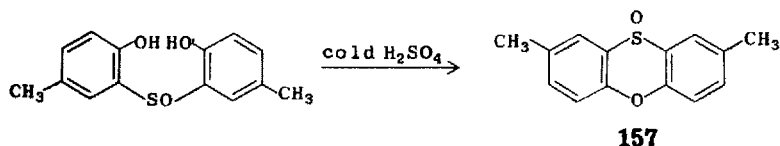
Suter and Green²⁹⁰ prepared 2-, 3-, and 4-methylphenoxathiin from *p*-, *m*-, and *o*-tolyl phenyl ether, respectively, by the above reaction in 46-77% yields, the best arising when the directive influence of the methyl group and ether group coincide. They presumed that the preparation of the 1-isomer by this method is not probable. The 1-isomer has yet to be reported by any method.

These three methylphenoxathiins were oxidized by Suter and Green²⁹⁰ to the respective 10, 10-dioxides by heating with excess hydrogen peroxide in glacial acetic acid on a steam bath. Okamoto and Bunnet²²⁹ obtained a 1.6% yield of 2-methylphenoxathiin 10, 10-dioxide (**156**, R = H) as a by-product in the following rearrangement (R = H, Cl, or Br):



Lescot and Buu-Hoi¹⁸⁶ extended Suter, McKenzie, and Maxwell's modification of the Ferrario reaction to the preparation of higher acylphenoxathiins, from which the alkylphenoxathiins were prepared through the Wolff-Kishner-Huang-Minlon reduction. Thus, 2-ethylphenoxathiin was prepared in 88% yield by the reduction of 2-acetylphenoxathiin with 95% hydrazine hydrate and potassium hydroxide in diethylene glycol. Other alkylphenoxathiins similarly prepared were 2-*n*-pentyl-, 2-*n*-decyl-, and 2-benzyl.

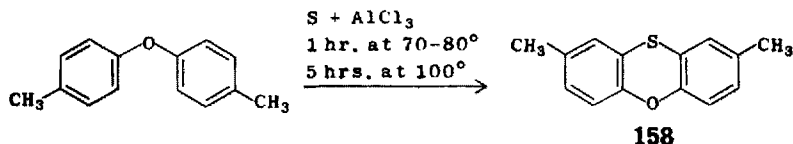
Di-, tri-, and higher alkylphenoxathiins have been prepared similarly to the monoalkylphenoxathiins and phenoxathiin. Hilditch and Smiles¹⁵³⁻⁴ prepared 2, 8-dimethylphenoxathiin 10-monoxide (**157**) by moderately prolonged action of cold sulfuric acid on di(*p*-cresol) sulfoxide.



Reduction of the 10-monoxide with zinc in acetic acid or treatment with dilute sodium hydroxide gave 2, 8-dimethylphenoxathiin (**158**). The sulfoxide (**157**), whose sulfuric acid solution has an intense blue color, was also prepared by the oxidation of 2, 8-dimethylphenoxathiin with hydrogen peroxide in acetic acid. Oxidation with permanganate in acetic acid gave the 10, 10-dioxide. When zinc chloride at 120° and 200°, or

thionyl chloride at refluxing temperature, or phosphorus oxychloride alone or in xylene, or boiling phosphorus trichloride was used in place of sulfuric acid in the condensation of di(*p*-cresol) sulfide or sulfoxide, no phenoxathiin resulted.

Tomita²⁹⁵ prepared 2,8-dimethylphenoxathiin by the Ferrario reaction.



He prepared 2,8-diethylphenoxathiin by the reduction of 2,8-di(chloroacetyl)- or diacetylphenoxathiin with zinc amalgam. The 10,10-dioxide was prepared by oxidation with chromic oxide.

Smith and Moll in several patents^{269,274} on the preparation of substituted phenoxathiins obtained mixtures of monoalkyl and polyalkyl derivatives. Thus, on condensing 5 moles phenoxathiin with 5 moles ethylene in the presence of Retrol, an acid derived from clay, they obtained two diethylphenoxathiin fractions and a polyethylphenoxathiin fraction. In the condensation with propylene, they obtained, in addition to the propylphenoxathiin fraction, a mixture of dipropylphenoxathiin fractions, and a residue of tetrapropylphenoxathiins. Similar products were obtained on condensation with butene. On using alcohols containing 8-17 carbon atoms in the condensation, Smith and Moll²⁷⁴ reported the following: trioctylphenoxathiin, mono- and didodecylphenoxathiin, monoheptadecylphenoxathiin, dioctylphenoxathiin, mono- and didecylphenoxathiin, and hexadecylphenoxathiin. The position of the alkyl groups were not designated. The products were said to be useful as intermediates and as modifiers in plastics. Table 17 lists the alkylphenoxathiins.

(2) Cycloalkylphenoxathiins

Smith and Moll^{270-1,273} prepared cycloalkylphenoxathiins by reacting phenoxathiin with cyclohexene, cyclopentanol, 2-methyl-5-isopropylcyclohexyl chloride, and other cycloalkylating agents in the presence of Retrol. Thus, the reaction of equimolar quantities of phenoxathiin and cyclohexene yielded a mixture of mono-, di- and polycyclohexylphenoxathiin. These compounds have been described as high boiling, soluble in many organic solvents, insoluble in water, and useful as modifiers in plastic compositions, as intermediates, as antioxidants, gum inhibitors, and as insecticidal toxicants against oak leaf roller, Colorado potato beetle larvae, and poplar aphids.

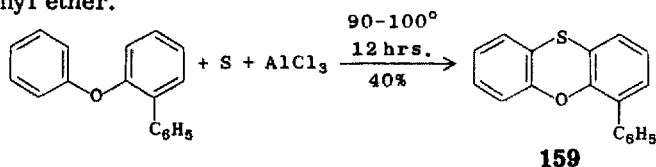
Treatment of monocyclohexylphenoxathiin with 70% nitric acid in acetic acid for 25 minutes at 95° yielded the sulfoxide as a fluorescent, red, viscous oil, insoluble in water and somewhat soluble in common organic solvents.²⁷³ Treatment of monocyclohexylphenoxathiin with 30% hydrogen peroxide in glacial acetic acid at 95° for two hours yielded the sul-

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fone as a viscous, fluorescent oil, insoluble in water, and soluble in organic solvents.²⁷³ The sulfoxide and sulfone were described as useful for modifying plastic materials, as intermediates, and as insecticides. According to Boyer,³⁵ the sulfoxide in a concentration of 2-5% is a heat stabilizer for vinyls. The cycloalkylphenoxathiins are listed in Table 17.

(3) Arylphenoxathiins

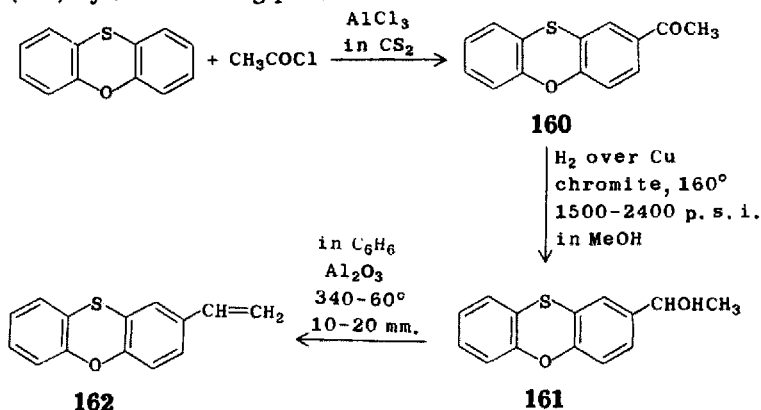
The only arylphenoxathiins reported are the phenyl substituted phenoxathiins. These are listed in Table 17. Smith and Moll²⁶⁹ prepared 4-phenylphenoxathiin (159) by the Ferrario reaction from 2-diphenyl phenyl ether.



This compound was included among those described as useful as modifiers in plastic compositions, as intermediates, and as having insecticidal, antioxidant, and rubber and gum inhibitor properties. It has been cycloalkylated with cyclohexene in the presence of Retrol to give the monocyclohexyl-4-phenylphenoxathiin and a mixture of dicyclohexyl-4-phenylphenoxathiins.²⁷⁰ The sulfoxide, an oily, fluorescent liquid, insoluble in water and soluble in organic solvents, was prepared by oxidizing monocyclohexyl 4-phenylphenoxathiin with 70% nitric acid in glacial acetic acid at 95° for 1 hour.²⁷³ The sulfone was prepared by oxidizing monocyclohexyl 4-phenylphenoxathiin with 30% hydrogen peroxide at 95° for thirty minutes.²⁷³ These compounds also have been described as vinyl heat stabilizers.³⁴

(4) Vinylphenoxathiins

Flowers and Flowers^{37,87-9} prepared 2-vinylphenoxathiin (see Table 17) (162) by the following procedure:



[For references, see pp. 939-951.]

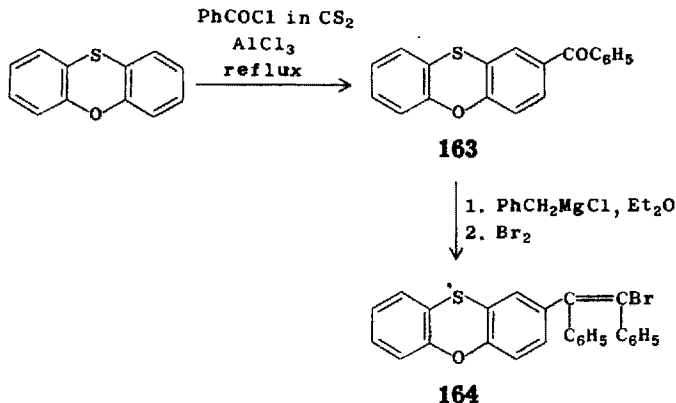
The monomer was polymerized in benzene with BF_3 etherate within a few minutes with evolution of heat, with benzoyl peroxide in 6 hours at 100° , and with *t*-butyl hydroperoxide in $3\frac{1}{2}$ hours at 100° . The polymer was precipitated by addition of methyl alcohol as a fine, moldable, white powder. It was also polymerized at 130° in contact with air without a catalyst to a hard, transparent, brittle polymer which was pliable above 200° . The physical, electrical, and compatibility properties of this polymer were described as being comparable to those of polystyrene with the added advantage of a higher softening point. The polymer was described as useful as a dielectric, for coatings or films, and as a solventless varnish or impregnant.

2-Vinylphenoxathiin and divinylphenoxathiin were copolymerized with vinyl acetate, acrylonitrile, acenaphthylene, styrene, and maleic anhydride. The copolymer with butadiene was rubber-like and yielded a tough film.⁸⁸

According to Ham,^{119a,119b} a blend of poly(vinyl chloride) and poly(vinylphenoxathiin) is suitable for forming fibers and blending poly(vinylphenoxathiin) into polyacrylonitrile improves the dyeability of the polyacrylonitrile.

(5) Miscellaneous Derivatives

Lescot and Buu-Hoi¹⁸⁶ prepared α -bromo- β -2-phenoxathiinylstilbene (**164**), an estrogenic compound, by the following procedure:



Several functional derivatives of alkylphenoxathiins have been described. Flowers and Flowers^{87,89,90} prepared 2-(α -hydroxyethyl)-phenoxathiin (**161**) from 2-acetylphenoxathiin (**160**); dehydration of this alcohol to 2-vinylphenoxathiin has been discussed. Tomita²⁹⁵ prepared 2,8-bis(α -hydroxy- β -piperidylethyl)-phenoxathiin (**167**) by the following series of reactions (see opposite page):

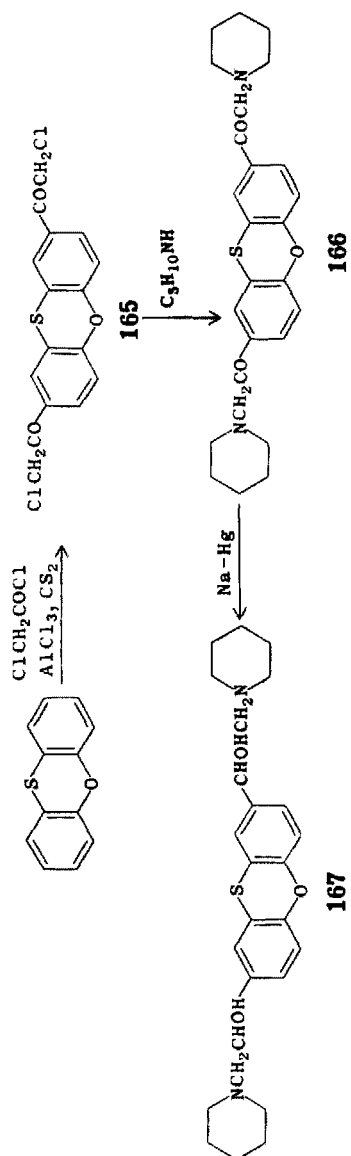


TABLE 17. Hydrocarbon Substituted Phenoxathiins

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
2-CH ₃ -	49	38-39				290
		36	185-187	12		1a
2-CH ₃ - 10, 10-dioxide		134-135				290
	1.6	135-137				229
3-CH ₃ -	77	83-84				290
3-CH ₃ - 10, 10-dioxide		138-139				290
4-CH ₃ -	46		186-187	14	d_{25}^{25} 1.213	290
					n_D^{25} 1.6403	290
		141-142				290
4-CH ₃ - 10, 10-dioxide						186
2-C ₂ H ₅ -	88		217-219	25	n_D^{23} 1.6548	186
x-C ₃ H ₇ -			200-216	20	d_{25}^{25} 1.199	269
x-C ₄ H ₉ -			245-264	20	d_{25}^{25} 1.134	269
2-C ₃ H ₁₁ -			249-250	18	n_D^{22} 1.6152	186
2-C ₁₂ H ₂₅ -			305-307	22	n_D^{22} 1.5758	186
x-Cyclohexyl-	31		232-238	20	d_{25}^{25} 1.167	270
x-Cyclohexyl 10-monoxide					n_D^{60} 1.6151	273
x-Cyclohexyl 10, 10-dioxide					n_D^{60} 1.5938	273

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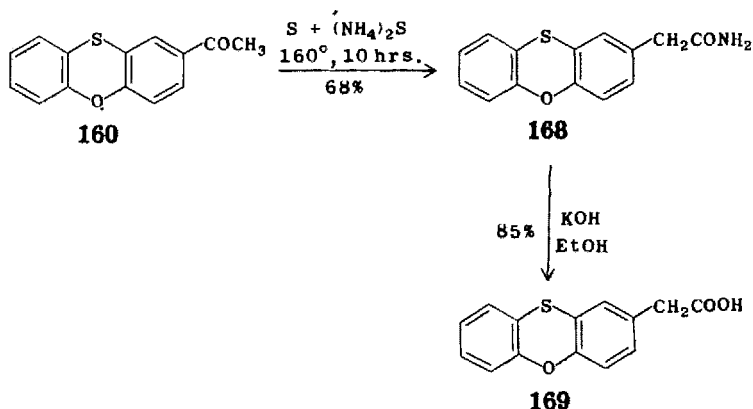
4-C ₆ H ₅ -	40	70.5-71.5	203-210	5	269
2-(CH ₂ =CH-)	79	39.5-41			87, 89, 90
2-CH ₃ CH(OH)-	90	65-67			87, 89, 90
2-NCCH ₂ -		85-88	190-205	10	310
2-H ₂ NCOCH ₂ -		200-202			310
2-HO ₂ CCH ₂ -	68	202-203			104
		193-194			310
	85	136-137			104
2-[C(C ₆ H ₅)(Br)=C(C ₆ H ₅)-]		129-130			186
2,8-(CH ₃ -) ₂		74			153
		71			154
		73-74			295
2,8-(CH ₃ -) ₂ 10-monoxide		132-133			153
2,8-(CH ₃ -) ₂ 10,10-dioxide		172			153
2,8-(C ₂ H ₅ -) ₂			203-204	4	295
			205-206	5	295
2,8-(C ₂ H ₅ -) ₂ 10,10-dioxide			200-215	20	269
			215-226	20	269
			216-227	20	269
			264-280	20	269
			300-360	3.5	270
x,y-[C ₃ H ₇ -] ₂			d ₂₂₅ 1.215		
x,y-[C ₄ H ₉ -] ₂			d ₂₂₅ 1.177		
x,y-Dicyclohexyl-			d ₂₂₅ 1.146		
			d ₂₂₅ 1.118		
			d ₂₂₅ 1.126		

TABLE 17. Hydrocarbon Substituted Phenoxathilins (contd)

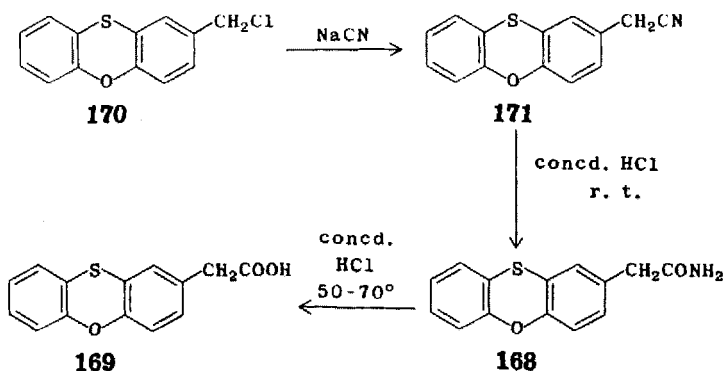
Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	B.p. (mm)	Other properties	Ref.
<i>x</i> -Cyclohexyl-4-C ₆ H ₅ -	37		215-270	3.5	d_{20}^{20} 1.091-1.156	270
<i>x</i> -Cyclohexyl-4-C ₆ H ₅ -10-monoxide						273
<i>x</i> -Cyclohexyl-4-C ₆ H ₅ -10,10-dioxide		82-84.5				273
Polyethyl, $n > 2$			>226(dec.)	5		269
Polycyclohexyl, $n > 2$			>360	3.5		270
<i>x, y</i> -Dicyclohexyl-4-C ₆ H ₅ -			270-330	3.5		270
<i>w, x, y, z</i> -[C ₃ H ₇] ₄			>244	20		269
2,8-[C ₅ H ₁₀ NCH ₂ CH(OH)-] ₂		133				295

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Gilman and Avakian¹⁰⁴ prepared 2-phenoxathiinacetic acid (**169**) in 85% yield by hydrolyzing 2-phenoxathiinacetamide (**168**) with ethanolic potassium hydroxide. The acetamide was obtained by subjecting 2-acetylphenoxathiin to the Willgerodt reaction.



Wenner³¹⁰ prepared 2-phenoxathiinacetic acid (**169**) by the following procedure:



These compounds are listed in Table 17.

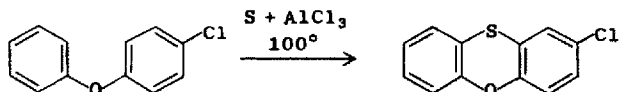
d. Halophenoxathiins

(1) Chlorophenoxathiins

The four possible monochlorophenoxathiins, 1-, 2-, 3-, and 4-chloro-, but only two dichlorophenoxathiins, 2, 8- and 10, 10-dichloro, have been reported. Several chloro substituted phenoxathiins have been reported, such as 3-chloro-8-methyl-, 3-chloro-8-methoxy-, and 3-chloro-cyclohexylphenoxathiin. These are listed in Table 18. Other substituted phenoxathiins containing chlorine are discussed in subsequent sections, such as nitrophenoxathiins, hydroxyphenoxathiins, and others.

Ring closure has been used to prepare several of the chlorophenoxathiins; Ackerman^{1a} prepared the 2-chloro compound (**172**) by heating phenyl chlorophenyl ether with sulfur and aluminum chloride.

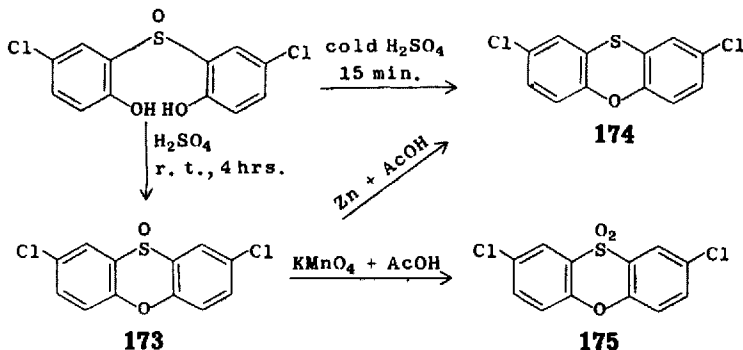
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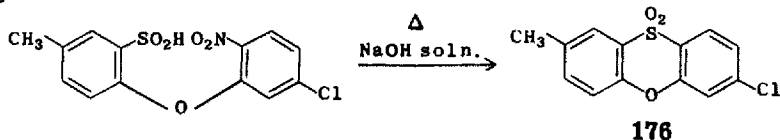
This compound has a blue color in sulfuric acid. Oxidation of 2-chlorophenoxathiin with excess hydrogen peroxide in glacial acetic acid on a steam bath gives the sulfone, ²⁹⁰ whose sulfuric acid solution is colorless.

Hilditch and Smiles¹⁵⁴ prepared 2,8-dichlorophenoxathiin by treating bis(5-chloro-2-hydroxyphenyl) sulfoxide with cold sulfuric acid for 15 minutes. Prolonged treatment with sulfuric acid gave 2,8-dichlorophenoxathiin 10-monoxide (**173**) which on reduction with zinc and acetic acid yielded the phenoxathiin (**174**) and on oxidation with permanganate in acetic acid yielded the sulfone (**175**).¹⁵³

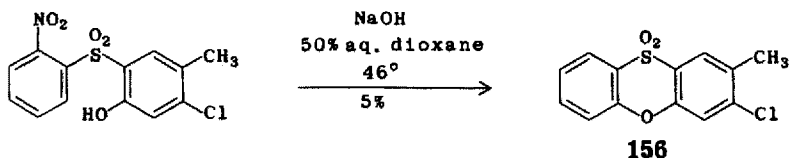


Using zinc chloride at 120° and 200°, thionyl chloride at boiling temperature, phosphorus oxychloride alone and in xylene, boiling phosphorus trichloride, and hot sulfuric acid did not cause ring closure.

Kent and Smiles¹⁷⁷ studied the conditions required for the following ring closure:



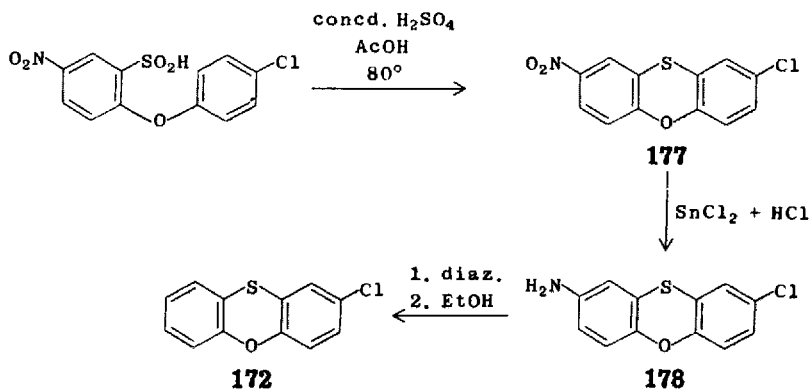
The yield was low, the reaction slow, and prolonged heating was required. Okamoto and Bunnett²²⁹ studied the reaction using a 20% excess of sodium hydroxide in 50% aqueous dioxane at 46° on *o*-nitrophenyl 4-chloro-2-hydroxy-5-methylphenyl sulfone; they obtained a 4.9% yield of 3-chloro-2-methylphenoxathiin 10,10-dioxide (**156**).



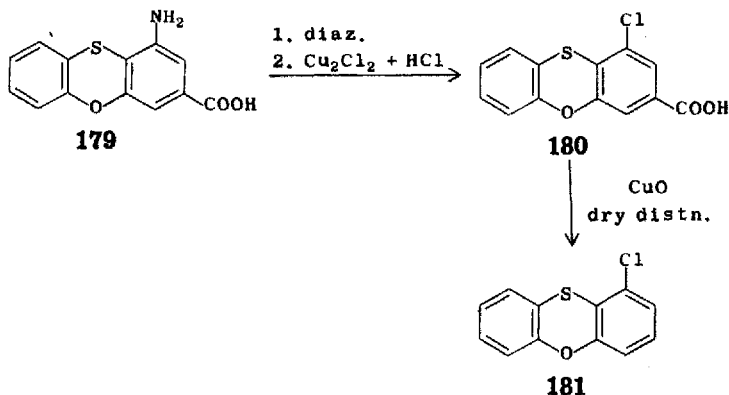
In their studies on the Ferrario reaction, Suter and Green²⁹⁰ treated 1.3 moles *o*-, *m*-, and *p*-chlorophenyl phenyl ether with 1 mole sulfur and 0.5 mole aluminum chloride at 100° for 30-36 minutes. They obtained 50-71% yields of the 2-, 3-, and 4-chlorophenoxathiins. These were converted to the sulfones by treatment with excess hydrogen peroxide in glacial acetic acid on a steam bath.

Smith and Moll^{270, 273} alkylated 3-chlorophenoxathiin with cyclohexene at 200-250° in the presence of Retrol to the mono-, di-, and polycyclohexyl-3-chlorophenoxathiins. The monocyclohexyl derivative was oxidized with nitric acid in acetic acid at 95° to the sulfoxide, a viscous, fluorescent, red oil, insoluble in water, and soluble in organic solvents.

The Sandmeyer reaction has been used for the preparation of chlorophenoxathiins from aminophenoxathiins. Thus, Gilman, Van Ess, and Willis¹⁰¹ prepared 4-chlorophenoxathiin 10, 10-dioxide in 17.1% yield from 4-aminophenoxathiin. Eidt⁷⁸ prepared 3-chlorophenoxathiin 10, 10-dioxide from 3-aminophenoxathiin 10, 10-dioxide. Irie¹⁷¹ prepared 2-chlorophenoxathiin (172) by the following series of reactions:



Irie prepared 1-chlorophenoxathiin (181) by the following series of reactions:



On treating phenoxathiin-2, 8-disulfonyl chloride with phosphorus pentachloride, Suter, McKenzie, and Maxwell²⁸⁹ obtained 2, 8-dichlorophenoxathiin (174).

Eidt⁷⁸ prepared a chlorophenoxathiin, melting about 60°, as well as a dichlorophenoxathiin, melting at 168-169°, by the treatment of phenoxathiin with sulfuryl chloride. It is probable that the monochlorination occurred at position 2, para to the oxygen. The dichlorination theoretically should have occurred at 2, 8-, the two positions para to the oxygen, but the melting point is about 20° too high compared with that reported by others.^{153-4,289}

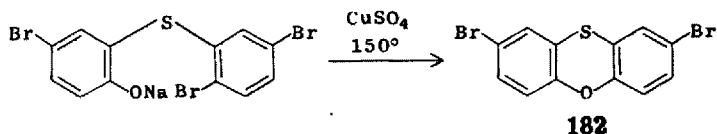
Irie,¹⁷¹ on treating phenoxathiin in dry benzene with dry chlorine, obtained 10, 10-dichlorophenoxathiin, red-yellow crystals decomposing at about 71°. Exposure to the atmosphere or treatment with water converts this compound to phenoxathiin 10-monoxide. Keeping it in dry benzene for one day yields a mixture of a monochloro-, melting at 78-79°, and a dichlorophenoxathiin, melting at 166-167°. Apparently 1-chlorophenoxathiin results from the treatment of phenoxathiin in concentrated sulfuric acid with concentrated hydrochloric acid at room temperature

(2) Bromophenoxathiins

The following bromophenoxathiins have been reported: 2-bromo-; 3-bromo- 10, 10-dioxide; 4-bromo- 10, 10-dioxide; 3-bromo-2-methyl-10, 10-dioxide; 2, 8-dibromo-; and 2, 8-dibromo- 10, 10-dioxide. These are listed in Table 18.

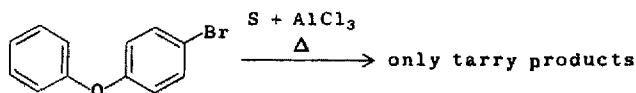
Bromination of phenoxathiin with bromine in carbon tetrachloride gave an 88% yield of 2-bromophenoxathiin.^{101,289} Bromination with two moles bromine gave a 75% yield of 2, 8-dibromophenoxathiin (182), which was easily oxidized to the sulfone (183) with 30% hydrogen peroxide.

These and other bromophenoxathiins have been prepared by ring closure reactions. Stevenson and Smiles²⁸⁷ prepared 2, 8-dibromophenoxathiin by heating the sodium salt of 5-bromo-2-hydroxyphenyl 2, 5-dibromophenyl sulfide with copper sulfate to 150° or above at 1 mm pressure:

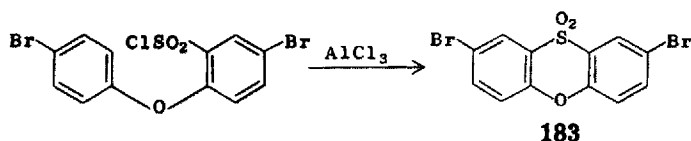


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Suter, McKenzie, and Maxwell²⁸⁹ were not able to prepare 2-bromophenoxathiin by the reaction Ackerman used to prepare 2-chlorophenoxathiin:



Treatment of 2-(4-bromophenoxy)-5-bromobenzenesulfonyl chloride in tetrachlorethane with aluminum chloride yielded 2, 8-dibromophenoxathiin 10, 10-dioxide (183).



Rearrangement of 2-hydroxy-4-chloro-5-methyl-2'-nitrodiphenyl sulfone with excess sodium hydroxide in 50% dioxane at 46° gave 3.5% 3-bromo-2-methylphenoxathiin 10, 10-dioxide.²²⁹

Eidt⁷⁸ prepared 3-bromophenoxathiin from the 3-amino compound by the Sandmeyer reaction.

(3) Iodophenoxathiins

The following iodophenoxathiins have been reported: 2-iodo-; 3-iodo-; 3-iodo- 10, 10-dioxide; and 4-iodo. These are listed in Table 18.

Iodination of phenoxathiin resulted in monoiodination and oxidation to 3-iodophenoxathiin 10, 10-dioxide.⁷⁸ Nobis²²⁵ obtained a 21% yield of 4-iodophenoxathiin on iodination of 4-phenoxathiinyl lithium. Nobis prepared 3-iodophenoxathiin in 15% yield and 2-iodophenoxathiin in 10% yield from the respective aminophenoxathiin by diazotization and treatment of the diazonium salt with urea and potassium iodide.

(4) Uses

3-Chlorophenoxathiin 10, 10-dioxide was 100% effective against walnut worms.²⁷² Chlorophenoxathiin was active at 0.25 molar concentration in killing horse strongyle larvae in feces.¹⁸⁹ 1, 3, 7, 9-Tetrachlorophenoxathiin showed no insecticidal activity.²³⁵ Chlorophenoxathiins were much less effective than chlorinated camphene against fleece worms.¹¹⁵ Cyclohexyl-3-chlorophenoxathiins had a 100% kill of southern

TABLE 18. Halophenoxathiins

Substituent	Yield (%)	M.p. (°C)	(°C)	(mm)	Other properties	Ref.
1-Cl		78-80				171
2-Cl	65	88-89				290
		88-89				171
			176	12		1a
		<i>ca.</i> 80				78
2-Cl 10, 10-dioxide		158-159				290
						242b
3-Cl	71	59-60				290
3-Cl 10, 10-dioxide		152-153				290
						78
4-Cl	50		192-193	7	d_{44}^{25} 1.401 n_D^{25} 1.6618	290
4-Cl 10, 10-dioxide		148-149				290
<i>x</i> -Cl	17.1	148-149				101
		78-79				171
<i>x</i> -Cl 10, 10-dioxide		172-174				171
2-Br	88	58-59				101

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3-Br 10, 10-dioxide	83	59-60	289
4-Br 10, 10-dioxide		177-178	78
2-I	10.4	157.5-158.0	78
3-I	15	92-94	225
3-I 10, 10-dioxide		70-72	225
4-I	21	171-172	78
		42.5-43.0	225
3-Cl-8-CH ₃ -10, 10-dioxide			177
3-Cl-2-CH ₃ -10, 10-dioxide	4.9	178-180	229
3-Br-2-CH ₃ -10, 10-dioxide	3.5	189-191	229
3-Cl-8-CH ₃ O-10, 10-dioxide		173	177
3-Cl-x-cyclohexyl-	28	215-231	270
3-Cl-x-cyclohexyl-10-monoxide		4	273
3-Cl-x-cyclohexyl-10, 10-dioxide		195-196	273
3-Cl-x, y-dicyclohexyl-		260-270	270
2, 8-Cl ₂		142-145	154
		135	153
		134-135	289
2, 8-Cl ₂ 10-monoxide		166	154
	25	168	153
2, 8-Cl ₂ 10, 10-dioxide		196	153

TABLE 18. Halophenoxathiins (cont'd.)

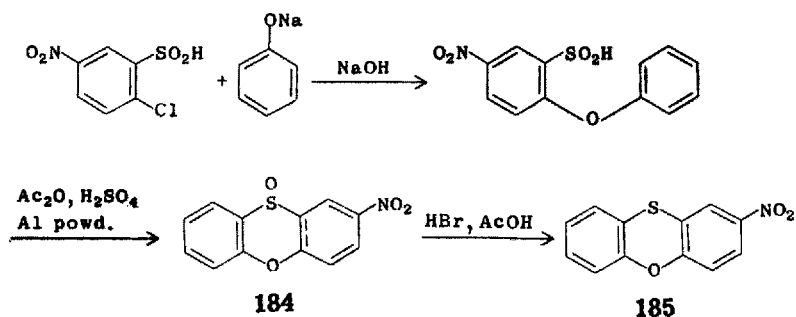
Substituent	Yield (%)	M.p. (°C)	(°C)	(mm)	Other properties	Ref.
<i>x, y</i> -Cl ₂		168-169				78
		166-167				171
<i>x, y</i> -Cl ₂ 10, 10-dioxide		208-210				171
10, 10-Cl ₂		ca. 71(dec.)				171
2, 8-Br ₂	75	92-93				289
		92				287
2, 8-Br ₂ 10, 10-dioxide	92	185-186				289

army worms.^{270-1,273} Chlorophenoxathiins, such as the 2-chloro 10-monoxide and *x*-cyclohexyl-2-chloro 10-monoxide have been described as heat stabilizers for vinylidene chloride polymers and copolymers.³⁴

e. Nitrophenoxathiins

(1) Mononitrophenoxathiins

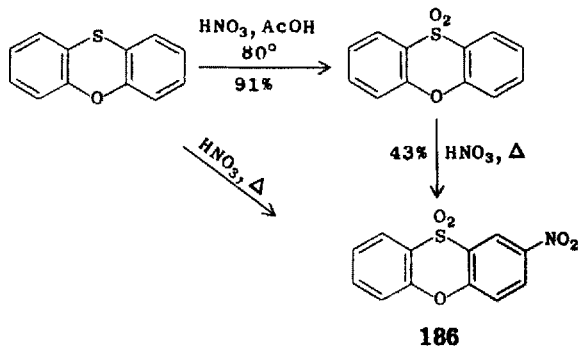
Krishna¹⁸² prepared 2-nitrophenoxathiin (**185**) by the condensation of 2-chloro-5-nitrobenzenesulfinic acid and phenol in boiling alkaline solution and dehydrating the resulting diphenyl ether sulfinic acid with acetic anhydride in the presence of aluminum powder.



The sulfone (**192**) was prepared by oxidation with nitric acid in glacial acetic acid. Condensation of 2-chloro-5-nitrobenzenesulfinic acid with *p*-cresol and with *p*-chlorophenol gave 2-nitro-8-methyl- and 2-nitro-8-chlorophenoxathiin, respectively. The sulfone of 2-nitro-8-chlorophenoxathiin was prepared using chromic acid in acetic acid. Irie¹⁷¹ also used this method to prepare 2-nitrophenoxathiin by employing concentrated sulfuric acid in glacial acetic acid at 80° for the ring closure. Other compounds prepared by this method were 2-nitro-8-methyl-, 2-nitro-8-methoxy-, and 2-nitro-8-chlorophenoxathiin. 2-Nitro-8-chlorophenoxathiin was described as being unstable on heating at 100° for 20-30 minutes. It is difficult to account for this instability.

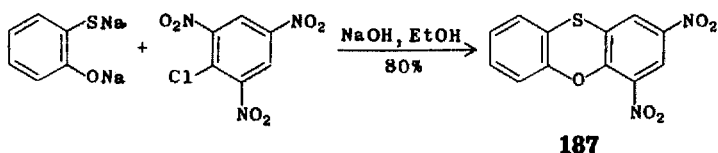
Treatment of phenoxathiin in glacial acetic acid with fuming nitric acid at 80° gives the sulfone. Nitration of phenoxathiin or its sulfone occurs with fuming nitric acid at steam bath or acetic acid reflux temperature to give 2-nitrophenoxathiin 10, 10-dioxide (**186**).^{171,224}

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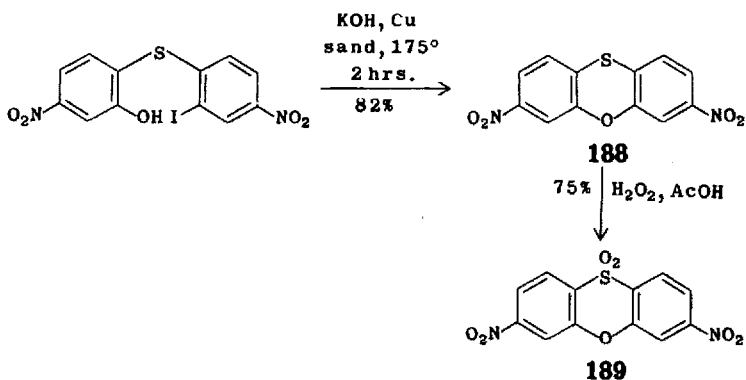
(2) Dinitrophenoxathiins

Both ring closure and nitration methods have been described for the preparation of dinitrophenoxathiins. 2, 4-Dinitrophenoxathiin (**187**) has been prepared only by ring closure. Mauthner,²⁰¹ who was the first to describe phenoxathiins, prepared 2, 4-dinitrophenoxathiin in 80% yield by the reaction of thiocatechol and picryl chloride in the presence of sodium hydroxide in ethyl alcohol.



The sulfoxide was prepared using nitric acid and heat. The sulfone was prepared using chromic acid in acetic acid under reflux.

3, 7-Dinitrophenoxathiin (**188**) has been prepared only by the following ring closure method:⁵



2, 8-Dinitrophenoxathiin (**190**) has been prepared by both ring closure and nitration methods. Irie¹⁷¹ obtained 2, 8-dinitrophenoxathiin in 45%

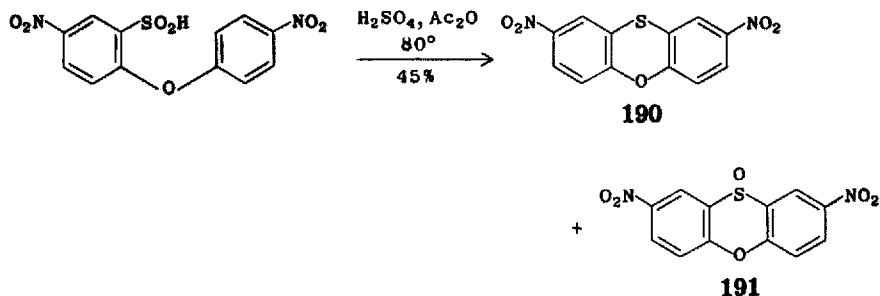
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TABLE 19. Nitrophenoxathiins

Substituent	Yield (%)	M.p.(°C)	Ref.
2-NO ₂		160	171
		140	182
2-NO ₂ 10-monoxide			182
2-NO ₂ 10, 10-dioxide	43	192-194	224
	30	187-188	224
		196.5	171
		205-206	182
			242b
2-NO ₂ -8-CH ₃ -		160	171
		156	182
2-NO ₂ -8-CH ₃ - 10, 10-dioxide		196-197	171
2-NO ₂ -8-Cl		195	171
			182
2-NO ₂ -8-Cl 10, 10-dioxide		183-185	182
2-NO ₂ -8-CH ₃ O-		ca. 300	171
2-NO ₂ -8-CH ₃ O- 10, 10-dioxide		>300	171
2, 4-(NO ₂) ₂	80	187	201
2, 4-(NO ₂) ₂ 10-monoxide	76	202-203	201
2, 4-(NO ₂) ₂ 10, 10-dioxide	90	256.5-257.0	201
2, 8-(NO ₂) ₂	45	143	171
2, 8-(NO ₂) ₂ 10, 10-dioxide	30	283-286	224
		280	171
	41	277-280	224
3, 7-(NO ₂) ₂	82	204-205	5
3, 7-(NO ₂) ₂ 10, 10-dioxide	75	246-247	6
3, 8-(NO ₂) ₂ -2-CH ₃ CONH-		174-176.5	225

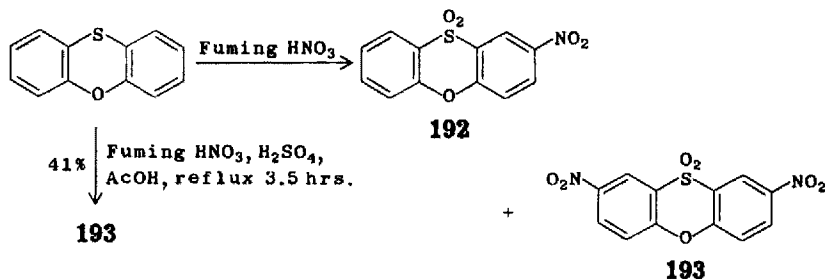
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yield by the ring closure of 3-nitro-6-(*p*-nitrophenoxy)benzenesulfinic acid with sulfuric acid in acetic anhydride at 80°.



The sulfoxide (191) was reduced to the desired phenoxathiin by treatment with 35% hydrobromic acid at 100°.

Nitration of phenoxathiin yields both 2-nitro- (192) and 2, 8-dinitro-phenoxathiin 10, 10-dioxide (193).^{171, 224}



Nobis and Burske²²⁵ were unsuccessful in attempts to nitrate 2-acetamidophenoxathiin 10, 10-dioxide; however, they did obtain 2-acetamido-3, 8-dinitrophenoxathiin in very low yield on nitrating 2-acetamidophenoxathiin in acetic anhydride and concentrated sulfuric acid at -4°.

According to Pfaff, 1, 3, 7, 9-tetranitrophenoxathiin 10-monoxide exhibits no insecticidal action.²³⁵

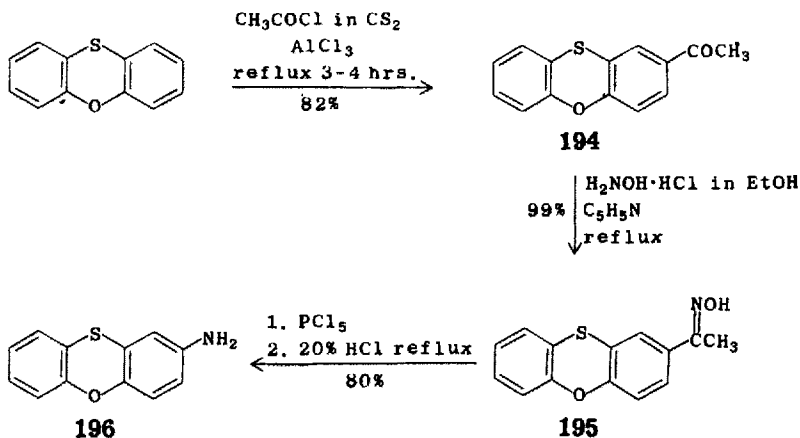
The nitrophenoxathiins are listed in Table 19. The nitrophenoxathiins and their sulfoxides are colored, usually violet or red, in concentrated sulfuric acid; the sulfones are colorless in concentrated sulfuric acid.

f. Aminophenoxathiins

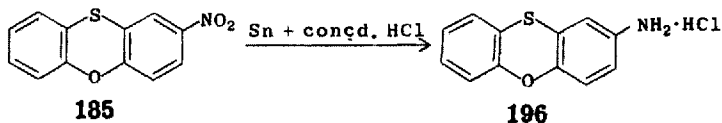
(1) Monoaminophenoxathiins

1-Aminophenoxathiin has not been reported. 2-Aminophenoxathiin (196) was readily prepared in fair yields by the Friedel-Crafts reaction of phenoxathiin with acetyl chloride and by subjecting the oxime to the Beckman rearrangement.^{186, 224}

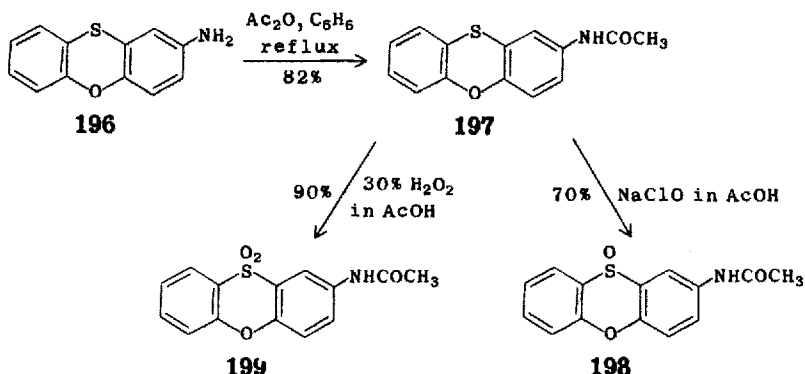
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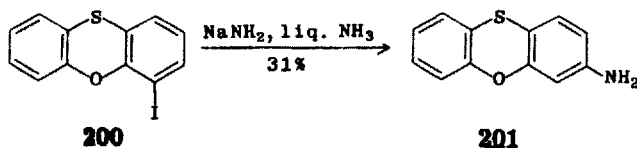
Irie¹⁷¹ prepared 2-aminophenoxathiin by reducing 2-nitrophenoxathiin.



A concentrated sulfuric acid solution of 2-aminophenoxathiin is red-violet in color.¹⁷¹ 2-Aminophenoxathiin is easily acetylated with acetic anhydride and the acetamido derivative oxidized to the 10-monoxide (198) with sodium hypochlorite or to the 10,10-dioxide (199) with 30% hydrogen peroxide.²²⁴

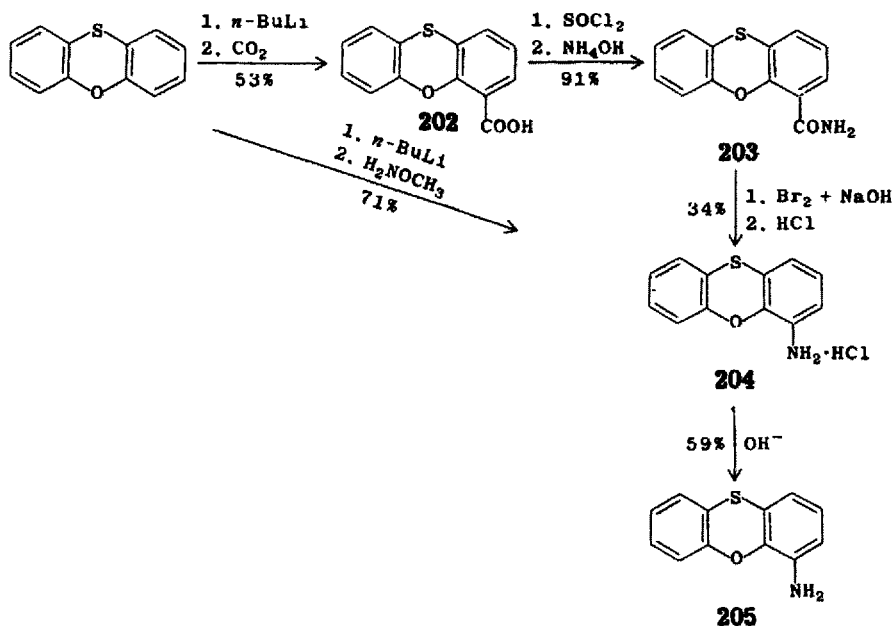


Eidt⁷⁸ prepared 3-aminophenoxathiin (201) by the hydrogenation of the 3-nitro compound. Nobis and Burske²²⁵ employed the rearrangement reaction of Gilman and Avakian¹⁰³ which occurs when a compound containing any halogen ortho to an ether linkage is treated with sodamide in liquid ammonia to give an amino compound in the meta position. Thus, the reaction of 4-iodophenoxathiin (200) with sodamide in liquid ammonia gave a 31% yield of 3-aminophenoxathiin (201).



This amine (**201**) was converted by diazotization and reaction of the diazonium compound with potassium iodide to 3-iodophenoxathiin. The 2- and 3-aminophenoxathiins are diazotized with some difficulty and special conditions are necessary: a relatively long reaction time is required and temperatures in the 5-10° range must be used. Acetylation of 3-aminophenoxathiin (**201**) gave a 25% yield of 3-acetamidophenoxathiin. Tomita and Fukunaga²⁹⁷ converted 3-aminophenoxathiin to 3-(*p*-acetamidophenylsulfonamido)- and this, in turn, to 3-(*p*-aminophenylsulfonamido)phenoxathiin.

Gilman, Van Ess, Willis, and Stuckwisch¹⁰¹ prepared 4-aminophenoxathiin (**205**) by the following series of reactions:

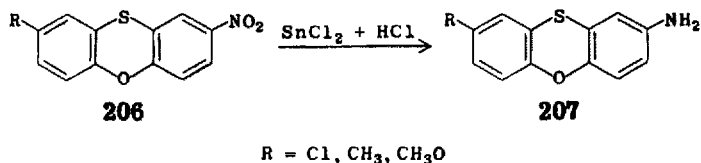


Diazotization of 4-aminophenoxathiin (**205**) and treatment of the diazonium compound with cuprous chloride gave a 17% yield of the 4-chloro compound. On treating the 4-amine (**205**) with *p*-acetaminobenzenesulfonyl chloride, Gilman and Stuckwisch¹⁰² obtained, in 81% yield, 4-(acetylsulfanilamido)phenoxathiin, which, on hydrolysis with 10% sodium hydroxide, was converted to 4-(sulfanilamido)phenoxathiin in 87% yield.

Several substituted 2-aminophenoxathiins (**207**) have been prepared by ring closure of the corresponding 5-nitro-2-phenoxybenzenesulfinic

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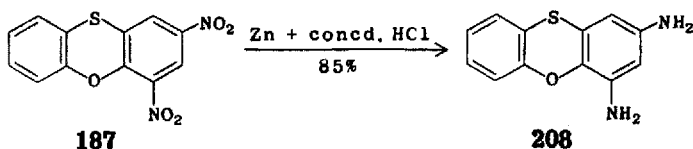
acid and hydrogenation of the nitrophenoxathiin (**206**) to the amine.¹⁷¹



(2) Diaminophenoxathiins

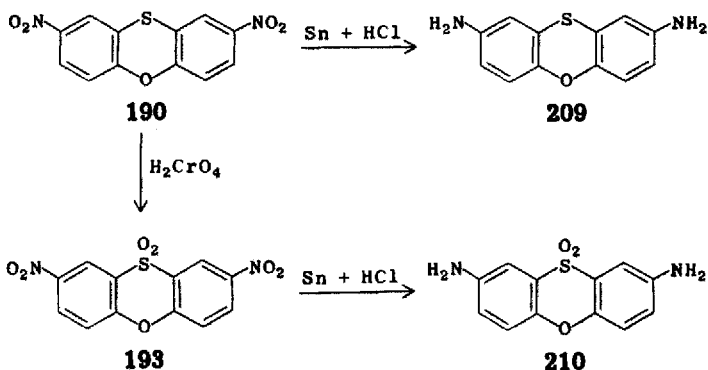
Irie¹⁷⁰⁻¹ studied 1, 3- and 2, 8-diaminophenoxathiins because they exhibited high bactericidal activity against hemolytic *streptococci* and *E. coli*. Acetylation of 1, 3-diaminophenoxathiin gave the diacetamido derivative. The diacetamido compound was easily oxidized with 30% hydrogen peroxide to the monoxide, which was hydrolyzed with 2 N sodium hydroxide to 1, 3-diaminophenoxathiin 10-monoxide (sulfuric acid solution violet red).

Mauthner²⁰¹ prepared 2, 4-diaminophenoxathiin (**208**) by the reduction of the dinitro compound (**187**).



Reduction of 2, 4-dinitrophenoxathiin 10-monoxide with zinc and acetic acid also gave the 2, 4-diamine; reduction of the dinitro sulfone with zinc chloride and concentrated hydrochloric acid gave the 2, 4-diamine sulfone.

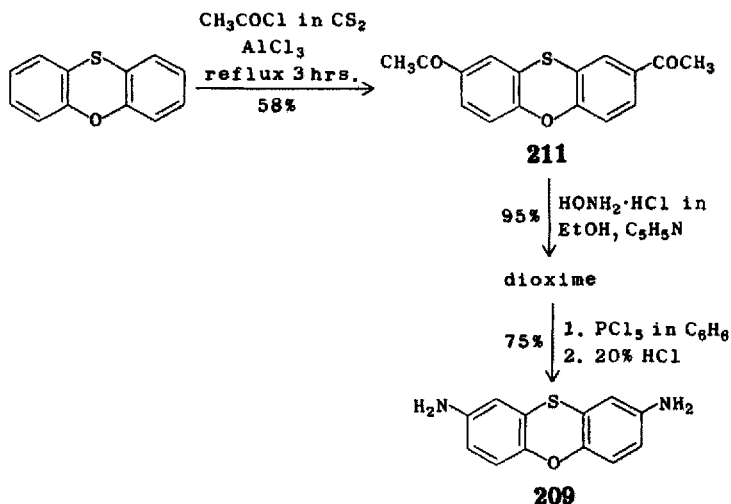
Irie¹⁷¹ prepared 2, 8-diaminophenoxathiin (**209**) by reducing the dinitro compound (**190**).



Nobis, Blardinelli, and Blaney²²⁴ prepared 2, 8-diaminophenoxathiin (**209**) in good yield by direct nuclear substitution of phenoxathiin with

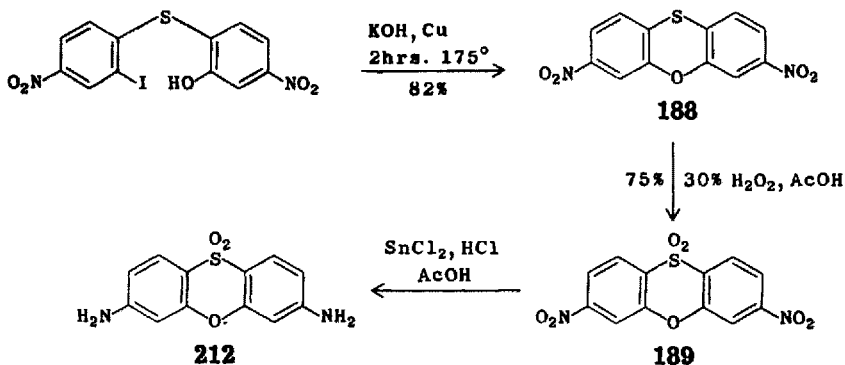
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acetyl chloride in a Friedel-Crafts reaction followed by a Beckmann rearrangement of the ketoxime.



Acetylation of 2,8-diaminophenoxathiin gave the *N,N*-diacetyl derivative in 88% yield. This was oxidized with 30% hydrogen peroxide to the sulfone in 61% yield.

Amstutz⁵ prepared 3,7-diaminophenoxathiin 10,10-dioxide (**212**) by ring closure of 2-hydroxy-2'-iodo-4,4'-dinitro diphenyl sulfide to 3,7-dinitrophenoxathiin (**188**) and reduction of the dinitro sulfone (**189**).



Acetylation of 3,7-diaminophenoxathiin 10,10-dioxide gave the *N,N*-diacetyl derivative in 90% yield.

The various aminophenoxathiins reported in the literature are listed in Table 20.

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TABLE 20. Aminophenoxathiins

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Ref.
2-NH ₂	75	93-95			224
			250-260	20	186
		98			171
2-NH ₂ · HCl		235(dec.)			171
2-NH ₂ 10, 10-dioxide	62	164-165			224
3-NH ₂	31	81, 5-83, 0			225
3-NH ₂ 10, 10-dioxide		175-176			78
4-NH ₂	59		209	5	101
4-NH ₂ · HCl	71	222-224			101
2-CH ₃ CONH-	80	159			186
	82	129-130			224
2-CH ₃ CONH- 10-monoxide		234-235			224
2-CH ₃ CONH- 10, 10-dioxide	90	279, 5-281			224
3-CH ₃ CONH-	25	181-182, 5			225
3-(<i>p</i> -H ₂ NC ₆ H ₄ SO ₂ NH-)		186-187			297
3-(<i>p</i> -CH ₃ CONHC ₆ H ₄ SO ₂ NH-)		195-196			297
4-(<i>p</i> -H ₂ NC ₆ H ₄ SO ₂ NH-)	87	168			102
4-(<i>p</i> -CH ₃ CONHC ₆ H ₄ SO ₂ NH-)	81	192			102
2-NH ₂ -8-CH ₃ -		97			171
2-NH ₂ -8-CH ₃ - 10, 10-dioxide		196-197			171
2-NH ₂ -8-CH ₃ O-		277			171
2-NH ₂ -8-Cl- · HCl		220, 1			171
1, 3-(NH ₂) ₂					171
1, 3-(NH ₂) ₂ 10-monoxide		262-263			171
2, 4-(NH ₂) ₂	85	158			201
2, 4-(NH ₂) ₂ 10, 10-dioxide	86	228			201
2, 8-(NH ₂) ₂	75	171-173			224
		118			171
2, 8-(NH ₂) ₂ 10, 10-dioxide	81	244-247, 5			224
		239-240			171

[For references, see pp. 939-951.]

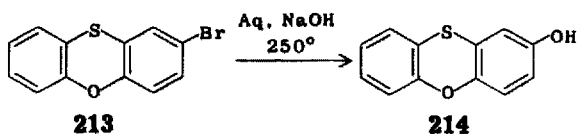
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TABLE 20. Aminophenoxathiins (contd)

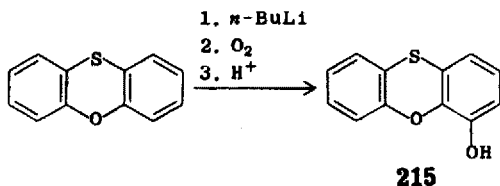
Substituent	Yield (%)	M.p. (°C)	B.p. (°C) (mm)	Ref.
3, 7-(NH ₂) ₂		167-168		171
3, 7-(NH ₂) ₂ 10, 10-dioxide	78	224-225.5		5
1, 3-(CH ₃ CONH-) ₂		242		171
1, 3-(CH ₃ CONH-) ₂ 10-monoxide		286		171
2, 4-(CH ₃ CONH-) ₂	67	224-225		201
2, 4-(C ₆ H ₅ CONH-) ₂	90	257		201
2, 8-(CH ₃ CONH-) ₂	88	253-254		224
2, 8-(CH ₃ CONH-) ₂ 10, 10-dioxide	61	349-353		224
3, 7-(CH ₃ CONH-) ₂		289-290		171
3, 7-(CH ₃ CONH-) ₂ 10, 10-dioxide	90	359-362		5

g. Hydroxyphenoxathiins and Derivatives

2-Hydroxyphenoxathiin (**214**) has been prepared by the hydrolysis²⁴³ of 2-bromophenoxathiin (**213**).

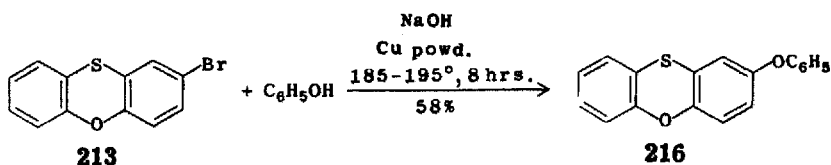


Gilman and Esmay¹⁰⁶ prepared 4-hydroxyphenoxathiin (**215**) through the metalation of phenoxathiin.

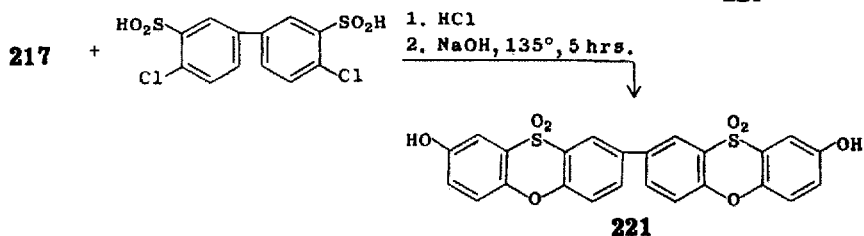
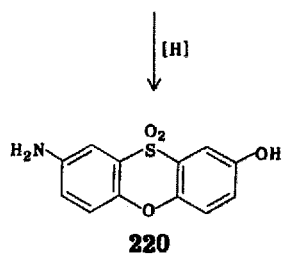
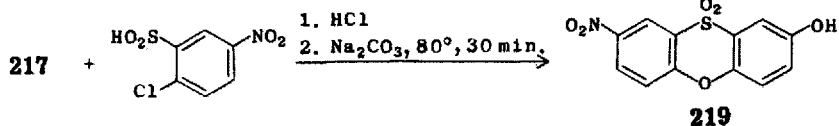
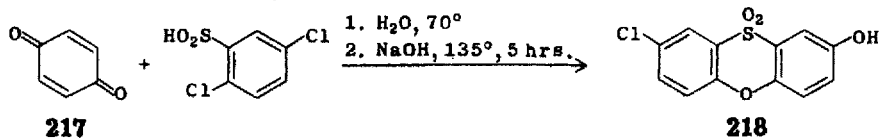


2-Phenoxyphenoxathiin (**216**) has been prepared by the reaction of 2-bromophenoxathiin with phenol and sodium hydroxide in the presence of a trace of copper powder.²⁹⁰

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Pütter and Suckfüll²⁴² prepared several hydroxyphenoxathiins in good yields by the condensation of quinone with a substituted benzene-sulfinic acid in weakly acid to alkaline media at 80-135°.



These compounds were described as valuable dye intermediates.⁶⁶⁻⁷

Desai and Wali⁶⁴ described the preparation of tetrahydrophenoxathiindiones (**222** and **223**).

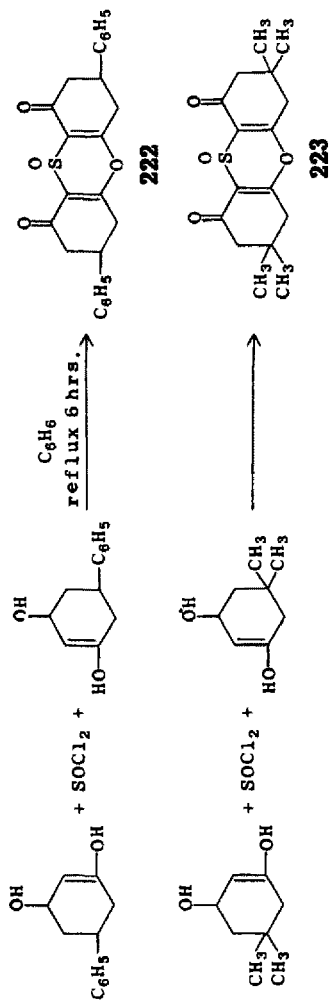


TABLE 21. Hydroxyphenoxathins and Derivatives

Substituent	Yield (%)	M.p. (°C)	B.p. (°C) (mm)	Ref.
2-OH				243
4-OH	47	98-99		106
2-C ₆ H ₅ O-	58	81-82	230 7	290
2-C ₆ H ₅ O- 10, 10-dioxide		112-113		290
2-OH-8-Cl 10, 10-dioxide		250		242
2-OH-8-NO ₂ 10, 10-dioxide		298		242
2-OH-8-NH ₂ 10, 10-dioxide		249		242
2-Bis(8-OH 10, 10-dioxide)		448		242
1, 9-(=O) ₂ -3, 7-(C ₆ H ₅ -) ₂ 10-oxide, 3, 4, 6, 7-tetrahydro-		216		64
1, 9-(=O) ₂ -3, 3, 7, 7-(CH ₃ -) ₄ 10-oxide, 3, 4, 6, 7-tetrahydro-		181-182		64

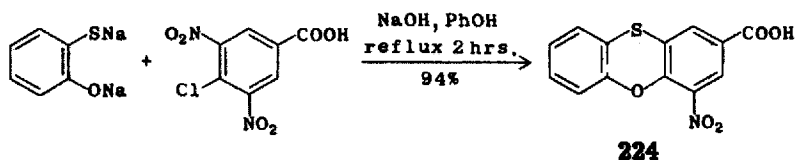
The solution of these compounds in heated concentrated sulfuric acid was blue. The structures were assigned only on the basis of elemental analysis.

The hydroxyphenoxathiins reported in the literature are listed in Table 21.

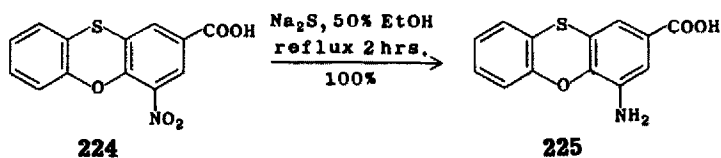
h. Phenoxathiin Carboxylic Acids and Derivatives

(1) Phenoxathiin monocarboxylic acids

Mauthner²⁰² prepared 4-nitrophenoxathiin-2-carboxylic acid (**224**) by the following condensation reaction:

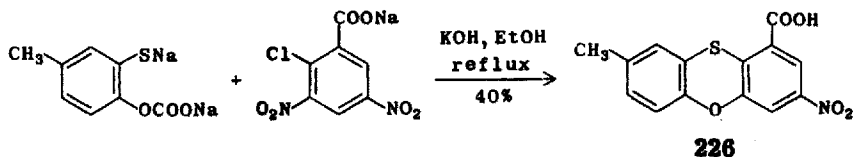


This compound was isolated as dark red needles; its solution in warm sodium hydroxide was red-brown and in concentrated sulfuric acid wine red. Its sulfone was prepared by oxidation in refluxing acetic acid with chromic acid; its sulfoxide was prepared by oxidation with nitric acid. Treatment with sodium sulfide under aqueous alcohol reflux yielded the colorless amine compound (**225**).



The amine (**225**) had weakly basic characteristics and its salts were completely dissociated in warm water. Acetylation yielded 4-acetamidophenoxathiin-2-carboxylic acid as colorless needles whose sulfuric acid solution was yellow. Diazotization of the amine gave phenoxathiin-2-carboxylic acid in 92% yield as colorless needles. Dry distillation of the acid caused decarboxylation to phenoxathiin.

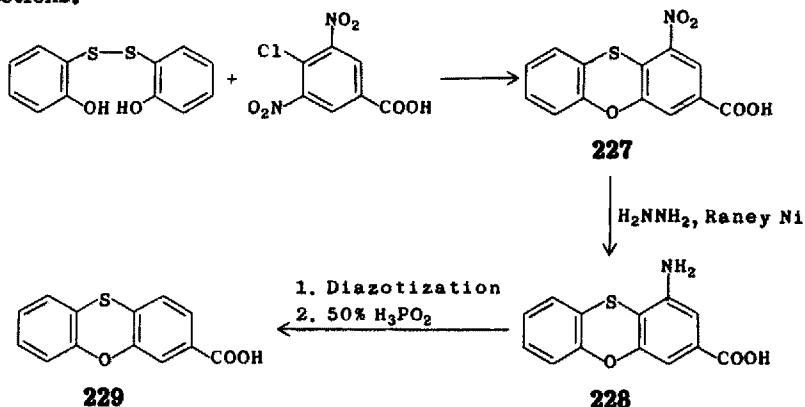
Bennett, Leslie, and Turner¹⁹ prepared 8-methyl-3-nitrophenoxathiin-1-carboxylic acid (**226**) in 40% yield by the following reaction:



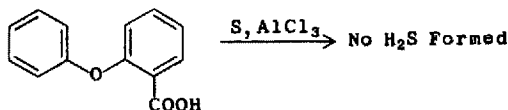
This compound, isolated as orange needles, provoked violent sneezing.

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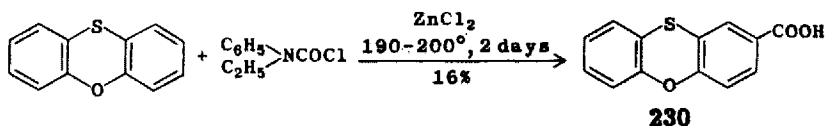
Shirley and Lehto²⁶² prepared phenoxathiin-3-carboxylic acid (**229**) in 24% yield based on the nitro compound by the following series of reactions:



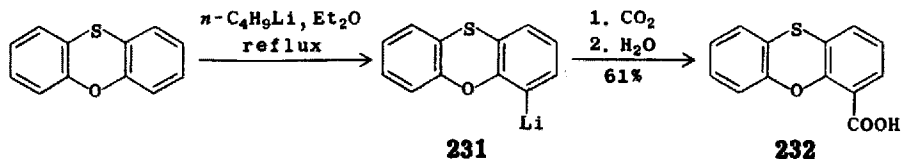
The Ferrario reaction was unsuccessful in the attempted preparation of phenoxathiin-4-carboxylic acid (**202**).¹⁰¹



Two methods have been used for introducing the carboxylic acid function directly into the phenoxathiin nucleus. Bennett, Leslie and Turner¹⁹⁵ prepared presumably phenoxathiin-2-carboxylic acid (**230**) in 16% yield by the reaction of phenoxathiin with phenylethylcarbonyl chloride in the presence of powdered anhydrous zinc chloride at 190–200° for two days.

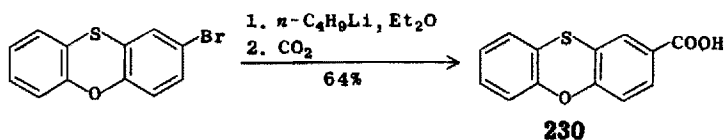


Metalation of phenoxathiin with *n*-butyllithium followed by carbonation led to 4-phenoxathiincarboxylic acid (**232**).^{88,91}



This compound was decarboxylated to phenoxathiin by heating with copper bronze in quinoline at 200°. 4-Phenoxathiincarboxylic acid was converted to the sulfone in 58% yield by treatment with hydrogen peroxide

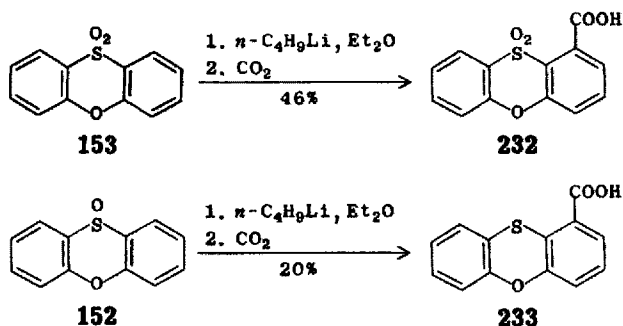
in acetic acid solution. 2-Phenoxathiincarboxylic acid (**230**) was prepared in 64% yield from 2-phenoxathiinyl lithium prepared by the metalation of 2-bromophenoxathiin:¹⁰¹



The preparation of 2-phenoxathiincarboxylic acid through the Grignard reagent gave a yield of only 8%.²⁸⁹

Metalation of phenoxathiin with phenylcalcium iodide under ether reflux and carbonation in the usual way gave a deep yellow crystalline compound melting at 260–262°, but its mixed melting point with 2-phenoxathiincarboxylic acid was depressed.¹⁰¹ This was later¹⁰⁷ shown to be a mixture of 4-phenoxathiincarboxylic acid and 4,6-phenoxathiindicarboxylic acid.

In contrast to phenoxathiin, the sulfone (**153**) and sulfoxide (**152**) direct metalation to position 1. Thus metalation and carbonation of phenoxathiin 10-monoxide or 10,10-dioxide yielded the corresponding 1-phenoxathiincarboxylic acid (**233**) or sulfone (**232**), the sulfoxide being reduced.^{109,111,261,262}

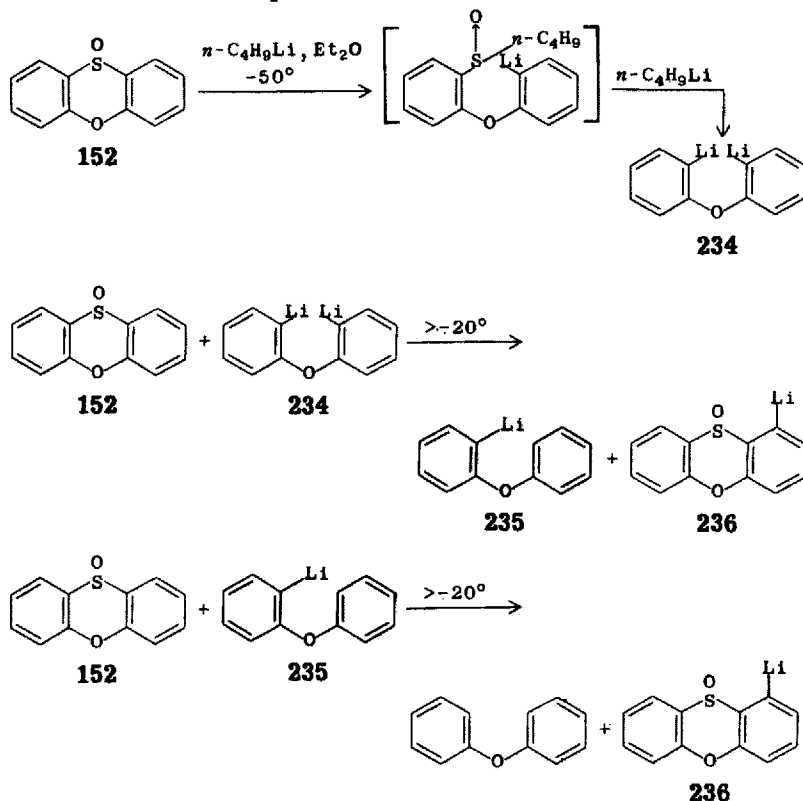


The hydrazides of these compounds as well as of 4-phenoxathiincarboxylic acid 10,10-dioxide, which were tested as antitubercular chemotherapeutic agents, were prepared by treating the acid with diazomethane and reacting the methyl ester with 85% hydrazine hydrate under reflux. Refluxing the sulfone of 1-phenoxathiincarboxylic acid with Raney nickel in 75% ethanol opened the heterocyclic ring and gave a 47% yield of 3-phenoxybenzoic acid.²⁶²

From the reaction of one equivalent of *n*-butyllithium and phenoxathiin 10-monoxide at –50°, Gilman and Eidt¹⁰⁸ obtained 24.5% phenoxathiin, 5.5% 1-phenoxathiincarboxylic acid, and various cleavage products, such as diphenyl ether and phenoxybenzoic acid. When two and three equivalents of *n*-butyllithium were used at –50°, 2,2'-dicarboxydiphenyl ether and *n*-butyl mercaptan were also obtained. Two equivalents of *n*-

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butyllithium at -20° to room temperature gave a moderate yield, 16%, of 1-phenoxathiincarboxylic acid. It was suggested that cleavage may have been initiated by attack of butyl carbanion on the heterocyclic sulfur and that metalation reactions may not occur to a significant extent until the mixture warms up to -20° .



Oxidation of 4-methylphenoxathiin 10, 10-dioxide with permanganate and heating 48 hours in the presence of potassium hydroxide gave no carboxylic acid.¹⁰¹ Treatment of 2-acetylphenoxathiin with hypochlorite in dilute sodium hydroxide on a steam bath for five hours gave a 60% yield of 2-phenoxathiincarboxylic acid 10, 10-dioxide.^{171, 289} Table 22 lists the various phenoxathiincarboxylic acids reported in the literature.

(2) Phenoxathiindicarboxylic Acids

Tomita²⁹⁵ and Eidt⁷⁸ prepared, 2,8-phenoxathiindicarboxylic acid 10, 10-dioxide by the hypochlorite oxidation of 2,8-diacetyl- or 2,8-bis(chloroacetyl)phenoxathiin.

In the metalation and carbonation of phenoxathiin, it was reasonable to assume that four dicarboxylic acids would result: 1,4-, 1,6-, 1,9-, and

TABLE 22. Phenoxathiin Carboxylic Acids

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Ref.
1-COOH	20	221-222			262
	16	223-224.5			108
1-COOH 10-monoxide		171-173			78
1-COOH 10, 10-dioxide	46	204-209			262
		228-229			262
1-COOCH ₃		95-96			262
1-COOCH ₃ 10, 10-dioxide	84	144-145			262
1-CONHNH ₂	89	197-198			262
1-CONHNH ₂ 10, 10-dioxide	70	240			262
2-COOH	64	260-265			101
	60	259-260			289
	16	230-238			19
	92	223			202
2-COOH 10, 10-dioxide		268-269			171
3-COOH	24	223-224			262
4-COOH	53	168-169			101
	37	171-173			78
4-COOH 10-monoxide	92	262 (dec.)			108

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4-COOH 10, 10-dioxide	58	262 (dec.)	78
		183-184	101
		189-190	261
	15	230-232	78, 107
4-COOCH ₃	76		183-187 1 262
4-COOCH ₃ 10, 10-dioxide		123-124	261
		124	101
4-CONHNH ₂		127-128	262
4-CONHNH ₂ 10, 10-dioxide		260	261
4-CONH ₂	91	185-186	101
2-COOH-4-NH ₂	100	250	202
2-COOH-4-NHCOCH ₃	78	294-295	202
2-COOH-4-NO ₂	94	262	202
2-COOH-4-NO ₂ 10-monoxide		251-252	202
2-COOH-4-NO ₂ 10, 10-dioxide		296-297	202
3-COOH-1-NH ₂		259	171
		248-249	262
3-COOH-1-NO ₂		260-262	262
4-COOH-9-NO ₂ 10, 10-dioxide		351-353 (dec.)	78
1-COOH-3-NO ₂ -8-CH ₃ -	40	253-254	19
1, 6-(COOH) ₂	9	350 (dec.)	78, 107
1, 6-(COOH) ₂ 10, 10-dioxide	81	351. 3	107

TABLE 22. Phenoxathiin Carboxylic Acids (contd)

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	B.p. (mm)	Ref.
1, 6-(COOCH ₃) ₂	57	150.5-151.5			107
1, 6-(COOCH ₃) ₂ 10, 10-dioxide	46	170-171			107
1, 6-(COOC ₂ H ₅) ₂ 10, 10-dioxide	68	143-143.5			107
1, 9-(COOH) ₂	35	266-267			107
1, 9-(COOH) ₂ 10, 10-dioxide	48	350-352 (dec.)			78
	82	329-331 (dec.)			107
1, 9-(COOCH ₃) ₂	80	81-83			107
1, 9-(COOCH ₃) ₂ 10, 10-dioxide		170-171			78
1, 9-(COOC ₂ H ₅) ₂ 10, 10-dioxide		143-143.5			78
2, 9-(COOH) ₂ 10, 10-dioxide	92	354-357			107
2, 8-(COOH) ₂ 10, 10-dioxide		>300			295
		392-394 (dec.)			78
2, 8-(COOCH ₃) ₂ 10, 10-dioxide		204-208			295
4, 6-(COOH) ₂		265-267			113
	35	266-267			78
4, 6-(COOH) ₂ 10, 10-dioxide		329-331 (dec.)			78

4, 6-, in which metalation could presumably occur in the position ortho to the heterocyclic atom. Since monometalation occurs at position 4, this position apparently is particularly reactive in this reaction. Metalation with two equivalents of *n*-butyllithium and carbonation was shown by Gilman and Eidt^{78,107} to give simultaneously 8.9% 1,6-phenoxathiindicarboxylic acid and 34.7% 4,6-phenoxathiindicarboxylic acid. The 1,6-derivative was also obtained when phenoxathiin 10-monoxide was treated with *n*-butyllithium at room temperature. Metalation of phenoxathiin with one equivalent of *n*-butyllithium and carbonation gave 36.9% 4-phenoxathiincarboxylic acid and 1.4% 1,6-phenoxathiindicarboxylic acid.

Metalation of phenoxathiin with phenylcalcium iodide and carbonation gave 4,6-phenoxathiindicarboxylic acid. When methylolithium was used to metalate phenoxathiin, only 4-phenoxathiincarboxylic acid was obtained and no dimetalation occurred. Metalation of phenoxathiin 10-monoxide with three equivalents of *n*-butyllithium and carbonation gave an 8% yield of 1,6-phenoxathiindicarboxylic acid. Phenoxathiin 10,10-dioxide and two equivalents of *n*-butyllithium gave a 92.5% yield of 1,9-phenoxathiindicarboxylic acid 10,10-dioxide; using 1.5 equivalents *n*-butyllithium, 48.1% 1,9-phenoxathiindicarboxylic acid 10,10-dioxide and 14.9% 1-phenoxathiincarboxylic acid 10,10-dioxide were obtained; using one equivalent methylolithium 18.1% 1-phenoxathiincarboxylic acid 10,10-dioxide and 2.8% 1,9-phenoxathiindicarboxylic acid 10,10-dioxide were obtained.

Metalation of phenoxathiin with lithium in tetrahydrofuran followed by carbonation gave a small quantity of 4,6-phenoxathiindicarboxylic acid along with 16% of 2-mercaptophenol. The similar reaction with phenoxathiin 10,10-dioxide gave only acidic material which could not be characterized.¹¹³

Hydrogenolysis of 1,6-phenoxathiindicarboxylic acid with Raney nickel gave 2,3'-dicarboxydiphenyl ether; 4,6-phenoxathiindicarboxylic acid gave 2,2'-dicarboxydiphenyl ether; and 1,9-phenoxathiindicarboxylic acid gave 3,3'-dicarboxydiphenyl ether. The sulfones and sulfoxides of the dicarboxylic acids have been prepared in the usual way, using hydrogen peroxide or dilute nitric acid under acetic acid reflux. Esterifications have been carried out using diazomethane for the dimethyl esters and using ethyl alcohol with hydrochloric acid for the diethyl esters.^{78,107}

Table 22 lists the phenoxathiindicarboxylic acids which have been recorded in the literature.

The condensation of one mole phenoxathiindicarboxylic acid with two moles 1-amino-5-benzamidoanthraquinone yields a brick-red powder useful as a vat dye for dyeing cotton a lightfast reddish yellow.⁴⁹

i. Acylphenoxathiins

In the Friedel-Crafts reaction of phenoxathiin to give acylphenoxathiins, the acyl group enters para to the heterocyclic oxygen atom. The

TABLE 23. Acylphenoxathins

Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	B.p. (mm)	Ref.
2-CH ₃ CO-	31	111-112	165-185	1	87, 89, 90
	82	113	258-260	20	186
	58	111-112			289
	26	117.5-118.0			224
2-[C(CH ₃)=NOH]	99	158-159.5			224
		142-143			289
		153			186
2-[C(CH ₃)=NNHC ₆ H ₅]		93.5-94.5			289
2-BrCH ₂ CO-	83	134			186
2-CH ₃ CH ₂ CO-	78	71-72	275-277	25	186
2-CH ₃ (CH ₂) ₂ CO-	89	64	276-278	21	186
2-HO ₂ C(CH ₂) ₂ CO-		191-192			38
	7	167			186
3-HO ₂ C(CH ₂) ₂ CO-		159-161			38
3-HO ₂ CCH ₂ CHBrCO-					39
2-HO ₂ CCH=CHCO-		167			186
3-HO ₂ CCH=CHCO-		190			39

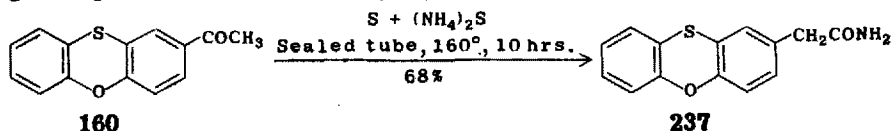
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3-CH ₃ O ₂ C(CH ₂) ₂ CO-	60-62	214-222	0.5	38
2-CH ₃ (CH ₂) ₃ CO-	77	279-280	20	186
2-CH ₃ (CH ₂) ₁₀ CO-	80			186
2-C ₆ H ₅ CO-	33			289
2- <i>o</i> -HO ₂ CC ₆ H ₄ CO-	186			186
2-C ₆ H ₅ CH ₂ CO-	79	310-311	18	186
2- <i>p</i> -ClC ₆ H ₄ CH=CHCO-	195			186
2- <i>p</i> -CH ₃ OC ₆ H ₄ CH=CHCO-	122			186
5-CH ₃ CO-2-C ₂ H ₅ -	80	249-250	13	186
5-[C(CH ₃)=NNHCONH ₂]-2-C ₂ H ₅ -	212	n_D^{25} 1.6561		186
2,8-(CH ₃ CO-) ₂	58	184-186		224
2,8-[C(CH ₃)=NOH] ₂	95	220-221		224
2,8-(ClCH ₂ CO-)	95	193		295
2,8-(ClCH ₂ CO-) ₂ 10-monoxide		224-229		296
2,8-(ClCH ₂ CO-) ₂ 10,10-dioxide				295
2,8-(C ₃ H ₁₀ NCH ₂ CO-) ₂	105			295
2,8-(C ₆ H ₅ CO-) ₂	197			289

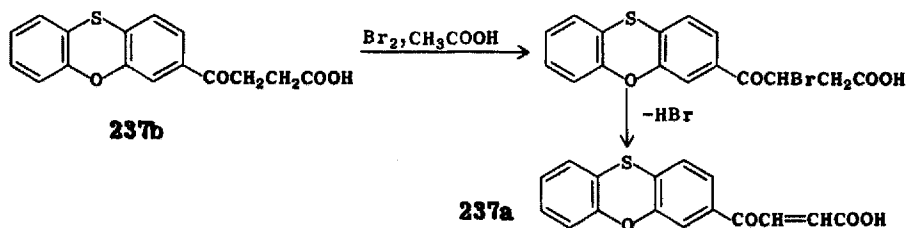
acylations have been carried out using acyl chlorides as the acylating agent in refluxing carbon disulfide for several hours, and aluminum chloride as the catalyst. Acetylation and benzylation, depending upon the severity of the conditions, give either or both the 2- and 2,8-acylated phenoxathiin. ^{87,89,90,186,224,289,295} Acylation with anhydrides, specifically succinic anhydride and phthalic anhydride, ^{38,186} is carried out using nitrobenzene as the solvent.

Acylphenoxathiins undergo the usual reactions of similar carbonyl compounds. They form oximes, phenylhydrazones, and semicarbazones. ^{186,224,289} The carbonyl is easily reduced to the secondary alcohol and dehydrated to the olefin, which in the case of 2-acetylphenoxathiin results in 2-vinylphenoxathiin, a monomer convertible to polymers and copolymers having valuable properties. ^{87,89,90} The Wolff-Kishner-Huang-Minlon reduction of acylphenoxathiins has been used as a route to 2-alkyl- and 2-aralkylphenoxathiins. ¹⁸⁶ From 2-benzoylphenoxathiin and benzylmagnesium chloride, a trisubstituted ethylene was obtained which underwent bromination to the estrogenic α -bromo- β -2-phenoxathiinylstilbene. Beckmann rearrangement of the oxime from 2-acetylphenoxathiin gave 2-acetamidophenoxathiin, which, on hydrolysis, yielded 2-aminophenoxathiin, a tuberculostatic agent. ^{186,224}

Oxidation of 2-acylphenoxathiins with hypochlorite yields 2-phenoxathiincarboxylic acid. ²⁹⁵ Oxidation with hydrogen peroxide yields the sulfone. ²⁹⁵⁻⁶ 2-Acetylphenoxathiin undergoes the Willgerodt reaction to give 2-phenoxathiinacetamide (**237**). ¹⁰⁴



2- and 3-Phenoxathiin- γ -oxobutyric acid fed intravenously in dogs had relative chloretic activities of 65 and 54 compared to 100 for dehydrocholic acid. ¹¹⁹ Burtner treated 3-phenoxathiin- γ -oxobutyric acid with bromine in acetic acid to obtain the β -bromo compound which was dehydrobrominated to give 3-phenoxathiin- γ -oxobutenoic acid (**237a**), a chloretic agent and bacterial antimetabolite. ³⁹

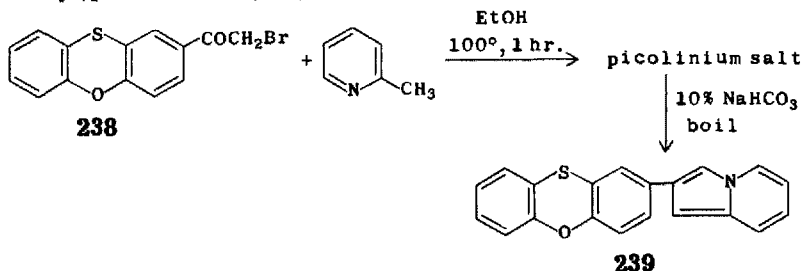


2-Acetylphenoxathiin and 2-bromoacetylphenoxathiin undergo various condensations through the activated methyl group to give heterocyclic compounds, ¹⁸⁶ which are described in the next section.

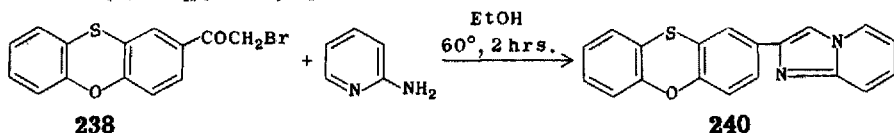
Table 23 lists the various acylphenoxathiins which have been reported.

j. Heterocyclic Derivatives of Phenoxathiin

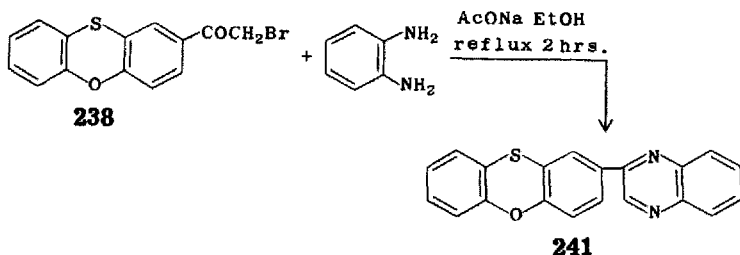
Lescot, Buu-Hoi, and Xuong¹⁸⁶ prepared various phenoxathiins substituted with nitrogen-heterocyclic substituents. They used two intermediates for these syntheses, 2-acetylphenoxathiin and 2-bromoacetylphenoxathiin. Condensation of the 2-bromoacetylphenoxathiin with 2-picoline, 2, 4-lutidine, and 5-ethyl-2-methylpyridine, and the Tschitschibabin cyclization of the resulting quaternary derivatives yielded 2-(2'-indoliziny)phenoxathiin (**239**) or the respective alkyl derivative.



Condensation with 2-aminopyridine, in a similar manner, yielded 2-(2'-imidazo[1, 2-*a*]pyridinyl)phenoxathiin (**240**).



On prolonged heating of bromoacetylphenoxathiin with *o*-phenylenediamine, condensation and dehydrogenation occurred to give 2-(2'-quinoxaliny)phenoxathiin (**241**).



An indole-substituted phenoxathiin (**242**) was prepared as follows:

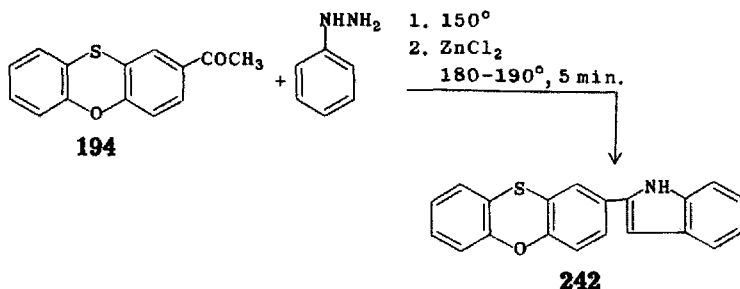


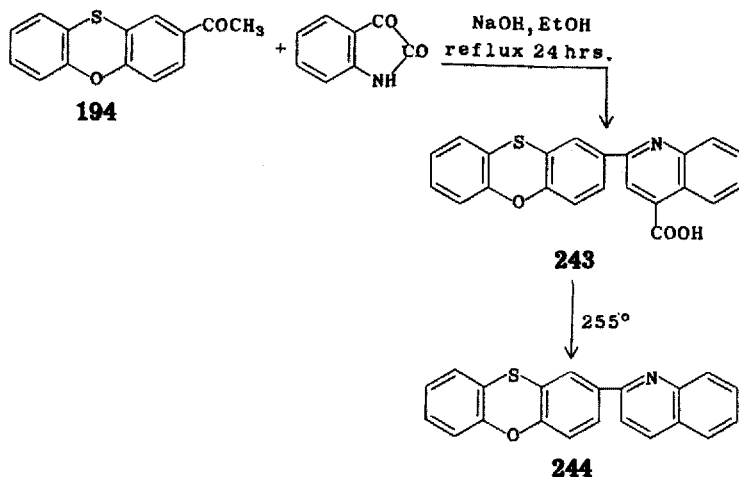
TABLE 24. Heterocyclic Derivatives of Phenoxathiin

Substituent	Yield (%)	M.p. (°C)	Ref.
2-(2'-Indolyl)	90	202	186
2-(2'-Indoliziny1)		199-200	186
2-(2'-Indoliziny1-6'-ethyl)		155	186
2-(2'-Indoliziny1-7'-methyl)		209	186
2-(2'-Indoliziny1-7'-methyl) nitroso derivative		245	186
2-(2'-Cinchonic acid)	80	255	186
2-(2'-Quinoly1)		132	186
2-(2'-Quinoly1) picrate		223	186
2-(2'-Imidazo[1, 2- α]pyridiny1)		185	186
2-(2'-Quinoxaliny1)		174	186
2-[3'-C ₆ H ₅ -2'-(C ₆ H ₅ N=)-4'- Δ^4 -thiazoliny1]		151	186
2-[3'- <i>p</i> -CH ₃ C ₆ H ₄ -2'-(<i>p</i> -CH ₃ C ₆ H ₄ N=)-4'- Δ^4 -thiazoliny1]		159	186
2-[3'- <i>p</i> -CH ₃ CH ₂ CH ₂ C ₆ H ₄ -2'-(<i>p</i> -CH ₃ CH ₂ CH ₂ C ₆ H ₄ N=)-4'- Δ^4 -thiazoliny1]		143	186
2-(3'- <i>p</i> - <i>n</i> -Heptylphenyl-2'- <i>p</i> - <i>n</i> -heptylphenylimino-4'- Δ^4 -thiazoliny1)		113	186
2-[3'-(2, 4-Xylyl)-2'-(2, 4-xylylimino)-4'- Δ^4 -thiazoliny1]		143	186
2-[3'-(2-Diphenylyl)-2'-(2-diphenylylimino)-4'- Δ^4 -thiazoliny1]		129	186

2-[3'-(4-Diphenyl)-2'-(4-diphenylimino)-4'-Δ ⁴ -thiazoliny]	199	186
2-[3'-(α-Naphthyl)-2'-(α-naphthylimino)-4'-Δ ⁴ -thiazoliny]	156	186
2-[3'-p-FC ₆ H ₄ -2'-(p-FC ₆ H ₄ N=)-4'-Δ ⁴ -thiazoliny]	188	186
2-[3'-p-ClC ₆ H ₄ -2'-(p-ClC ₆ H ₄ N=)-4'-Δ ⁴ -thiazoliny]	176	186
2-[3'-p-BrC ₆ H ₄ -2'-(p-BrC ₆ H ₄ N=)-4'-Δ ⁴ -thiazoliny]	176	186
2-(3'-p-Phenethyl)-2'-p-phenethylimino-4'-Δ ⁴ -thiazoliny]	176	186

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Using 2-propionylphenoxathiin, the 3-methylindole-substituted phenoxathiin resulted. The quinoline-substituted phenoxathiin (**244**) was prepared through the cinchoninic acid derivative (**243**), which was prepared by the condensation of 2-acetylphenoxathiin with isatin.



The von Walther reaction of 2-bromoacetylphenoxathiin with *N,N'*-diarylthiureas gave a series of 3-aryl-2-arylimino-4-(2'-phenoxathiinyl)- Δ^4 -thiazolines (**245**), where the aryl group is phenyl, 4-tolyl, 4-*n*-propylphenyl, 4-*n*-heptylphenyl, 2, 4-xylyl, 2-diphenyl, α -naphthyl, *p*-phenethyl, and *p*-fluoro-, chloro-, and bromophenyl.

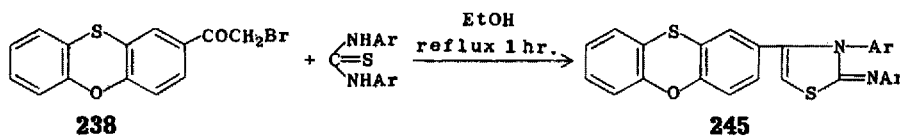
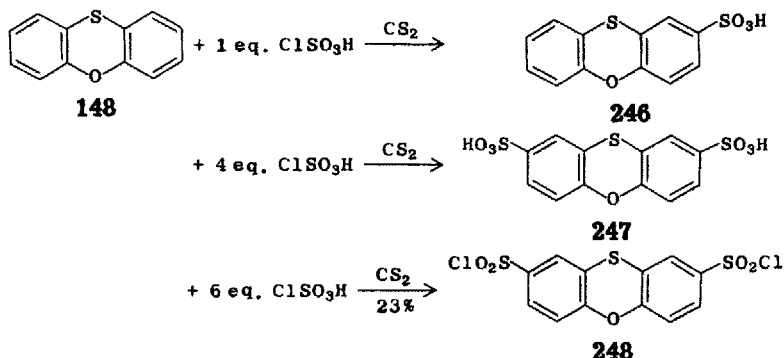


Table 24 lists the various heterocyclic derivatives of phenoxathiin which have been reported.

k. Phenoxathiin Sulfur Derivatives

Sulfonation of phenoxathiin occurs at position 2 or positions 2 and 8, which are *para* to the heterocyclic oxygen. Suter, McKenzie, and Maxwell,²⁸⁹ on using equimolar quantities of phenoxathiin and chlorosulfonic acid in carbon disulfide obtained only 2-phenoxathiinsulfonic acid (**246**); on using four times as much chlorosulfonic acid they obtained 2, 8-phenoxathiindisulfonic acid (**247**); on using six times as much chlorosulfonic acid, they obtained 2, 8-phenoxathiindisulfonyl chloride (**248**).

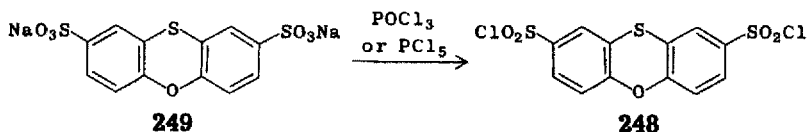
C₄OS Ring Systems



Tomita and Yameda²⁹⁸ obtained a 46% yield of 2, 8-phenoxathiindisulfonic acid on treating phenoxathiin with concentrated sulfuric acid.

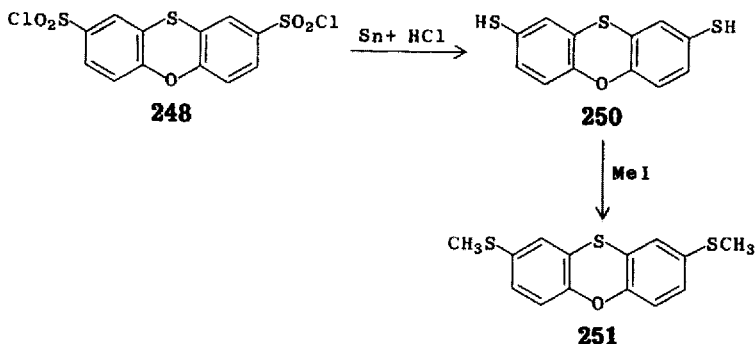
Sulfonation of diisopropyl- or *t*-butylphenoxathiin (prepared by the Friedel-Crafts reaction of phenoxathiin with isopropyl chloride or isobutyl chloride in the presence of aluminum chloride with chlorosulfonic acid) gave the monosulfonic acid derivative, said to be useful as a surfactant.²¹

2-Phenoxathiinsulfonic acid and 2, 8-phenoxathiindisulfonic acid, as the sodium salt, are easily converted to the corresponding sulfonyl chloride, on treatment with POCl₃ or with PCl₅ under mild conditions.^{171,289,298}



More drastic treatment of the 2, 8-disulfonyl chloride with PCl₅ converts it to 2, 8-dichlorophenoxathiin.²⁸⁹ The sulfonamide has been prepared by the treatment of the sulfonyl chloride with ammonia¹⁷¹ or ammonium hydroxide.²⁸⁹ The silver salt has been prepared by the treatment of the 2, 8-disodium sulfonate (249) with silver nitrate.²⁸⁹

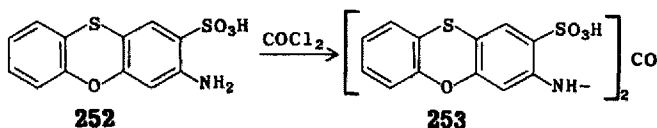
Reduction of the 2, 8-disulfonyl chloride with tin and hydrochloric acid yielded the dithiol (250), which was methylated to the 2, 8-bis(methylthio)phenoxathiin (251).²⁸⁹



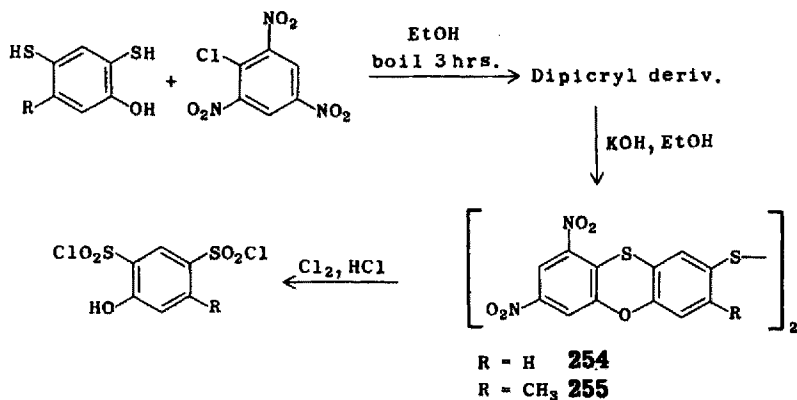
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The 2, 8-dithiol was ineffective as a bactericide.²⁹⁹

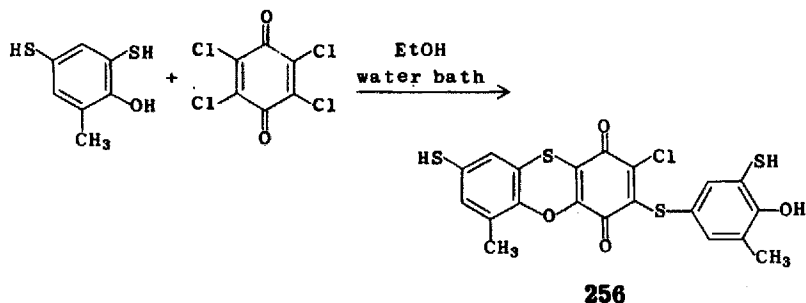
According to a Geigy patent,⁹⁶ the reaction product (253) of 3-amino-2-phenoxathiinsulfonic acid (252) and phosgene can be used to protect wool against moths, is fast to fulling and washing, and may also be useful as a bactericide and fungicide.



Pollak and Riesz²³⁷⁻²³⁹ obtained a dipicryl derivative, on condensing 2, 4-dimercaptophenol with picryl chloride, which yielded, on further treatment, 2, 2'-dithiobis(7, 9-dinitrophenoxathiin) (254).

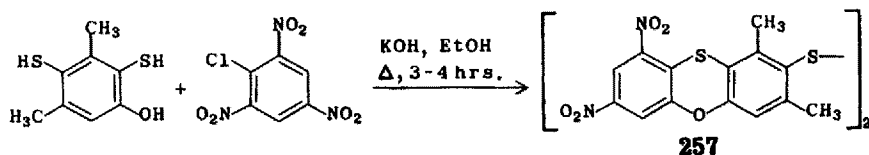


This compound decomposed explosively on heating. The condensation of dimercapto-*o*-cresol with picryl chloride yielded 2, 2'-dithiobis(3-methyl-7, 9-dinitrophenoxathiin) (255). The condensation of dimercapto-resorcinol with picryl chloride yielded a corresponding product which decomposed on heating above 280°. The heterocyclic ring of these bis-phenoxathiins was easily ruptured on treatment with chlorine in concentrated hydrochloric acid. Dimercapto-*o*-cresol condensed with chloranil as follows:



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The condensation of dimercapto-*m*-xylenol with picryl chloride yielded a dark red product (257) which dyed wool light red-brown.¹⁷⁶



No evidence for these structural assignments was presented. The various compounds reported are listed in Table 25.

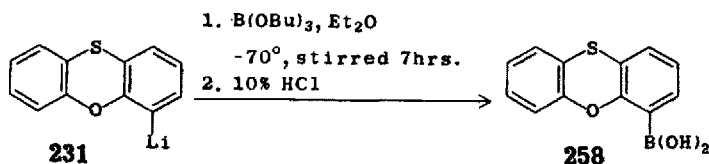
TABLE 25. Phenoxathiins Containing -SR, -S-, SO₂R, and SO₃R Groups.

Substituent	Yield (%)	M.p. (°C)	Ref.
2-SO ₃ Na			289
2-SO ₂ Cl		127-128	289
2-SO ₂ NH ₂		177-178	289
2, 8-(SO ₃ Na) ₂			289
2, 8-(SO ₃ Ag) ₂			289
2, 8-(SO ₂ Cl) ₂	23	142-143	289
	46	150-160	298
		171	
2, 8-(SO ₂ NH ₂) ₂		192	171
2, 8-(SH) ₂			298
2, 8-(SCOCH ₃) ₂		108-109	298
2, 8-(SCH ₃) ₂		68-69	298
1, 4-(=O) ₂ -2-Cl-6-CH ₃ -8-SH-3			
			250°(dec.) 239
2, 2'-Dithiobis[7, 9-(NO ₂) ₂]			237-8
2, 2'-Dithiobis[3-CH ₃ -7, 9-(NO ₂) ₂]		255-257	176
			96

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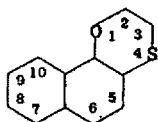
1. Phenoxathiinboronic Acid

In a program of synthesis of boronic acids for testing in tumor therapy, Santucci and Gilman²⁵³ obtained 4-phenoxathiinboronic acid (**258**) in 26% yield by the boronation of 4-phenoxathiinyl lithium.



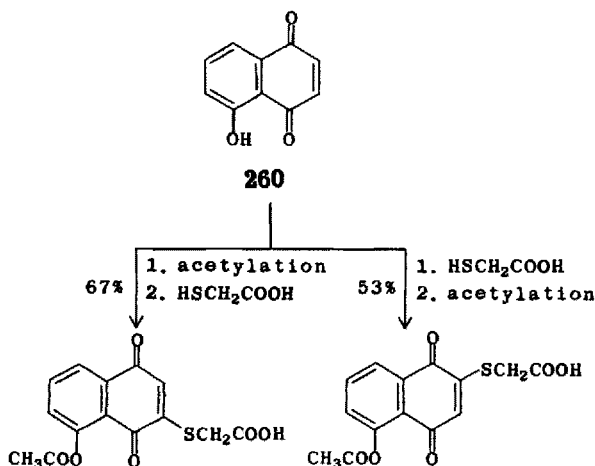
The pure boronic acid melted at 156.8–157.5° and resolidified at 158.7°, presumably as a result of anhydride formation.

2. Naphth[1, 2-*b*]-*p*-oxathiin (**259**)

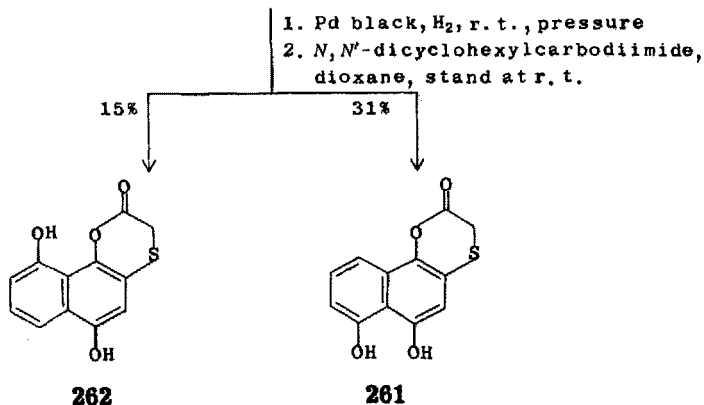


259

Naphth[1, 2-*b*]-*p*-oxathiin is known by only two dihydro derivatives which have been reported recently by Rothman.²⁵⁰ The treatment of juglone (**260**) with thioglycolic acid yielded juglone 2- and 3-thioglycolic acids; these on hydrogenation over palladium black yielded 6, 7-(**261**) and 6, 10-dihydroxy-2-oxa-2, 3-dihydronaphth[1, 2-*b*]-*p*-oxathiin (**262**), respectively.

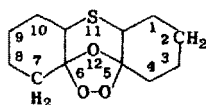


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The 6, 10-dihydroxy compound (**262**) melts at 193-203° with decomposition. The 6, 7-dihydroxy compound (**261**), a light tan, amorphous solid, sublimes at 160° at 0.1 mm. These structures were assigned only on the basis of elemental analysis.

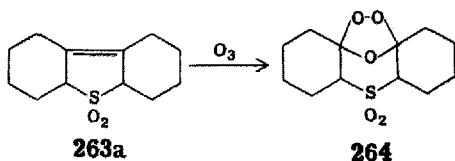
J. C₂O₃-C₄OS-C₆-C₆ 2*H*, 7*H*-4*a*, 6*a*-EPOXYDIBENZO[1, 2, 5]DIOXATHIEPIN (**263**)



263

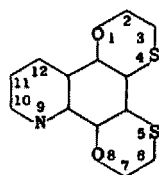
(RRI 4385)

Criegee and Lohaus,⁵⁶ in their studies on the ozonolysis of unsaturated cyclic sulfones (see section III B), treated **263a** with ozone in carbon tetrachloride at 20°. The ozonide (**264**) obtained showed no definite melting point but decomposed gradually above 200°. It was soluble in chloroform, difficultly soluble in carbon tetrachloride and acetic acid, and insoluble in water. It is stable for some time on heating with 2 *N* sulfuric acid.



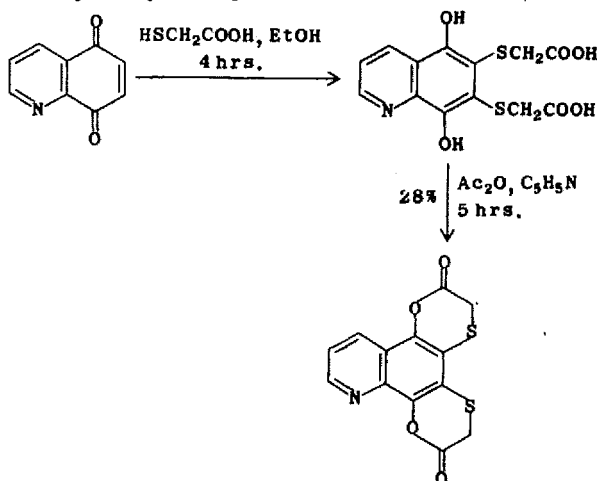
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K. $C_4OS-C_4OS-C_5N-C_6$ BIS[1,4]OXATHINO[2,3-*f*:3',2'-*h*]QUINO- LINE (264a)



264a

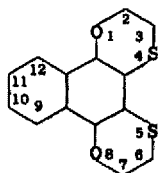
Zinner and Fiedler³²³ prepared the 2,3,6,7-tetrahydro-2,7-dione derivative (264b) by the reaction of thioglycolic acid and quinoline-5,8-quinone followed by dehydration of the resulting 5,8-dihydroxy-6,7-bis(carboxymethylthio)quinoline with acetic anhydride in pyridine.



264b

264b, obtained as needles from acetic acid, melted at 313-315° with decomposition.

L. $C_4OS-C_4OS-C_6-C_6$ NAPHTHO[1,2-*b*:4,3-*b'*]BIS-[1,4]OXATHIIN (265)

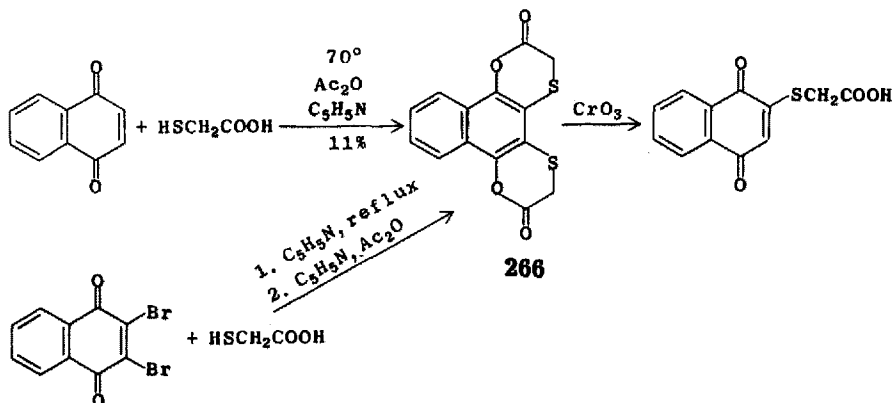


265

(RRI 5021)

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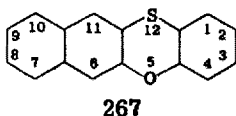
The parent compound is not known. Its only reported derivative,²³ naphtho[1,2-*b*:4,3-*b'*]bis-[1,4]oxathiin-2,7(3*H*,6*H*)-dione (**266**), m.p. 271-275° (dec.), was obtained from the reaction of 1,4-naphthoquinone or 2,3-dibromo-1,4-naphthoquinone and thioglycolic acid.



The crude product obtained in the above reactions could not be purified because of its sensitivity to air oxidation. Oxidation with chromic acid yielded a mixture of quinones, from which 2-carboxymethylthio-1,4-naphthoquinone could be isolated.

M. C₄OS-C₆-C₆-C₆

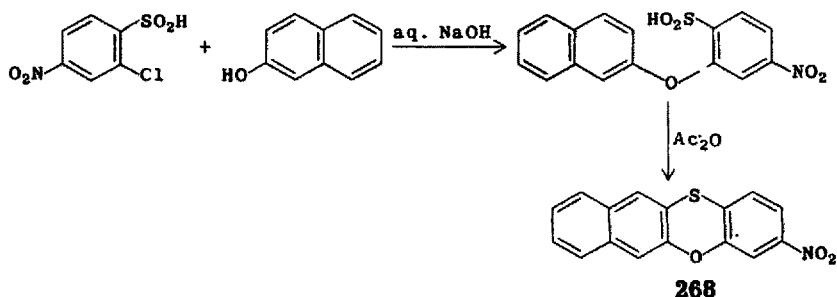
1. Benzo[*b*]phenoxathiin (**267**)



(RRI 5024)

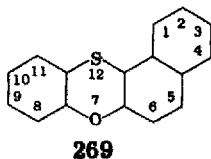
Only one compound in this ring system has been reported, 3-nitrobenzo[*b*]phenoxathiin (**268**),¹⁸² which Chemical Abstracts indexed under β -benzophenothioxin. Two other names have been assigned: 5-oxa-12-thianaphthacene and β -naphthaphenothioxin. This compound (**268**) was prepared by Krishna by the condensation of 2-chloro-4-nitrobenzenesulfinic acid and β -naphthol in alkaline media and cyclization of the resulting ether in the presence of acetic anhydride.

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268 is an orange-yellow powder, m.p. 128°. Its sulfuric acid solution is colored green. It is oxidized by treatment with chromic acid in acetic acid to the 12, 12-dioxide, m.p. 182°, whose sulfuric acid solution is colored light yellow.

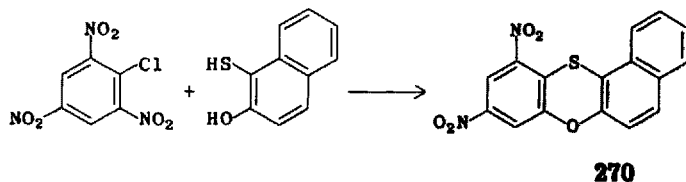
2. Benzo[*a*]phenoxathiin (269)



(RRI 5026)

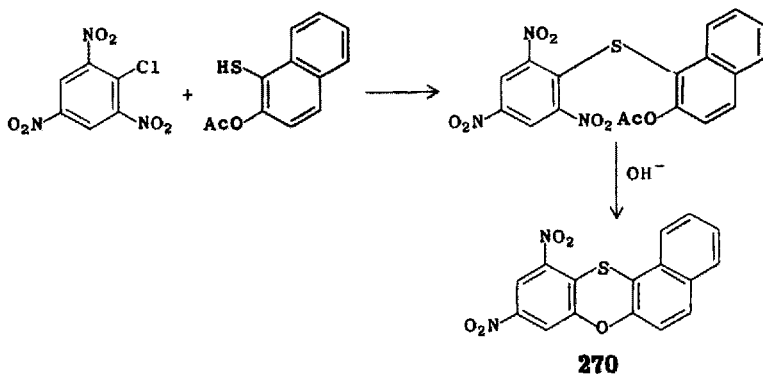
The parent heterocycle and two derivatives have been reported.^{287,307} Chemical Abstracts indexed them under benzo[*a*]phenothioxin. Two other names have been used: α -benzophenothioxin and benz- α , β -naphthathioxin.

Using the Mauthner mercaptan-picryl chloride synthesis, Stevenson and Smiles²⁸⁷ obtained 9, 11-dinitrobenzo[*a*]phenoxathiin (**270**) by the reaction of 2-hydroxy-1-naphthyl mercaptan and picryl chloride.



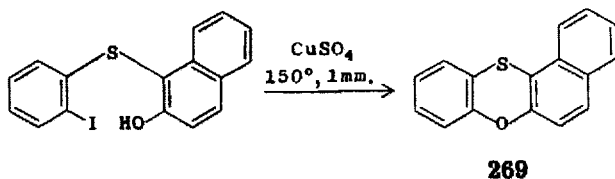
The positions of the nitro groups were established through the preparation of the identical compound by the action of alkali on the *S*-picryl derivative of 2-acetoxy-1-naphthyl mercaptan.

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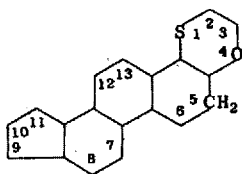
The reaction of 2-hydroxy-1-naphthyl mercaptan and picryl chloride in ethanolic sodium hydroxide gave almost quantitative yield of **270** as red needles, m.p. 300°.

Stevenson and Smiles also applied the method used for the preparation of dinaphthophenoxathiin⁵⁴ to the preparation of benzophenoxathiins. Thus, the parent compound (**269**) was obtained in good yield as bright yellow needles, m.p. 63°, by heating 2'-iodophenyl 2-hydroxynaphthyl sulfide with copper sulfate.



Similarly prepared from 2', 5'-dibromophenyl 2-hydroxynaphthyl sulfide was 10-bromobenzo[*a*]phenoxathiin, in good yield, as pale yellow prisms, m.p. 142°.

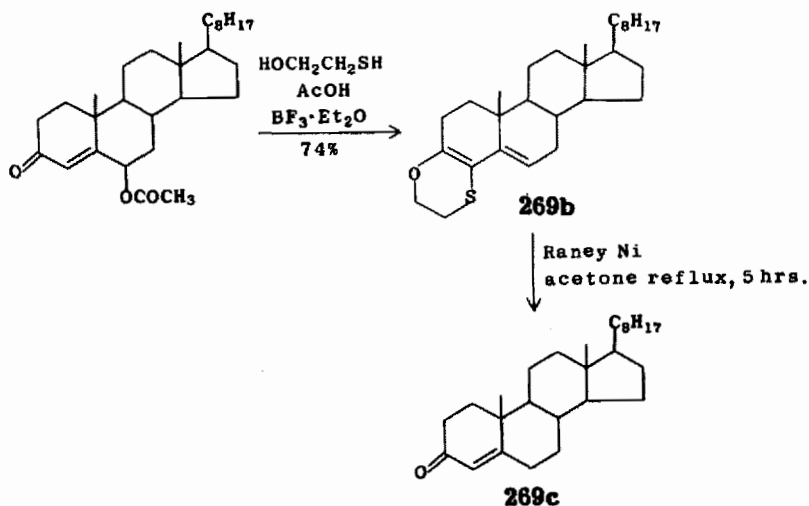
N. C₄OS-C₅-C₆-C₆-C₆ 5*H*-CYCLOPENTA[7, 8]PHENANTHRO[1, 2-*b*] [1, 4]-OXATHIIN (**269a**)



269a

Fieser, Yuan, and Goto^{84a} prepared a cyclopenta[7, 8]phenanthro [1, 2-*b*] [1, 4]-oxathiin derivative (**269b**), the only reported member of this ring system, by the reaction of Δ^4 -cholesten-6 β -ol-3-one acetate in acetic acid with 2-mercaptoethanol in the presence of boron fluoride

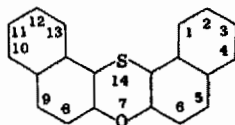
etherate. The following properties of **269b** were reported: m.p. 154-155°, $\alpha_D -122^\circ$, dienic ultraviolet absorption λ (ethanol) 266 m μ (9340), brown color with tetranitromethane. Desulfurization with Raney nickel in refluxing acetone yielded Δ^4 -cholesten-3-one (**269c**).



The shift of the double bond from position 4 in Δ^4 -cholesten-6- β -ol-3-one acetate to position 3 in the hemithioketal (**269b**) was also shown to be the case in the reaction product when dimercaptoethane was the reactant. This abnormal reaction is discussed in detail in Chapter 5. Desulfurization of **269b** obviously placed the oxygen at position 3. The positions of the principal n.m.r. peaks helped to confirm the structure assigned to **269b**.

O. C₄OS-C₆-C₆-C₆-C₆

1. **Dibenzo[*a,j*]phenoxathiin (271)**



(271)

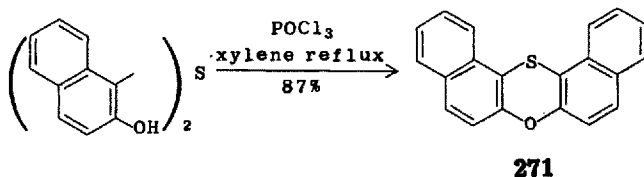
(RRI 6234)

Other names assigned to dibenzo[*a,j*]phenoxathiin (**271**) have been: γ, γ' -dibenzophenothioxin; $\alpha, \beta, \alpha', \beta'$ -dinaphthathioxin; naphthoxthin; and $\alpha, \beta, \alpha', \beta'$ -naphthathioxin. Chemical Abstracts indexed it under dibenzophenothioxin through the third decennial index.

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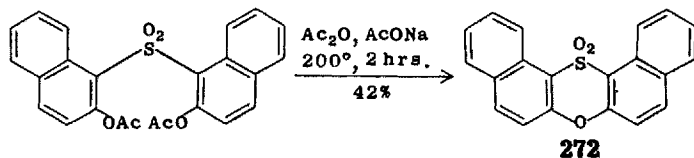
a. Preparation

Dibenzo[*a,j*]phenoxathiin (**271**) was first prepared by Mauthner²⁰² in 1906 by the treatment of 2,2'-dihydroxy-1,1'-dinaphthyl sulfide with phosphorus oxychloride in refluxing xylene.



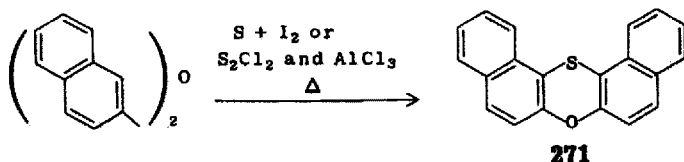
Its concentrated sulfuric acid solution had a violet color. Christopher and Smiles⁴⁸ used tetrachloroethane as the solvent instead of xylene because Mauthner's method did not always give good yields and the purification was difficult; they obtained 45-50% yields of the heterocycle (**271**) in good purity. When Stevenson and Smiles²⁸⁷ dehydrated the sulfide with phosphorus oxychloride and zinc chloride in tetrachloroethane, the yield was increased to 60-70%. They applied this method to the preparation of several derivatives, such as the 3-bromo and the 3,11-dibromo compounds. Hinsberg¹⁵⁷ similarly treated 2,2'-diacetoxy-1,1'-dinaphthyl sulfone with phosphorus oxychloride in xylene, but observed no ring closure; treatment of the diacetoxydinaphthyl sulfone with phosphorus oxychloride, using chloroform as the solvent, in a closed tube at 160-170° for 2 hours gave a low yield of a chlorinated dibenzophenoxathiin, m.p. 220-40°.

Hinsberg¹⁵⁷ prepared dibenzo[*a,j*]phenoxathiin 14,14-dioxide (**272**) as colorless needles by reacting 2,2'-diacetoxy-1,1'-dinaphthyl sulfone with acetic anhydride and sodium acetate in a tube at 200° for 2 hours.



Crymble, Ross, and Smiles⁵⁸ prepared dibenzo[*a,j*]phenoxathiin by treating β -naphthol with sulfur or sulfur monochloride in alkaline solution and refluxing the β -naphthol sulfide with phosphorus oxychloride in tetrachlorethane or by treating the β -naphthol sulfide with cold sulfuric acid (hot sulfuric acid gave only tars).

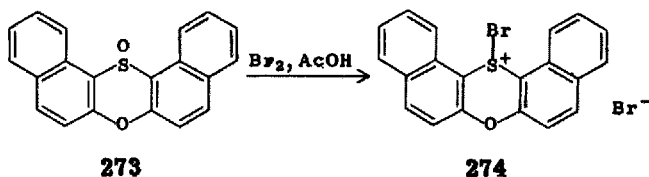
Child and Smiles⁴⁷ obtained a low yield of dibenzo[*a,j*]phenoxathiin, which was isolated through its picrate, by reacting di- β -naphthyl ether with sulfur in the presence of a trace of iodine at 280° for 3 hours or with sulfur monochloride in the presence of aluminum chloride.



b. Reactions

Treatment of dibenzo[*a,j*]phenoxathiin with chromic acid in acetic acid gives the sulfoxide (**273**) in 57% yield as red-yellow needles, melting at about 220° with decomposition.^{153,202} Its sulfuric acid solution is colored green. The sulfoxide (**273**) has been prepared in 100% yield by treating dibenzo[*a,j*]phenoxathiin with nitric acid;⁴⁸ treatment with nitric acid in warm acetic acid yields the sulfoxide nitrate, which has a red tint, is not very stable, and is decomposed by cold ether or cold water. The 14, 14-dioxide (**272**) is prepared by oxidizing dibenzo[*a,j*]phenoxathiin with potassium permanganate in acetic acid solution;²²⁸ its sulfuric acid solution is colorless.

Chlorination of dibenzo[*a,j*]phenoxathiin with hydrogen chloride resulted in a mixture of mono- and dichloro derivatives, neither one of which was identical to the chloro derivative obtained by treating β -naphthasulfonium quinone with acetyl chloride (see section III 0-2).²²⁸ Direct halogenation of the sulfoxide (**273**) probably led to the formation of a thionium intermediate (**274**).



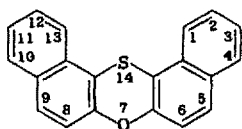
Heating the thionium compound (**274**) on a water bath gave a dibromodibenzo[*a,j*]phenoxathiin as yellow needles; its sulfuric acid solution had a green color. Direct bromination of dibenzo[*a,j*]phenoxathiin yielded presumably the same dibromo derivative, which was not identical to the 3, 11-dibromo derivative, as the mixed m.p. was 215–50°. ²⁸⁷ Warming the sulfoxide (**273**) with acetic acid and concentrated hydrochloric acid on a water bath gave a dichlorodibenzo[*a,j*]phenoxathiin; its sulfuric acid solution had a green color.²²⁸

Treatment of dibenzo[*a,j*]phenoxathiin with ferric chloride in cold ether solution gave a green thionium complex. Dibenzo[*a,j*]phenoxathiin with picric acid in refluxing ethanol gave a red-brown picrate, which, on treatment with aqueous sodium hydroxide regenerated dibenzo[*a,j*]phenoxathiin.

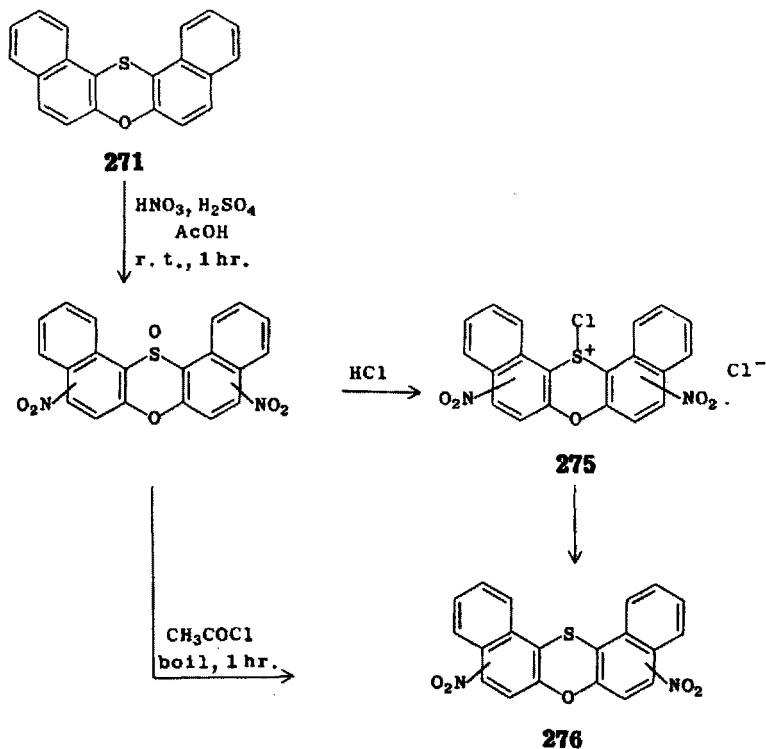
Under mild nitration, dibenzo[*a,j*]phenoxathiin yields the dinitro derivative of the sulfoxide (**273**).¹⁰⁰ This product, however, was not characterized as it could not be obtained pure; the sulfoxide group was reduced with hydrochloric acid to **276**.

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TABLE 26. Dibenzo[*a,j*]phenoxathiins



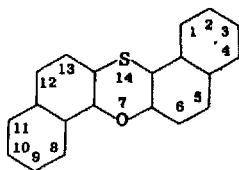
Substituent	Yield (%)	M.p. (°C)	Ref.
None	87	165-166	202
	21	166	58
	low	165	47
	45-50		48
	60-70		287
14-Monoxide	57	220(dec.)	202
	100	219	48
		221	153
14-Monoxide . HNO ₃		177	48
14, 14-Dioxide	42	295	157
		293-295	228
3-Br		119	287
<i>x</i> -Cl	low	220-240	157
2, 11-Br ₂		275	287
<i>x, y</i> -Br ₂		280	287
		279-280	228
<i>x</i> -Cl- <i>y</i> -NO ₂			100
<i>x</i> -Cl- <i>y</i> -NO ₂ 14-monoxide		268	100
5, 9-(COOCH ₃) ₂		153	188
<i>x, y</i> -Cl ₂ 14-monoxide		273	228
<i>x, y</i> -(NO ₂) ₂		>300	87



More drastic conditions in the reaction with hydrochloric acid led to replacement of a nitro group with chlorine.

These compounds are listed in Table 26.

2. Dibenzo[*a,h*]phenoxathiin (277)



277

(RRI 6235)

This ring system has been known by various names: $\alpha, \beta, \beta', \alpha'$ -naphthathioxin; $\alpha, \beta, \beta', \alpha'$ -dinaphthathioxin; isodinaphthathioxin; and α, γ' -dibenzophenothioxin, under which Chemical Abstracts indexed it.

a. Preparation

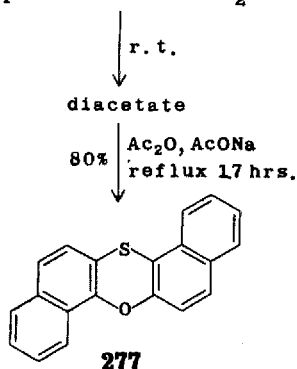
Henriques¹⁴⁹ may have unknowingly first prepared dibenzo[*a,h*]phenoxathiin when he treated dinaphthol sulfide with concentrated sulfuric

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acid at 100°, as the product obtained melted at 147° and dissolved in concentrated sulfuric acid with a blue-green color. There are two isomeric dinaphthol sulfides, one melting at 152-3° and the other at 212°, the higher melting yielding dibenzo[*a, j*]phenoxathiin. There is much confusion in the literature concerning the structure of the lower melting isomer. The lower melting isomer was called the iso- or unstable sulfide, as treatment with aqueous sodium hydroxide converted it to the higher melting isomer.

Ross and Smiles²⁴⁹ and Nolan and Smiles²²⁷⁻⁸ postulated the existence of two sulfides of β -naphthol as leading to the two different dibenzophenoxathiins. They obtained the lower melting dibenzophenoxathiin by the following series of reactions:

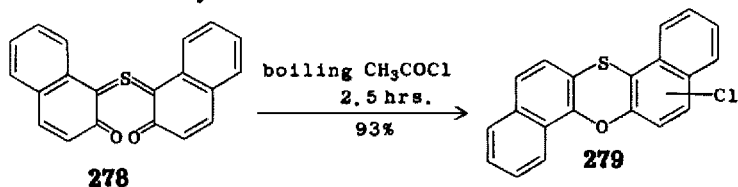
Unstable β -naphthol sulfide + Ac₂O + camphorsulfonic acid



They called **277**, which was obtained as lemon-yellow needles, the anhydride of the unstable sulfide. On treating the diacetate of the unstable sulfide with acetic anhydride and bromine, they obtained a monobromodibenzo[*a, h*]phenoxathiin. Treatment of the stable sulfide in a similar manner did not result in a reaction.

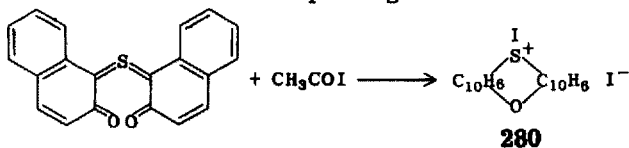
Treating β -naphthasulfonium quinone (**278**) in acetic anhydride with camphorsulfonic acid and thiolacetic acid, Ghosh and Smiles⁹⁸ obtained a good yield of acetylthiodibenzo[*a, h*]phenoxathiin. Using thioglycolic acid, under similar conditions, they obtained carboxymethylthiodibenzo[*a, h*]phenoxathiin.

Christopher and Smiles⁴⁸ obtained a monochlorodibenzophenoxathiin (**279**) by the action of acetyl chloride on β -naphthasulfonium quinone, whose structure they formulated as **278**.



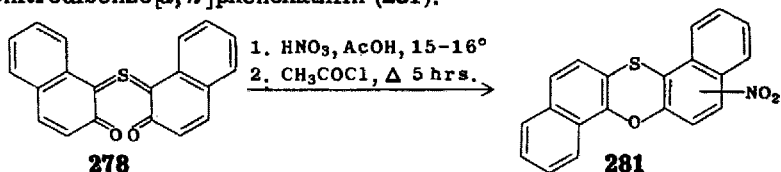
The same product was obtained by the action of hydrochloric acid and

acetic acid. Treatment of the monoxide of the monochloro compound (279) with hydrochloric acid yielded a dichloro derivative,²²⁸ which was not the same as the dichloro derivative obtained from the chlorination of dibenzo[*a,j*]phenoxathiin. It was therefore concluded that the penultimate product is the thionium-oxonium compound which loses HCl to give what was formulated by 278. This was presumed to be confirmed by the isolation of the corresponding bromide²²⁸ and iodide.⁹⁹

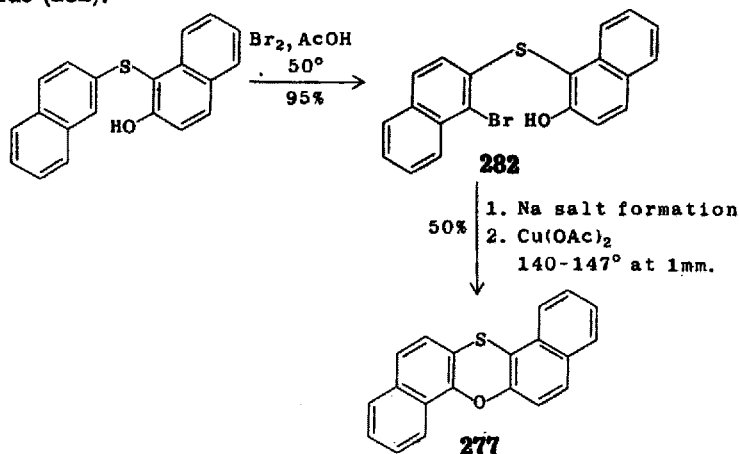


The iodide (280) was identified by the reaction with sodium thiosulfate which resulted in reduction to the dibenzophenoxathiin. Chlorination of dibenzo[*a,j*]phenoxathiin was assumed to lead to the same type of intermediate. Consequently the halogen had to enter the nucleus at the same point and it was reasoned that there are two isomeric dibenzophenoxathiins, the [*a,j*] and [*a,h*].

The acetyl chloride ring closure method has also been used for the preparation of nitro derivatives. Thus, the action of nitric acid and acetic acid on β -naphthosulfonium quinone (278) resulted in the mononitro derivative, which, on treatment with acetyl chloride, presumably gave a mononitrodibenzo[*a,h*]phenoxathiin (281).¹⁶⁸

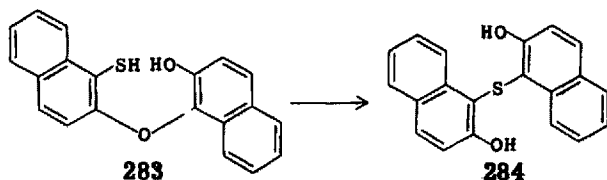


An unequivocal preparation of dibenzo[*a,h*]phenoxathiin was carried out by Cohen and Smiles⁵⁴ from 1-bromo-2'-hydroxy-2,1'-dinaphthyl sulfide (282).

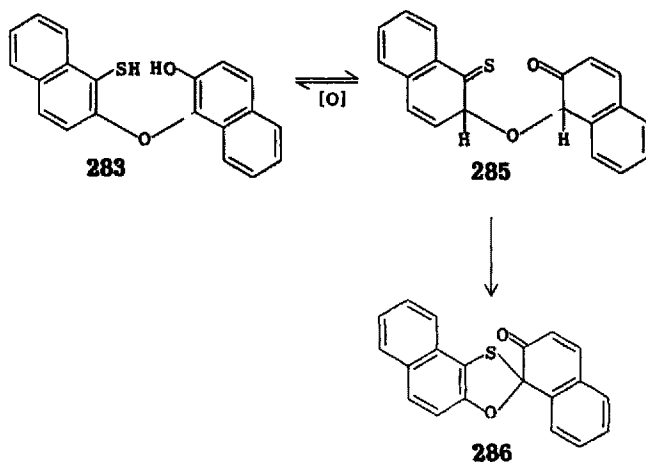


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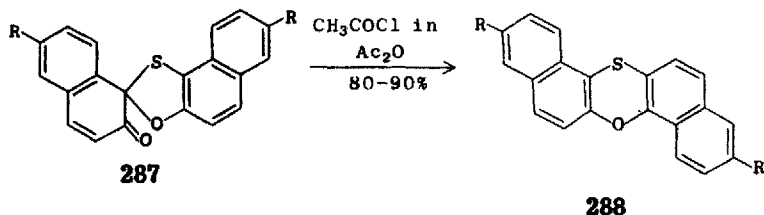
Iso- β -naphthol sulfide was finally shown to be **283**, a thiol derived from 1, 2'-dinaphthyl ether. Its conversion to 2-naphthol 1-sulfide (**284**) was thus considered to be a novel intramolecular change effected by heat, alone or in a solvent, or by alkali.



283 behaves as a quinone tautomer (**285**) which undergoes ring closure to **286** and results in **287**.



The acetyl chloride method already discussed was applied generally by Stevenson and Smiles²⁸⁷ to dehydro-2-naphthol sulfides (**287**) which contain an active quinone system.

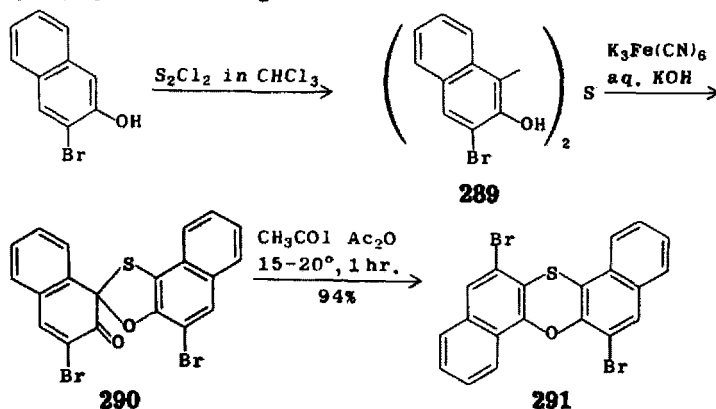


The process was regarded as involving the reduction of the dehydro sulfide with subsequent dehydration of the isosulfide.

McClelland and Smiles²⁰³ prepared 6, 13-dibromodibenzo[*a, h*]phen-

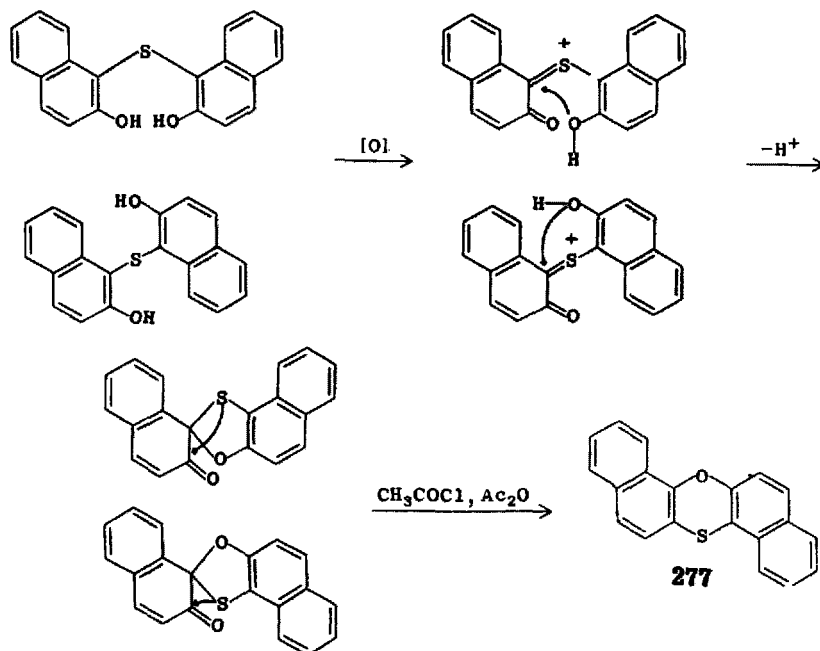
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oxathiin (**291**) from 3, 3'-dibromo-2, 2'-dihydroxy-1, 1'-dinaphthyl sulfide (**289**) by the following series of reactions:



Treatment of **290**, the dehydro derivative, with acetyl chloride in acetic anhydride caused a chlorine atom to enter the 6, 13-dibromodibenzo [*a, h*]phenoxathiin (**291**).

It thus appears that the following series of reactions is a likely course in the preparation of the [*a, h*] isomer from the two dinaphthol sulfides:



The attack of sulfur on the quinone oxygen position thus leads to the same product, the [*a, h*] isomer. This step, however, must involve an oxidation. That there is an oxidizing medium is shown by the isolation

of a chloro or dichloro derivative when acetyl chloride is one of the reagents; the use of acetyl iodide does not lead to iodinated derivatives as I^+ is an extremely weak halogenating reagent.

This mechanism explains the products Hinsberg¹⁵⁶ obtained, the mono-chloro- and dichloro- dibenzophenoxathiins, on treating β, β' -dinaphthol sulfone with acetyl chloride and then heating on the water bath, and the monochlorodibenzophenoxathiin on treating the dehydro sulfide in chloroform with hydrogen chloride and then letting the reaction mixture stand in methanolic hydrochloric acid for several days. It also explains the products obtained by Ghosh and Smiles⁹⁸ in one of their early studies.

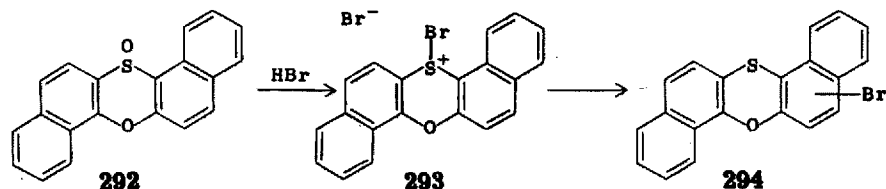
b. Reactions

Dibenzo[*a, h*]phenoxathiin has been described as yellow⁵⁴ or lemon-yellow²²⁷ needles. Reported melting points range from 147° to 154°; it sublimes at 154°;⁵⁴ its melting point with the [*a, j*] isomer is 120° for the 1 : 1 mixture.²²⁷

Whereas the [*a, j*] isomer develops a color almost immediately on being added to concentrated sulfuric acid, the [*a, h*] isomer does not until after some time.²²⁸ Treatment with nitric acid gives the sulfoxide, which by this method is difficult to purify because of nitration products.^{228, 249} The sulfoxide is best prepared using hydrogen peroxide and acetic acid which gives the product as colorless needles in 81% yield.²²⁸ The sulfoxide in concentrated sulfuric acid has an intense blue color. The 14, 14-dioxide is obtained as colorless plates by treatment with potassium permanganate in acetic acid.²²⁸

Dibenzo[*a, h*]phenoxathiin forms a dipicrate^{54, 99} and a green crystalline ferric chloride complex.⁹⁹ The sulfoxide forms a monoperchlorate, which is converted to an oxide on treatment with aqueous sodium hydroxide, and a diperchlorate, which yields an oxide which violently explodes at 150° on similar treatment. The sulfoxide, on treatment with sulfuric acid and acetic acid, yields a sulfate as dark green needles which decomposes at about 140°; the sulfate was described as being less stable than the perchlorate. The monochlorodibenzo[*a, h*]phenoxathiin gives similar complexes.⁹⁹

The halogenation of dibenzo[*a, h*]phenoxathiin 14-monoxide gives a mixture of monohalide and dihalide. The penultimate stage is undoubtedly the sulfonium form (293). Thus, treatment with hydrogen bromide probably proceeds as follows:²²⁶



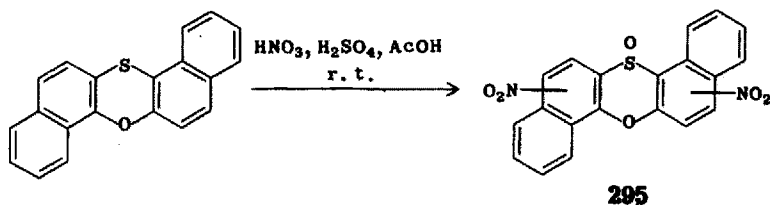
The iodo sulfonium compound is readily converted to dibenzo[*a, h*]phenoxathiin by treatment with sodium thiosulfate.⁹⁹

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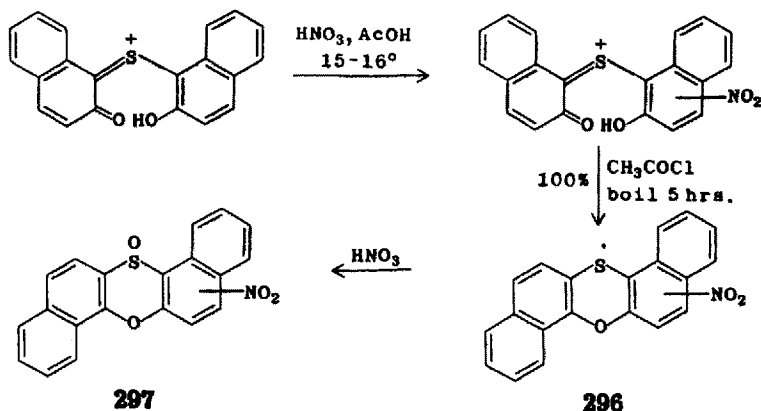
Treatment of dibenzo[*a, h*]phenoxathiin in warm acetic acid with bromine yields the dibromo derivative as yellow thread-like needles; its warm sulfuric acid solution is colored green.²²⁷ Similar treatment of the unstable sulfide (**283**) yields a mixture of the mono and dibromo derivatives.

Dichlorodibenzo[*a, h*]phenoxathiin, yellow needles, has been prepared in quantitative yield by treating monochlorodibenzo[*a, h*]phenoxathiin sulfoxide in acetic acid with excess concentrated hydrochloric acid.⁴⁸ The monochloro sulfoxide, prepared in quantitative yield by nitric acid oxidation of the monochloro compound, yields green needles on treatment with sulfuric acid. The dichloro- and dibromodibenzo[*a, h*]phenoxathiin also have been prepared by treating dibenzo[*a, h*]phenoxathiin with acetyl chloride or bromide; acetic acid, and hydrogen peroxide.²²⁸

Under moderate conditions of nitration, dibenzo[*a, h*]phenoxathiin yielded the dinitro sulfoxide.¹⁰⁰



Because the dinitro sulfoxide was a somewhat indefinitely characterized compound, it was reduced with acetyl chloride to the dinitrodibenzo[*a, h*]phenoxathiin, bright orange prisms. The mononitro derivative (**296**), orange-red needles, was prepared by nitration of β -naphthasulfonium quinone; the sulfoxide (**297**) is colorless.¹⁶⁸

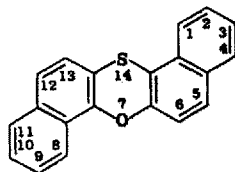


Treatment of acetylthiodibenzo[*a, h*]phenoxathiin with sodium ethoxide in boiling ethanol gave the mercaptan, a pale yellow powder. Boiling acetyldibenzo[*a, h*]phenoxathiin with sodium ethoxide in ethanol gave the hydroxy compound as colorless prisms.⁹⁸

These dibenzo[*a, h*]phenoxathiins are listed in Table 27.

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TABLE 27. Dibenzo[*a, h*]phenoxathiins

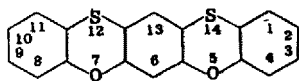


Substituent	Yield (%)	M.p. (°C)	Ref.
None	60	147	149
	80	152	227
		148	249
	50	154	54
14-Monoxide	81	278-279	228
14, 14-Dioxide		244	228
Ferric chloride			99
Dipicrate		177-178	54, 99
Perchlorate			99
Diperchlorate			99
Sulfate		about 140° (dec.)	99
<i>x</i> -Br		176	227
10-Br	80-85	173	287
<i>x</i> -Cl	93	173-174	48
<i>x</i> -Cl		170	156
<i>x</i> -Cl 14-monoxide	100	199-200 (dec.)	48
<i>x</i> -Cl 14-monoxide perchlorate			99
<i>x</i> -Cl 14-monoxide sulfate		145-147 (dec.)	99
<i>x</i> -Cl 14-monoxide nitrate		210 (dec.)	99
<i>x</i> -Cl 14, 14-dioxide		225	99
<i>x</i> -OH			48
<i>x</i> -CH ₃ COO-	70	199-200	48, 155
<i>x</i> -SH		223-228	98
<i>x</i> -CH ₃ COS-	69	173-174	98
<i>x</i> -HOOCCH ₂ S-		206	98

TABLE 27. Dibenzo[*a, h*]phenoxathiins (contd)

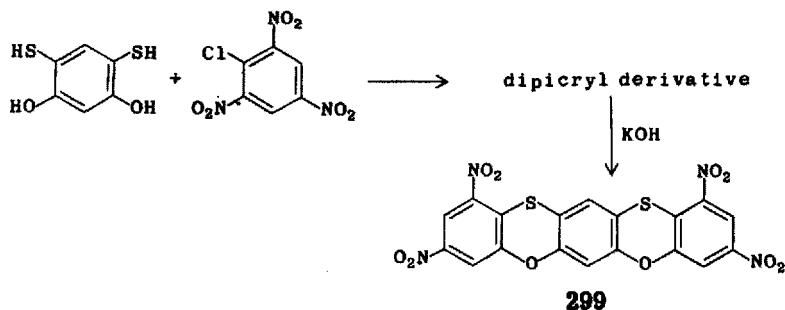
Substituent	Yield (%)	M.p.(°C)	Ref.
<i>x</i> -NO ₂	100	271	168
<i>x, y</i> -Br ₂		245	54, 99, 227, 22
3, 10-Br ₂	90	273	287
6, 13-Br ₂	94	248	203
<i>x, y</i> -Cl ₂	100	234-235	48, 156, 228, 2
<i>x</i> -NO ₂ - <i>y</i> -CH ₃ COO-		245-246	100
<i>x, y</i> -(NO ₂) ₂		274-275	100
<i>x, y</i> -(NO ₂) ₂ 14 monoxide			100
<i>x</i> -Cl-6, 13-Br ₂		264	203

P. C₄OS-C₄OS-C₆-C₆-C₆ [1, 4]-BENZOXATHIINO[3, 2-*b*]PHENOXA-
THIIN (298)

**298**

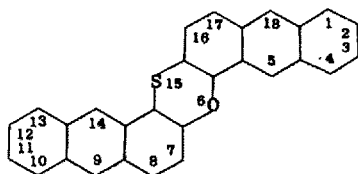
(RRI 6233)

Only one compound in this heterocyclic system has been reported: 1, 3, 9, 11-tetranitro-[1, 4]-benzoxathiino[3, 2-*b*]phenoxathiin (**299**). This compound was obtained as a dark red compound, decomposing on being heated above 280°, by Pollak and Riesz²³⁷ in 1928 through the following reaction:



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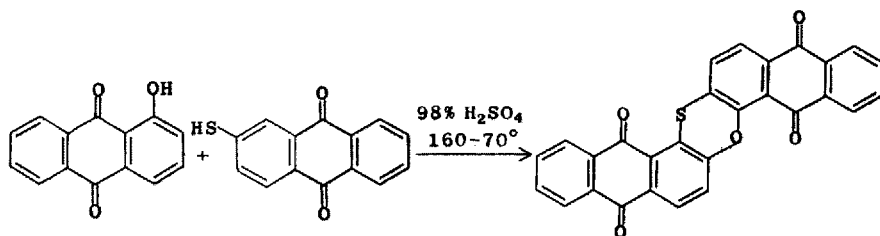
Q. C₄OS-C₆-C₆-C₆-C₆-C₆-C₆-C₆ DINAPHTHO [2, 3-*a*:2', 3'-*h*] PHENOXATHIN (300)



300

(RRI 7281)

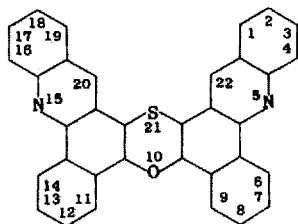
A 1910 German patent¹⁵ claims the preparation of the 5, 9, 14, 18-quinone derivative (301) by the following reaction:



301

This compound, brown-red needles, on treatment with concentrated sulfuric acid gave a green solution which the patent disclosed as being useful as a vat dye for dyeing wool yellow-red.

R. C₄OS-C₅N-C₅N-C₆-C₆-C₆-C₆-C₆-C₆ DIQUINOLINO[3, 2-*a*: 3', 2'-*j*]-DIBENZO[*c, h*]PHENOXATHIN (302)

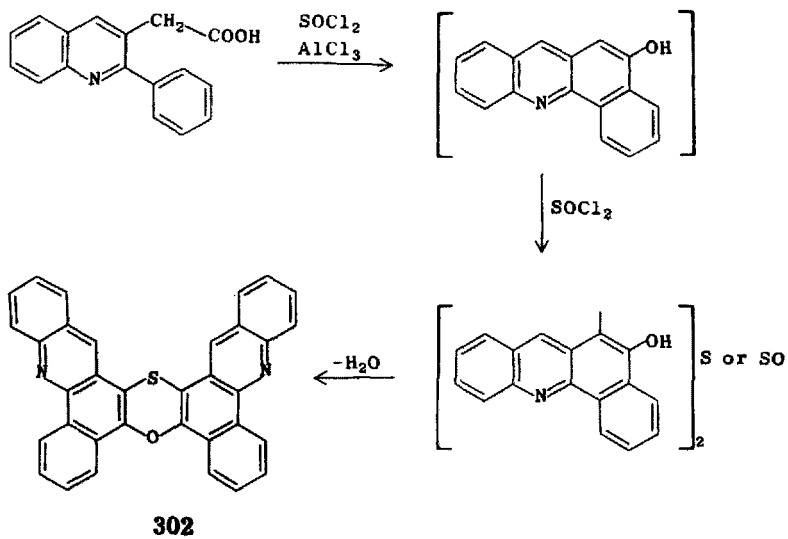


302

This compound, m.p. 367-370°, was isolated from the reaction of thionyl chloride with 2-phenylquinoline-3-acetic acid in the presence of aluminum chloride.³³ The objective in carrying out this reaction was the preparation of 3, 4-benzo-2-hydroxyacridine, which was not isolated.

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It was postulated that the following reaction occurred:



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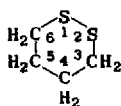
CHAPTER 12

C₄S₂ RING SYSTEMS

The C₄S₂ ring constitutes one of the major categories in this series of heterocyclic compounds. The literature on *o*-dithiane is meager compared to 1,2-dithiolane. Similarly, there are relatively few references to *m*-dithiane, primarily reaction products of 1,3-dimercaptans with carbonyl compounds, as compared to 1,3-dithiolane. However, there are a considerable number of references to ring systems containing the *p*-dithiane ring. Chief among these is thianthrene, and the literature on other members, *b*-dithiane and *p*-dithiin, 1,4-benzodithiin, etc., is increasing rapidly.

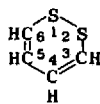
I. 1,2-DITHIA COMPOUNDS

A. C₄S₂ *o*-DITHIANE (1) AND *o*-DITHIIN (2)



1

(RRI 265)

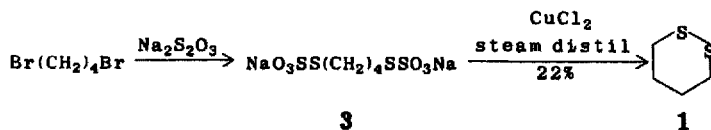


2

This ring system is known predominantly in its completely hydrogenated form; *o*-dithiin (2) has never been prepared, and only one dihydro derivative is known. 1 is indexed in Chemical Abstracts as *o*-dithiane, with the numbering as shown. It is frequently referred to as 1,2-dithiane, other names being 1,2-dithiocyclohexane and cyclotetramethylene disulfide.

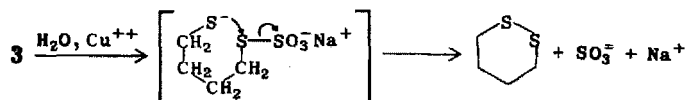
1. Preparation

The syntheses of *o*-dithiane compounds generally follow those of the 1,2-dithiolanes (Chapter 5, section I A-1a); the compounds reported are listed in Table 1. Thus, *o*-dithiane (1) was first prepared by Affleck and Dougherty^{1b} from the bis(Bunte salt) (3) and cupric chloride. The yield was surprisingly low and the compound was not obtained pure.

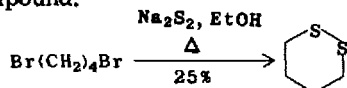


According to Schüberl and Gräfe⁴³³ the function of the copper salt is to liberate a mercaptide ion, which then displaces sulfite ion.

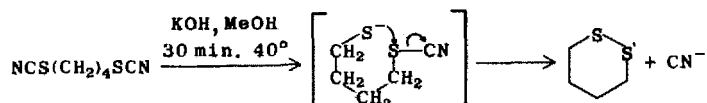
C₄S₂ Ring Systems



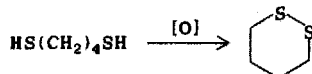
Barltrop, Hayes, and Calvin³³ prepared *o*-dithiane from tetramethylene dibromide and sodium disulfide and isolated it as a pure crystalline compound.



Brintzinger, Langheck, and Ellwanger⁷³ prepared **1** in unstated yield by alkaline hydrolysis of tetramethylene dithiocyanate; presumably a mercaptide ion is formed by hydrolysis of one thiocyanate group and this displaces cyanide from the second thiocyanate.

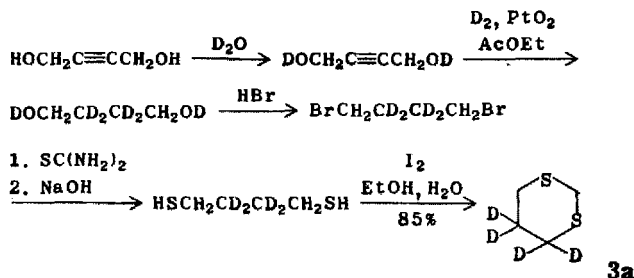


The best synthesis of *o*-dithiane appears to be the oxidation of 1, 4-dimercaptobutane. Thus, Schöberl and Gräffe^{432,433} reported an almost quantitative yield with *t*-butyl hydroperoxide, and Birch, Cullum, and Dean⁵⁰ a 92% yield with aqueous potassium triiodide.



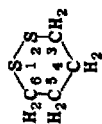
Jacini, Bacchetti, and Rosnati²⁸⁹ used bromine in carbon tetrachloride, but reported no yield.

Claeson, Androes, and Calvin^{122a,122b} prepared 4, 4, 5, 5-tetradeutero-*o*-dithiane (**3a**) in the following manner:



3a was also prepared by Lüttringhaus, Kabuss, and co-workers,^{335a} by a different, unstated procedure.

Cairns, Evans, and co-workers,⁸⁴ isolated a low yield of 3, 6-dimethyl-*o*-dithiane (**4**) from the reaction of acetonylacetone with hydrogen sulfide at extremely high pressure.

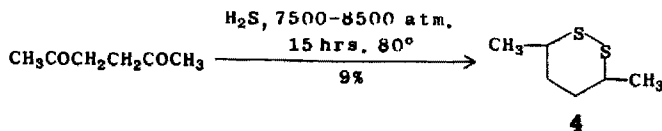
TABLE 1. *o*-Dithiane Derivatives

Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
None	22		ca. 60	5		1b
	25	32-33	82	150 (?)		33
	92	30-42	186	760	Purity 99.8%	50
			25	1.6		
		29	80	14		73
			58-63	4		289
	90-100	30.8-31.5	30-40	25	n_D^{25} 1.5981, n_D^{32} 1.5750	432, 433
3-(HO ₂ C-)		75-76				122
4-(HO ₂ C-)	59	115.2-116.2				121
(+)-4-(HO ₂ C-)		109-113			Impure $[\alpha]_D^{25} + 71.5^\circ$	121
(-)-4-(HO ₂ C-)		106.5-108			Impure $[\alpha]_D^{25} - 123.5^\circ$	121
3-(HO ₂ CCH ₂ CH ₂ CH ₂ -)	22	58				78-80
	29	57-57.5				91
3, 6-(CH ₃ -) ₂	9		66-69	10	n_D^{25} 1.5461	84
cis-3, 6-(HO ₂ C-) ₂	100	199				184

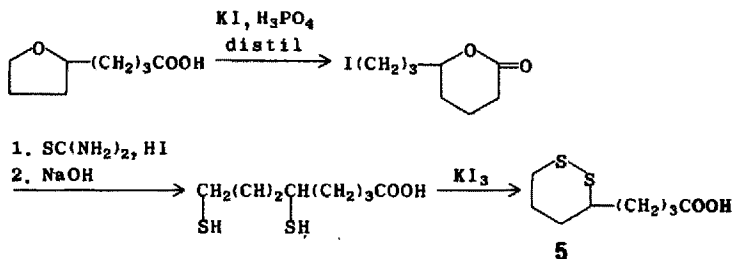
C_4S_2 Ring Systems

<i>cis</i> -3, 6-(HO ₂ C-) ₂ anhyd.	76-77			372
<i>cis</i> -3-CO ₂ CH ₃ -6-CO ₂ H		115-120	0.5	372
<i>cis</i> -3-CONH ₂ -6-COONH ₄	241 (dec.)			372
<i>trans</i> -3, 6-(HO ₂ C-) ₂	100	<i>ca.</i> 275 (dec.)		184
	41	<i>ca.</i> 270 (dec.)		186
	20-40	261 (dec.)		445
(+)-3, 6-(HO ₂ C-) ₂	257			184
(-)-3, 6-(HO ₂ C-) ₂	257			184
			$[\alpha]_D^{25} + 336.6^\circ (H_2O)$	189
			$[\alpha]_D^{25} - 335.8^\circ (H_2O)$	121
			+ 126° (dil HCl), -194.8° (EtOH)	335a
4, 4-(HO ₂ C-) ₂	52	152 (dec.)		335a
<i>cis</i> -4, 5-(HO-) ₂		128-129		335a
<i>trans</i> -4, 5-(HO-) ₂		129-130		335a
<i>cis</i> -4, 5-(CH ₃ CO ₂ -) ₂		74-75		122b
<i>trans</i> -4, 5-(CH ₃ CO ₂ -) ₂		54-55		122a, 122b
3, 3, 6, 6-(CH ₃ -) ₄	85	32-33	87-88	34
4, 4, 5, 5-D ₄ -	Trace		<i>ca.</i> 60	14
4, 5-Dehydro-	70	20		n_D^{25} 1.574 Impure
				433
				335a

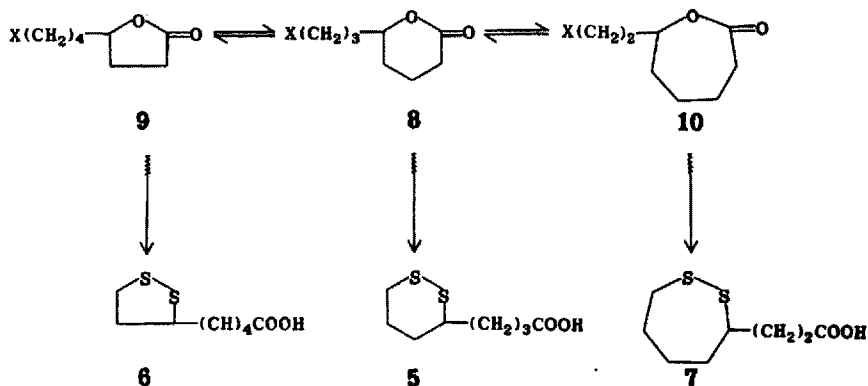
Chapter 12



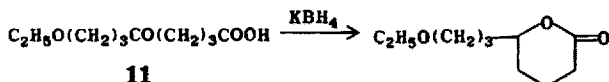
Before the elucidation of the structure of α -lipoic or 6-thioctic acid (see Chapter 5, section I A-1b), 4-(*o*-dithian-3-yl)butyric acid (**5**) was considered as a possible structure.^{74,77,266,267,341,411,412} The first synthesis by Bullock, Brockman, and co-workers,⁷⁷⁻⁸⁰ gave a 22% yield of **5**, called 5-thioctic acid, plus a 1% yield of the seven-membered cyclic disulfide, 4-thioctic acid (**7**), and a 5% yield of the five-membered disulfide, 6-thioctic acid (**6**).



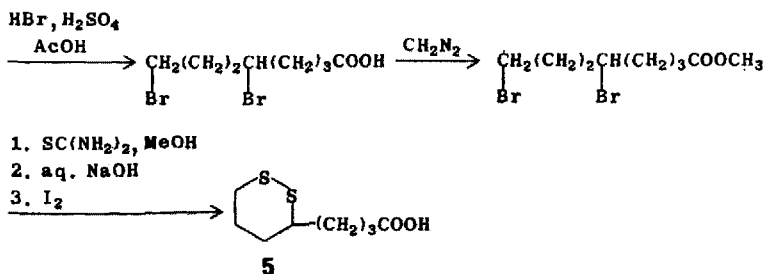
The synthesis was confirmed by Makino and Koike,³⁴¹ Hornberger, Heitmiller, and co-workers,²⁶⁷ who used hydrogen bromide to open the tetrahydrofuran ring, pointed out that the valerolactone (**8**), in the presence of acid, was in equilibrium with the butyrolactone (**9**), the latter being responsible for the formation of 6-thioctic acid (**6**). Presumably a trace of the corresponding caprolactone (**10**) was also present to account for the formation of 4-thioctic acid (**7**).



In view of these results, Campbell⁹¹ carried out a more straightforward synthesis of **5**, starting with 8-ethoxy-5-oxo-octanoic acid (**11**).

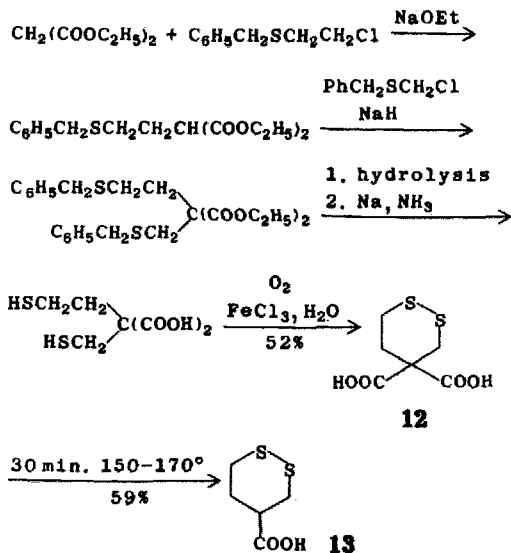


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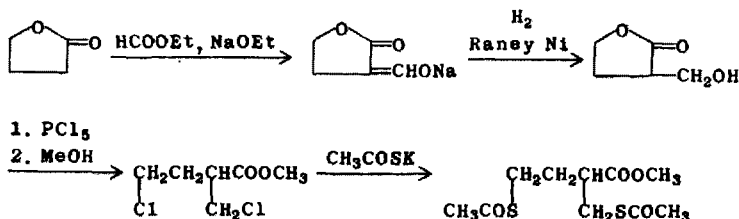


Contrary to the results of the previous workers, he found no evidence for lactonization or rearrangement of the dibromide. The compound has not been resolved into its stereoisomers.

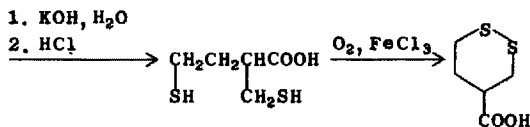
Both possible *o*-dithianecarboxylic acids have been reported. Claesson¹²² prepared *o*-dithiane-3-carboxylic acid in an unstated manner, while Claesson and Longsjoen¹²¹ prepared *o*-dithiane-4-carboxylic acid (**13**) from malonic ester; *o*-dithiane-4,4-dicarboxylic acid (**12**) was isolated as an intermediate.



The overall yield of **13** from diethyl β-benzylthioethylmalonate was 15%. An alternative synthesis of **13** from butyrolactone gave a very low yield.



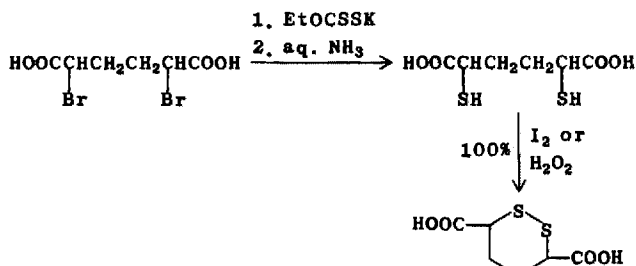
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13

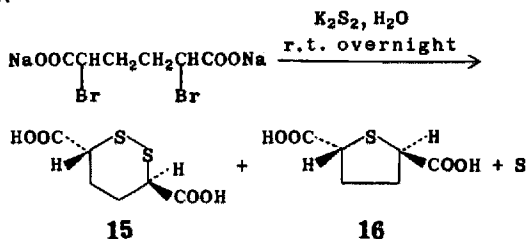
13 was partially resolved *via* its quinine and cinchonidine salts.

Fredga^{184,185} prepared *cis*- and *trans*-*o*-dithiane-3, 6-dicarboxylic acid (**14**), the former from *meso*- α, α' -dibromoadipic acid and the latter from DL- α, α' -dibromoadipic acid.



14

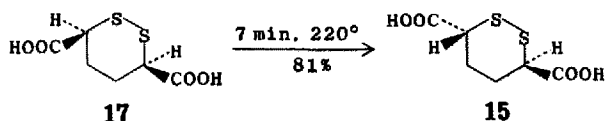
Therefore, essentially no isomerization occurred in the reaction of α, α' -dibromoadipic acid with potassium ethylxanthate; presumably both carbon atoms were inverted in a clean S_N2 displacement. According to Schotte,⁴⁴⁵ potassium thioacetate also reacted with α, α' -dibromoadipic acid without rearrangement. Rearrangement did occur, however, when α, α' -dimercaptoadipic acid was prepared from the methyl ester followed by alkaline hydrolysis, the rearrangement taking place presumably during the alkaline hydrolysis. The rearrangement was demonstrated by oxidation of the dimercaptans to the *o*-dithiane-3, 6-dicarboxylic acids (**14**). With neither iodine nor hydrogen peroxide was there any indication of polymer formation, a side reaction in the synthesis of 1, 2-dithiolanes (see Chapter 5, section I A-1a). The *trans* isomer (**15**) was also prepared by Fredga¹⁸⁶ from DL- α, α' -dibromoadipic acid and potassium disulfide. The yield was much lower because of the simultaneous formation of *trans*-tetrahydrothiophene-2, 5-dicarboxylic acid (**16**).



The *meso*-dibromo acid gave the same mixture, but *cis*-*o*-dithiane-3, 6-dicarboxylic acid (**17**) could not be isolated because of its much greater solubility in water, 14.1 g/l. at 25° vs. 0.54 g/l. for the *trans* isomer.

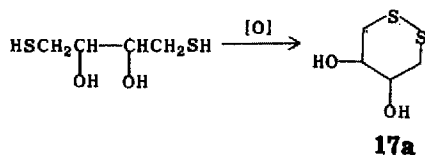
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Because of the ready availability of *meso*- α, α' -dibromoadipic acid and the unavailability of the DL-isomer, Fredga¹⁸⁴ claimed that *trans*-*o*-dithiane-3, 6-dicarboxylic acid (**15**) is best prepared by thermal isomerization of the *cis* isomer (**17**).



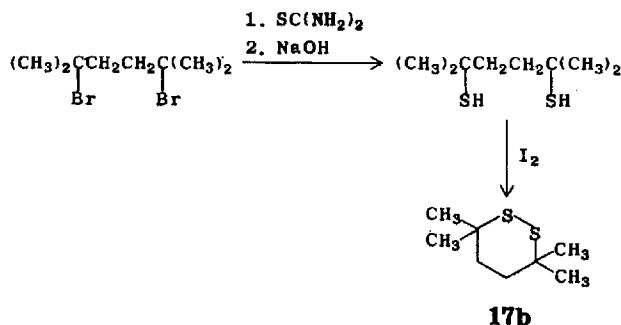
15, which formed a true racemic compound, was resolved, the (–)-isomer being obtained by recrystallization of its quinidine salt, and the (+)-isomer from the mother liquor through its cinchonine salt.

Lüttringhaus, Kabuss, and co-workers,^{335a} prepared *cis*- and *trans*-*o*-dithiane-4, 5-diol (**17a**) from *meso* and DL-1, 4-dimercaptobutane-2, 3-diol, respectively. The oxidizing agent used was not specified.

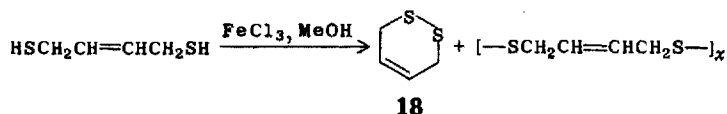


Although the two glycols had almost identical melting points, the corresponding diacetates melted sufficiently far apart to prove their non-identity.

Claeson, Androes, and Calvin^{122b} prepared 3, 3, 6, 6-tetramethyl-*o*-dithiane (**17b**).



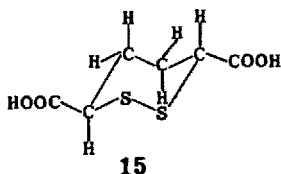
Schöberl and Gräffe⁴³³ reported the preparation of 3, 6-dihydro-*o*-dithiin (**18**) by the oxidation of 1, 4-dimercapto-2-butene. Only a trace of **18** was formed, the major product being polymer; the low yield was attributed to the dimercaptan being predominantly the *trans*-isomer.



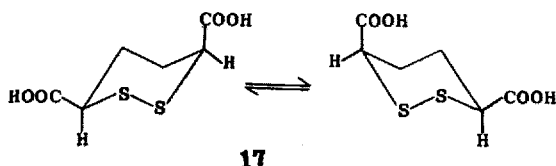
18 was isolated as an unstable yellow oil; it was not obtained pure. On the other hand, Lüttringhaus and co-workers^{335a} prepared 18 as a pure compound from *cis*-1, 4-dimercapto-2-butene in 70% yield using an unstated oxidizing agent.

2. Structure and Reactions

A crystallographic determination of the structure of *trans*-*o*-dithiane-3, 6-dicarboxylic acid (15) was carried out by Foss, Schotte, and Reidstad.^{182,183} The ring occurs as expected in the chair form, the substituents being in equatorial positions; an S-S distance of 2.069 Å was found.



Although an exact determination of the structure of the *cis*-dicarboxylic acid (17) has not been reported, Foss and Schotte¹⁸² have pointed out an interesting possibility. Crystal structure has indicated that the acid will exist in two equivalent mirror image forms. In solution the two forms will be interconverted. Inasmuch as this requires passage through a planar *cis*-disulfide form and inasmuch as the barrier to rotation through this form is quite high (10-14 kcal), this interconversion should take place less readily than for the cyclohexane analog.



Claeson, Androes, and Calvin^{122a,122b} determined the energy barrier involved in this interconversion from the proton magnetic resonance spectrum of 4, 4, 5, 5-tetradeutero-*o*-dithiane. At -43° the half-life for the enantiomers was found to be only 0.02 sec, with a $\Delta F^\ddagger$ for inversion of 11.6 kcal/mole, in excellent agreement with the estimate of Foss and Schotte.¹⁸² By a similar procedure 3, 3, 6, 6-tetramethyl-*o*-dithiane gave $\Delta E^\ddagger$ for inversion of 16.1 kcal/mole and $\Delta F^\ddagger$ of 13.8 kcal/mole. Because of the difference in $\Delta E^\ddagger$, $\Delta S^\ddagger$ and the frequency factors between the tetramethyl-*o*-dithiane and the corresponding cyclic peroxide, the authors felt that the two compounds invert by different mechanisms. Because of steric reasons they calculated that the disulfide inverts by flipping the 3- and 6-carbon atoms, while the peroxide flips the oxygen and the 4-carbon atom.

From a study of the inversions of 4, 4, 5, 5-tetradeutero-*o*-dithiane Lüttringhaus and co-workers^{335a} arrived at values in excellent agree-

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ment with those of Claeson, Androes, and Calvin. By comparing the two compounds it was shown that substitution decreases the ease of inversion. Introduction of a double bond, as illustrated by 3, 6-dihydro-*o*-dithiin, flattens the ring and makes inversion easier.

There are numerous indications that the *o*-dithiane ring is under some strain, although the strain is undoubtedly less than in the corresponding five-membered ring. Thus, Affleck and Dougherty^{1b} found *o*-dithiane to be stable in the absence of peroxide, whereas 1, 2-dithiolane polymerizes on removal of the solvent; both compounds, however, are polymerized by a trace of aluminum chloride. According to Birch, Cullum, and Dean,⁵⁰ *o*-dithiane can be stored at 0° in the dark, but polymerizes on exposure to light. Surprisingly, they reported two forms of polymer, a solid which depolymerized to *o*-dithiane on distillation at atmospheric pressure, and a rubbery form which would not depolymerize; the former would presumably be a linear polymeric disulfide, while the latter would be cross-linked, perhaps containing sulfide links as well as disulfide links. Jacini, Bacchetti, and Rosnati²⁸⁹ also reported a reversible polymerization and depolymerization. Schöberl and Gräffe^{432,433} have claimed, however, that *o*-dithiane is much less reactive than reported, being more stable than a linear aliphatic disulfide. Thus, they found that *o*-dithiane was not cleaved by cyanide ion and would not polymerize even in the presence of catalysts.

It is possible that the stability may be related to the purity of the sample. Schöberl and Gräffe described *o*-dithiane as having a terpene-like odor, while according to Brintzinger, Langheck, and Ellwanger⁷³ it has an unpleasant musty odor, perhaps indicative of sulfidic impurities. This might also explain the rather wide range of boiling and melting points reported for *o*-dithiane, although the method of determination of these constants might be a more important factor. Birch, Cullum, and Dean⁵⁰ reported the purity of their sample of *o*-dithiane to be 99.8 mole per cent, yet it had a melting range of 12°. This could be attributed to decomposition during a very slow melting point determination, although a typographical error might be suspected, as it might also be in the boiling point reported by Barltrop, Hayes and Calvin.³³

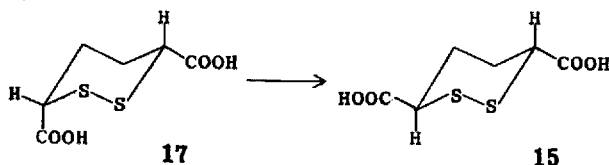
The instability of the *o*-dithiane ring can be attributed to the same factor which causes the instability of the 1, 2-dithiolane ring, namely the distortion of the dihedral angle about the S-S bond from the preferred value of about 90° to a value of about 70° in *o*-dithiane and about 0° in 1, 2-dithiolane, as estimated by Affleck and Dougherty.^{1b} Thus, according to Barltrop, Hayes, and Calvin,³³ there would be a repulsion between the two non-bonding pairs of p-electrons on the sulfur atoms, although this repulsion would of course be much less in *o*-dithiane than in 1, 2-dithiolane.

Sunner⁴⁷⁶ attempted to determine the strain in *o*-dithiane by measuring the heat of oxidation of 1, 4-dimercaptobutane with iodine; a spectrophotometric analysis showed *o*-dithiane to be the only product. Comparison with the oxidation of *n*-propyl mercaptan to the disulfide showed the ring strain to be on the borderline of accuracy, perhaps 0.5 kilocalorie

per mole. His results substantiate, therefore, those of Schöberl and Gräffe,^{432,433} who estimated that the 20-25° distortion in the dihedral angle involves a strain of at most 2.5 kcal. Bergson and Schotte,⁴⁸ on the other hand, calculated the strain in *o*-dithiane, involving stretching and torsion of bonds and bending of valence angles, using the data of Foss and Reistad¹⁸³ for *trans*-*o*-dithiane-3, 6-dicarboxylic acid. They found a strain of at least 5 kcal/mole, about 3 kcal of this being attributable to the deviation from 90° of the S-S dihedral angle. Although this is small compared to the 16 kcal calculated as the strain in the 1, 2-dithiolane ring, it is rather difficult to reconcile this ring strain with Schöberl and Gräffe's statement that *o*-dithiane is more stable than linear disulfides.

Dainton, Ivin, and Walmsley^{142a} measured the heat of polymerization of *o*-dithiane catalyzed by boron trifluoride, and found a value of 0.5 kcal/mole. A number of heterocyclic rings of varying size showed a minimum heat of polymerization for six-membered rings, indicating the least amount of strain with this ring size. The polymerization is in contrast to the claim of Schöberl and Gräffe^{432,433} that *o*-dithiane does not polymerize.

The necessity for heating *cis*-*o*-dithiane-3, 6-dicarboxylic acid (17) to 220° to isomerize it into the *trans* isomer (15), as reported by Fredga,¹⁸⁴ indicates the thermal stability of a substituted *o*-dithiane ring. The rearrangement is unusual. The first step would be expected to be homolytic cleavage of the S-S bond, but rearrangement must involve inversion at one of the carbon atoms. It would be interesting to know if the diester would rearrange under the same conditions. Irrespective of the detailed mechanism, the driving force is undoubtedly the formation of the isomer in which the two carboxyl groups can be equatorial.



3, 6-Dihydro-*o*-dithiin (18) is much less stable than *o*-dithiane, according to Schöberl and Gräffe,⁴³³ who found that it reacts with cyanide ion and polymerizes spontaneously on standing. Introduction of the double bond into the ring increases the dihedral angle strain to about 45°, leading to a ring strain of 5-7 kilocalories. Actually, 18 is even less stable than 3, 3, 5, 5-tetramethyl-1, 2-dithiolane.⁴³³

Barltrop, Hayes, and Calvin^{33,86} reported that *o*-dithiane and 5-thioctic acid (5) have almost identical ultraviolet absorption spectra, with a λ_{max} at about 286 m μ . Schotte^{443,444,447} attributed this bathochromic shift from the absorption maximum of about 250 m μ for linear disulfides to the repulsion between the non-bonding p-electrons on the sulfur atoms, resulting in excitation by less energy. The effect of substitution on the *o*-dithiane ring parallels that on the five-membered ring. Here, too, alkyl substituents have very little effect on the ultra-

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violet absorption spectrum, whereas carboxyl groups adjacent to the disulfide link do. Schotte^{443,447} found that both *cis*- and *trans*-*o*-dithiane-3, 6-dicarboxylic acid show essentially only end absorption as the free acids. The disodium salts, however, have inflections at about 275 mμ. The effect is reminiscent of that with 1, 2-dithiolane-3, 5-dicarboxylic acid, but much less pronounced. Claeson¹²² found two maxima in the spectrum of *o*-dithiane-3-carboxylic acid, one at 245 mμ corresponding to the 280 mμ maximum of 1, 2-dithiolane-3-carboxylic acid, and another at 282 mμ corresponding to the 333 mμ peak in the 1, 2-dithiolane analog. As with the 1, 2-dithiolanes, the 245 mμ band disappeared in base and the 282 mμ maximum was sharper. Here, too, Claeson attributed the two bands to the unsymmetrical environment of the two sulfur atoms.

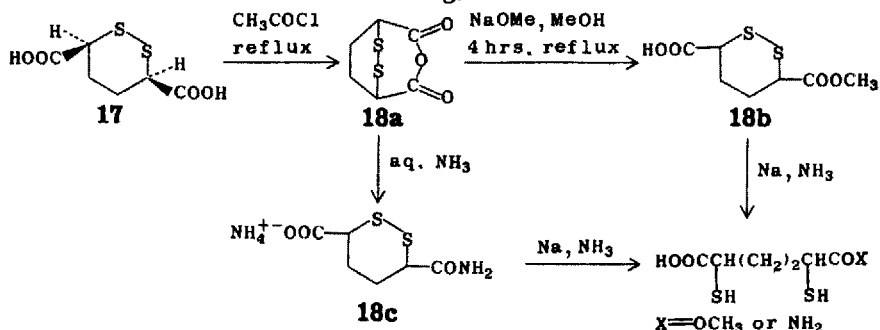
According to Djerassi, Fredga, and Sjöberg^{160a} both *o*-dithiane-4-carboxylic acid and *o*-dithiane-3, 6-dicarboxylic acid show strong Cotton effects in optical rotatory dispersion studies.

The infrared spectra of the two *o*-dithiane-3, 6-dicarboxylic acids have also been reported by Schotte,^{443,447} and Rosenberg and Shotte⁴²⁰ demonstrated that infrared can be used to determine the formation of quasi-racemic compounds in this series.

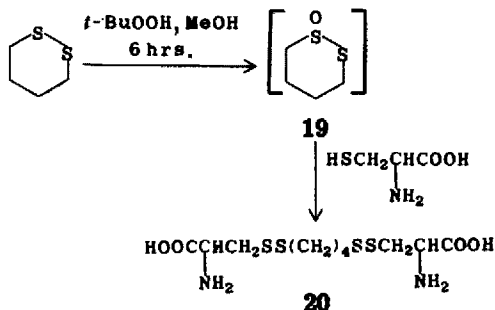
Optically active *trans*-*o*-dithiane-3, 6-dicarboxylic acid, unlike 1, 2-dithiolane-3, 5-dicarboxylic acid, is not racemized in hot water, a further indication of the greater stability of the six-membered ring.⁴⁴⁶

Relatively few reactions of *o*-dithiane compounds have been reported. Fredga¹⁸⁴ reduced *o*-dithiane-3, 6-dicarboxylic acid in dilute aqueous ammonia with zinc; the *trans* acid gave DL- α, α' -dimercaptodipic acid, while the two enantiomorphs gave the optically active dimercaptans with the same sign. Nygård and Schotte^{374,447} reduced both the *cis*- and the *trans*-acids polarographically. The acids gave waves (half-wave potential -0.75v) only in acid solution, and the shape of the waves indicated an irreversible electroreduction, more pronounced for the *cis* acid than for the *trans*.

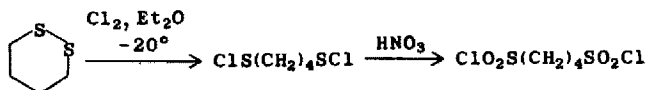
deMytt³⁷² has reported that *cis*-*o*-dithiane-3, 6-dicarboxylic acid (17) yields the cyclic anhydride (18a) on treatment with acetyl chloride. From 18a were prepared the monomethyl ester (18b) and the half amide ammonium salt (18c); these were reduced with sodium in liquid ammonia to the corresponding *meso*-adipic acid derivatives, which were claimed to be useful for hair-waving.



Cavallito and Small⁹⁵ claimed that *o*-dithiane could be oxidized to a monosulfoxide (19) with perbenzoic acid below 55°, but the product was not described. They reported it to have antibacterial and fungicidal activity. Similarly, Schöberl and Gräfe⁴³⁴ prepared a monosulfoxide or thiosulfinate ester (19), which was not isolated but was reacted directly with cysteine to the disulfide (20).

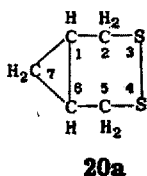


Brintzinger, Langheck, and Ellwanger⁷³ chlorinated *o*-dithiane to the unstable 1,4-butane-bis(sulfonyl chloride). Its structure was proved by oxidation to the corresponding bis(sulfonyl chloride).

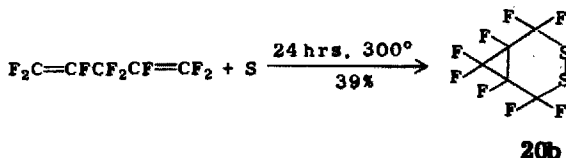


5-Thioctic acid is reported to be a more efficient antifogging agent in photographic emulsions than 6-thioctic (α -lipoic) acid.^{2a}

B. C₃-C₄S₂ 3,4-DITHIABICYCLO[4.1.0]HEPTANE (20a)

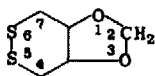


Benning^{45a} reacted perfluoro-1,4-pentadiene with sulfur and isolated a compound, m.p. 91.5°, b.p. 107.5° at 739 mm, formulated as perfluoro-3,4-dithiabicyclo[4.1.0]heptane (20b). The compound did not react with bromine or potassium permanganate; nuclear magnetic resonance confirmed the structure.



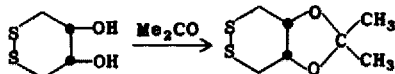
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C. C₃O₂-C₄S₂ 1, 3-DIOXOLO[4, 5-*d*]-*o*-DITHIIN (20c)



20c

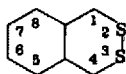
Lüttringhaus and co-workers^{335a} prepared *cis*-tetrahydro-2, 2-dimethyl-1, 3-dioxolo[4, 5-*d*]-*o*-dithiin (**20d**), m.p. 48-49°, from the corresponding *cis*-glycol and acetone.



20d

Proton magnetic resonance studies showed that fusion of a five-membered ring to the *o*-dithiane did not decrease the ease of inversion of the latter (see section I A-2).

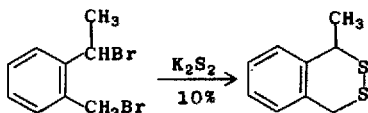
D. C₄S₂-C₆ 2, 3-BENZODITHIIN (21)



21

(RRI 1675)

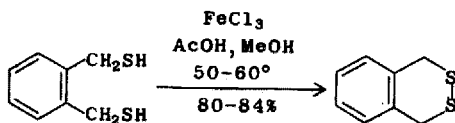
2, 3-Benzodithiin, also called 2, 3-dithiatetralin, is the only representative of the *o*-C₄S₂-C₆ family. The first member, 1-methyl-2, 3-benzodithiin (**22**), was prepared by v. Braun and Weissbach⁶⁸ from 1-(*o*-bromomethylphenyl)-1-bromoethane and potassium disulfide.



22

It was described as an unstable compound, m.p. 40°, b.p. 145-150° at 13 mm, which darkened on standing, and no reactions were investigated.

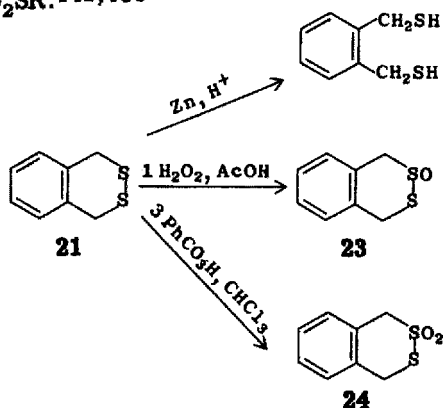
The parent compound, 2, 3-benzodithiin, was prepared in much better yield by Lüttringhaus and Hägele³³³ *via* the oxidation of *o*-bis(mercaptomethyl)benzene.



21

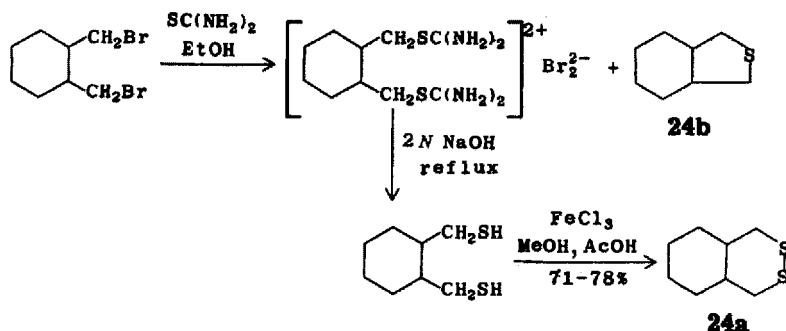
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The compound, isolated as colorless needles melting at 80° , smelled like naphthalene, and had properties expected of a disulfide. Reduction regenerated the parent dimercaptan, oxidation with one equivalent of peroxide gave 2, 3-benzodithiin 2-oxide (**23**), m.p. 143° , while three equivalents gave 2, 3-benzodithiin 2, 2-dioxide (**24**), m.p. 108° . That **24** was a sulfone and not a bis(sulfoxide) was shown by the similarity of its spectrum to that of $\text{C}_6\text{H}_5\text{CH}_2\text{SSO}_2\text{CH}_2\text{C}_6\text{H}_5$. Actually, 1, 2-disulfoxides are unknown, the dioxide existing only as the thioisulfonate, RSO_2SR .^{142,458}

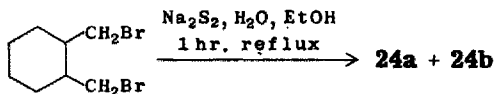


2, 3-Benzodithiin polymerized photochemically in the presence of a number of ketones, e.g. pyruvic acid, diacetyl, benzil, etc., presumably to a linear polymer. It is apparently very readily decomposed by alkali.³³⁵

Lüttringhaus and Brechlin³³⁵ prepared *cis*- and *trans*-hexahydro-2, 3-benzodithiin (**24a**), which they called 2, 3-dithiadecalin, by two routes, oxidation of 1, 2-bis(mercaptomethyl)cyclohexane and reaction of 1, 2-bis(bromomethyl)cyclohexane with sodium disulfide. The starting materials were prepared by lithium aluminum hydride reduction of the *cis*- and *trans*-hexahydrophthalate esters. *Cis*- and *trans*-1, 3-octahydroisothianaphthene (**24b**) were isolated as by-products of the disulfide preparation. **24b** was also formed in the synthesis of the dimercaptan, presumably *via* the intermediate monoisothiuronium salt.



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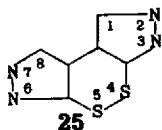


cis-**24a** melts at 41.5° and *trans*-**24a** at 56.5-57°; both have terpene-like odors. The two isomers are much more stable than 2,3-benzodithiin (**21**). Thus, they showed no reaction with aqueous acids or bases, were stable towards light and oxygen, and gave no precipitates with lead acetate or mercuric chloride. They did, however, cleave when exposed to ultraviolet light.

trans-Hexahydro-2,3-benzodithiin is apparently slightly less strained than the *cis* isomer, as evidenced by its absorption maxima in the ultraviolet being at slightly shorter wave lengths, 212 and 290 mμ vs. 213 and 295 mμ. Models indicate that the *trans* isomer can exist in the chair-chair form with a minimum of Pitzer strain and a deviation of only 15° from the preferred 90° dihedral angle of the C-S-S-C group. With the *cis* isomer a certain amount of distortion of this form is required to minimize hydrogen-hydrogen interactions in adjacent rings. However, both isomers are more stable than the more highly strained 2,3-benzodithiin, just as *o*-dithiane is more stable than 3,6-dihydro-*o*-dithiin.⁴³³

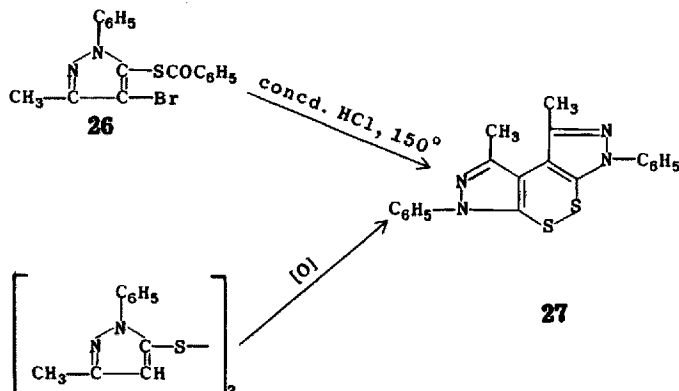
Proton magnetic resonance studies carried out by Lüttringhaus and co-workers^{335a} showed that 2,3-benzodithiin, like 3,6-dihydro-*o*-dithiin, undergoes inversion more readily than *o*-dithiane. *cis*-Hexahydro-2,3-benzodithiin, on the other hand, is more rigid than *o*-dithiane as a result of fusion of the six-membered ring to the heterocycle (see section I A-2).

E. C₃N₂-C₃N₂-C₄S₂ *o*-DITHIINO[3,4-*c*:6,5-*c'*]DIPYRAZOLE (**25**)



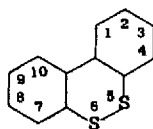
(RRI 2365)

Only one compound containing this ring system has been reported. In 1908 Michaelis³⁵⁹ reported that heating 1-phenyl-3-methyl-4-bromo-5-benzoylthiopyrazole (**26**) with concentrated hydrochloric acid or with alkali yielded 1,8-dimethyl-3,6-diphenyl-*o*-dithiino[3,4-*c*:6,5-*c'*]dipyrzole (**27**) which he called bis(1-phenyl-3-methyl-5-thiopyrazolone). The compound was also obtained by distilling *in vacuo* bis(1-phenyl-3-methylpyrazole)-5,5'-disulfide (**28**).



27 was obtained as white needles, m.p. 198° ; it formed a monomethiodide, which melted at 198° with loss of methyl iodide. It was very stable towards oxidizing and reducing agents. Although Michaelis considered other possible structures, he preferred **27**; in view of the lack of any chemical evidence, this structure requires further verification.

F. $\text{C}_4\text{S}_2\text{-C}_6\text{-C}_6$ DIBENZO[*c, e*]-*o*-DITHIIN (**29**)



29

(RRI 3450)

Several compounds with this ring system have been described; they are listed in Table 2. The parent compound was first prepared by Barber and Smiles,³² who called it 2, 2'-diphenylene disulfide. Starting with *o*-iodobenzenesulfonic acid, they prepared biphenyl-2, 2'-disulfonyl chloride. Reduction with zinc and acid gave 2, 2'-dimercaptobiphenyl, and oxidation with alcoholic ferric chloride gave the desired disulfide, the last step being quantitative. Treatment of the disulfonyl chloride with hot aqueous sulfite followed by acid yielded biphenyl-2, 2'-disulfonic acid. This was too unstable to be isolated; it cyclized spontaneously on standing to dibenzo[*c, e*]-*o*-dithiin 5, 5-dioxide (**30**). This could be reduced with hydrogen iodide to dibenzo[*c, e*]-*o*-dithiin (**29**). The latter was oxidized to the 5, 5-dioxide with nitric acid. Heating the disulfide with Cu yielded dibenzothiophene. Loudon, Sloan, and Summers³³¹ have pointed out the generality of sulfur elimination under

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these conditions if an aromatic compound results. The following shows these transformations:

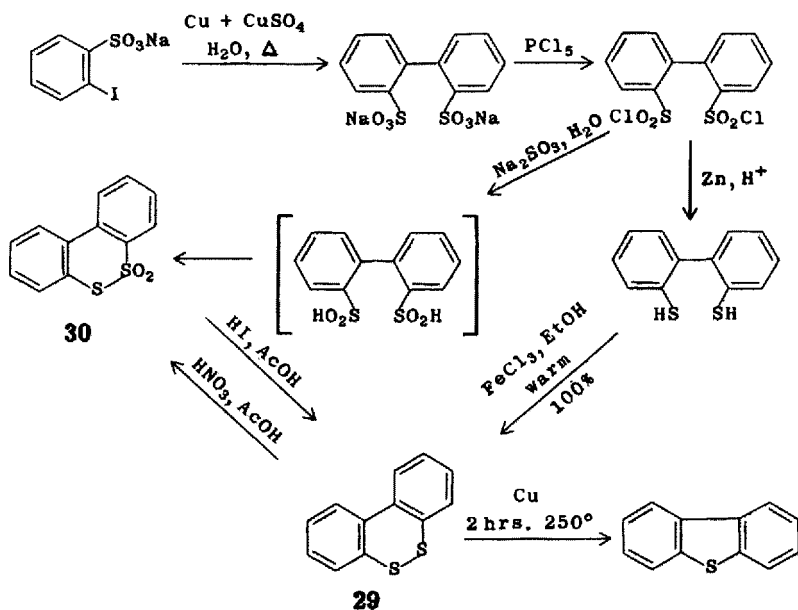
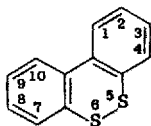


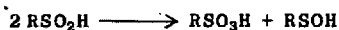
TABLE 2. Derivatives of Dibenzo[*c,e*]-*o*-dithiin



Substituents	Yield (%)	M.p. (°C)	Ref.
None	100	113	32
	55	113-114	7
		114.5	449
5, 5-Dioxide	60	128	32, 7
2, 9-(CH ₃ -) ₂	69	89-90	7
2, 9-(CH ₃ -) ₂ 5, 5-dioxide	45	146-147	7
3, 8-(CH ₃ -) ₂	81	114-115	7
3, 8-(CH ₃ -) ₂ 5, 5-dioxide	75	170-171	7
1, 3, 8, 10-(CH ₃ -) ₄ 5, 5-dioxide	72	177-178	8

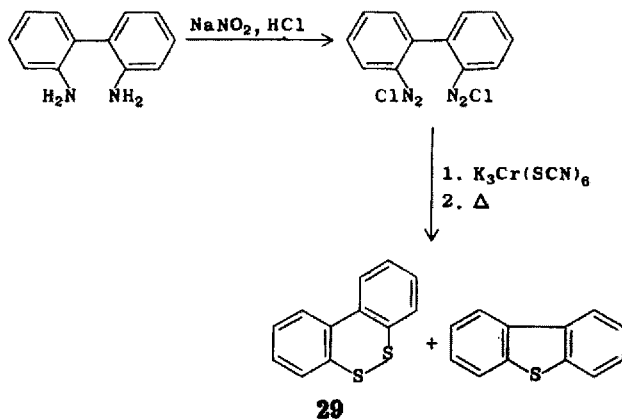
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Overberger and Godfrey,³⁷⁷ in connection with their interest in the use of sulfinic acids as polymerization catalysts, considered the mechanism of formation of the thioisulfonate (**30**) from biphenyl-2, 2'-disulfinic acid. Previous to this work the accepted mechanism for the conversion of a sulfinic acid to a thioisulfonate was that postulated by Hinsberg.²⁶² This involved disproportionation of a sulfinic acid to a mixture of sulfonic acid and sulfenic acid, followed by condensation of the latter with more sulfinic acid.



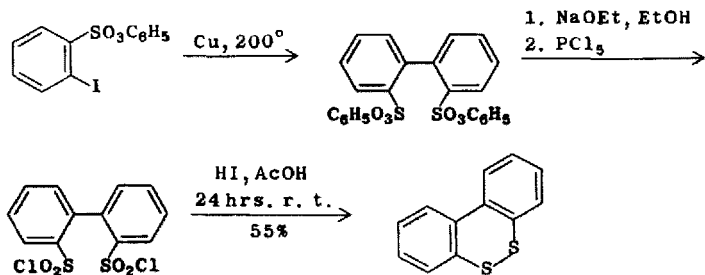
Overberger and Godfrey showed that this could not be the mechanism, as they obtained **30** in 87% yield from the sulfite reduction of biphenyl-2, 2'-disulfonyl chloride. According to the Hinsberg mechanism the maximum yield would be 50%, since one mole of biphenyl-2, 2'-disulfinic acid would be consumed in converting another mole into the 2-sulfenic-2'-sulfinic acid. The mechanism must involve the condensation of two sulfinic acid groups to form thioisulfonate with elimination of the elements of hydrogen peroxide.

Schwechten⁴⁴⁹ prepared dibenzo[*c, e*]-*o*-dithiin (**29**) by heating the hexathiocyanatochromium salt of tetrazotized 2, 2'-diaminobiphenyl; the major product, however, was dibenzothiophene.



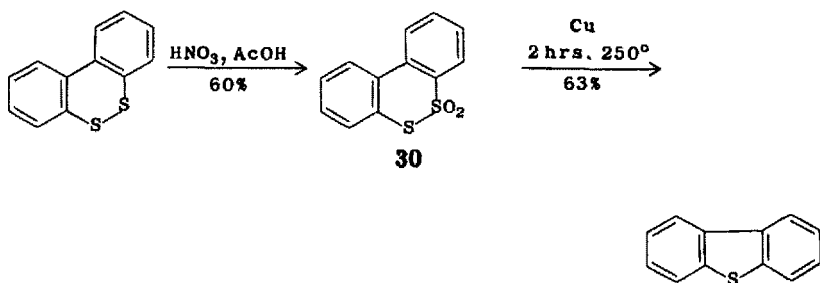
Armarego and Turner⁷ prepared several other members of this series. They found the treatment of phenyl *o*-iodobenzenesulfonate with copper to be superior to Baker and Smiles' copper-aqueous copper sulfate treatment for preparing the biphenyl derivatives. Also, hydriodic acid in acetic acid converted biphenyl-2, 2'-disulfonyl chloride directly into dibenzo[*c, e*]-*o*-dithiin (**29**).

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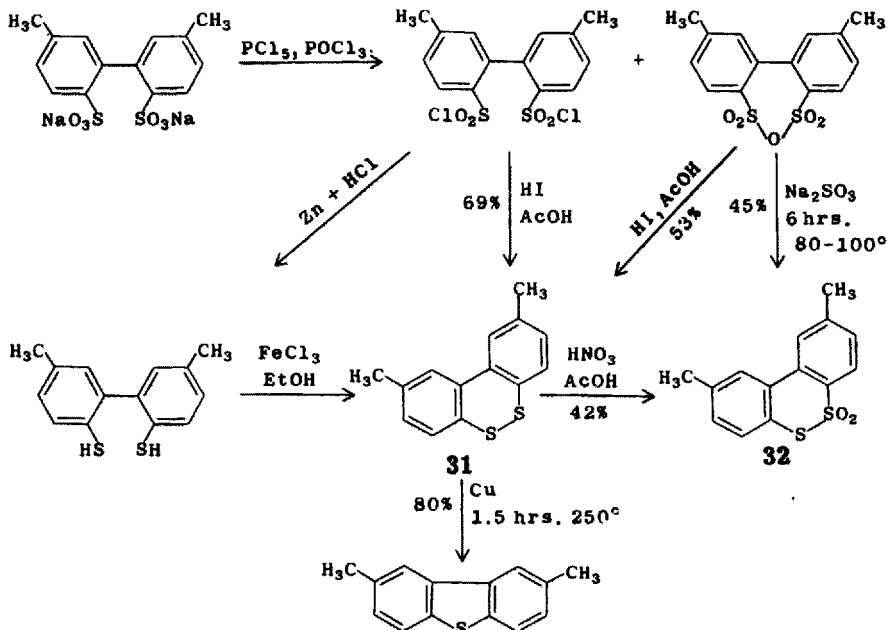
29

It is interesting that the thiol-sulfonate, dibenzo[*c, e*]-*o*-dithiin 5, 5-dioxide (30), also gave dibenzothiothiophene on heating with copper, indicating that a sulfone group is eliminated in preference to a sulfur atom.

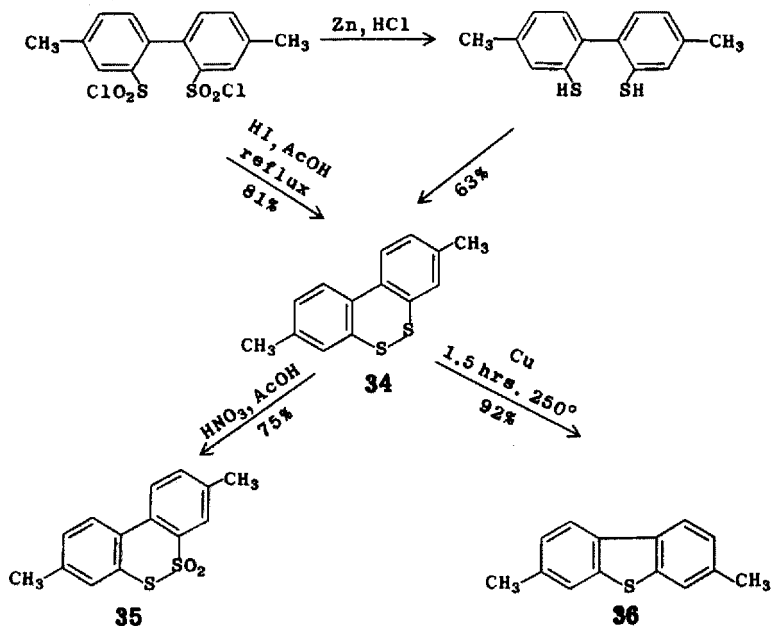


These reactions were applied to 5, 5'-dimethylbiphenyl-2, 2'-disulfonic acid, prepared by deamination of *o*-tolidine-6, 6'-disulfonic acid. Treatment of the disodium salt with phosphorus pentachloride gave a mixture of the disulfonyl chloride and the disulfonic anhydride, which could be reduced to 2, 9-dimethyldibenzo[*c, e*]-*o*-dithiin (31). This was also formed by reduction of either compound to the dimercaptan followed by oxidation. 2, 9-Dimethyldibenzo[*c, e*]-*o*-dithiin 5, 5-dioxide (32) was prepared by sulfite reduction of the mixture of sulfonyl chloride and anhydride, and by oxidation of 31. Removal of sulfur took place without rearrangement; 2, 8-dimethyldibenzothiothiophene (33), and not 2, 6-dimethyldibenzothiothiophene, was formed.

Chapter 12

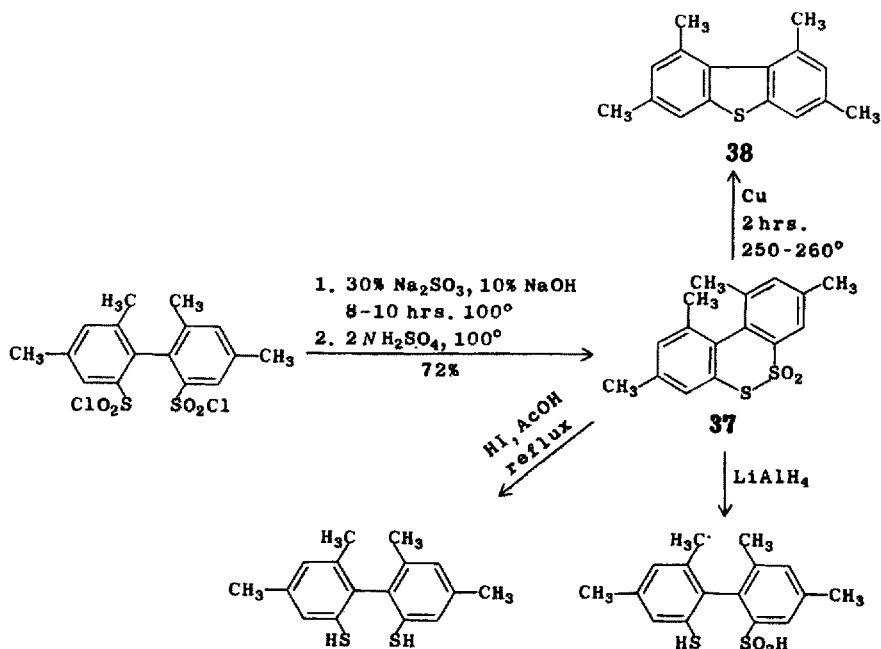


In a similar fashion 4,4'-dimethylbiphenyl-2,2'-disulfonyl chloride yielded 3,8-dimethyldibenzo[*c,e*]-*o*-dithiin (**34**), which was oxidized to the thiol sulfonate (**35**). **34** was converted by copper into 2,7-dimethyldibenzothiophene (**36**).



C₄S₂ Ring Systems

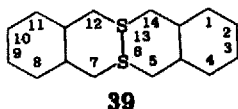
Armarego and Turner⁸ also attempted the preparation of the strained compounds, 1, 3, 8, 10-tetramethyldibenzo[*c, e*]-*o*-dithiin, but with no success. Reduction of 4, 6, 4', 6'-tetramethylbiphenyl-2, 2'-disulfonyl chloride with zinc and acid or with hydrogen iodide gave only polymeric material. Reduction with sulfite yielded the sodium disulfinate which, on acidification and further heating, cyclized to 1, 3, 8, 10-tetramethyl-dibenzo[*c, e*]-*o*-dithiin 5, 5-dioxide (**37**). The structure of **37** was proved by the similarity of its ultraviolet absorption spectrum with that of **30**.⁹ Reduction of **37** with hydrogen iodide yielded the unstable dimercaptan, which oxidized to a polymer rather than to the *o*-dithiin derivative. Lithium aluminum hydride reduction of the cyclic thiolsulfonate (**37**) gave the 2'-mercapto-2-sulfinic acid, while heating with copper eliminated the sulfone group and yielded 2, 4, 5, 7-tetramethyldibenzothiophene (**38**).



The instability of these compounds is the result of course of steric interference between the 1- and 10-methyl groups. The strain should be less than in the biphenyl compound, but it was still large enough for Armarego and Turner to be able to prepare the optically active thiol-sulfonate (**37**); the (+)-sodium salt gave the (+)-disulfonyl chloride, which gave the (-)-cyclic thiolsulfonate, $[\alpha]_{5461}^{20} -252^\circ$, while the (-)-salt yielded the (+)-thiolsulfonate, $[\alpha]_{5461}^{20} +253^\circ$. The considerable stability of these isomers was shown by their half-lives, 24 minutes in boiling ethylbenzene and 291 minutes in boiling toluene. Fitts, Siegel, and Mislow¹⁷⁹ have concluded that (+)-**37** has the S-configuration, the (-)-isomer having the R-configuration.

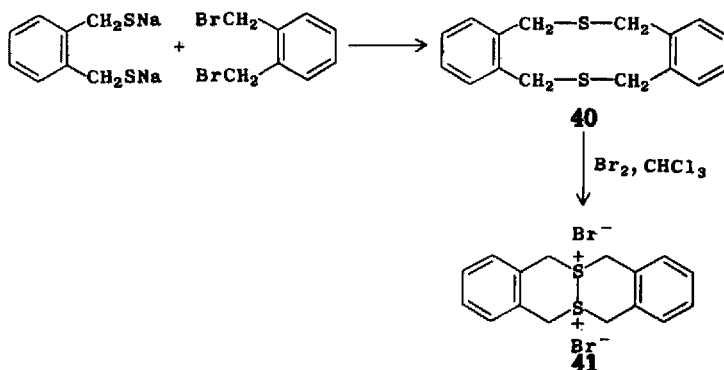
Schönberg, Rupp, and Gumlich⁴³⁶ found that dibenzo[*c, e*]-*o*-dithiin obeys Beer's Law in phenanthrene at 110°. They apparently felt, nonetheless, that it might dissociate into a diradical under these conditions, reasoning by analogy with other disulfides of similar structure.

G. $C_4S_2-C_4S_2-C_6-C_6$ [2, 3]BENZODITHIINO[2, 3-*b*] [2, 3]BENZODITHIIN (39)

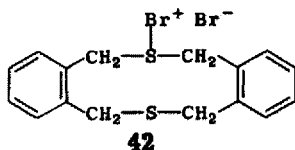


(RRI 5044)

In 1903 Autenrieth and Brüning¹⁸ reported the formation of a ten-membered cyclic disulfide (40) by several syntheses, one being the condensation of *o*-xylylene dimercaptan with *o*-xylylene dibromide. Reaction of this product with excess bromine led to a dibromide (41), m.p. 110-112°, rather than to the expected tetrabromide, and they postulated a ring closure during bromination, written thus in modern terminology:



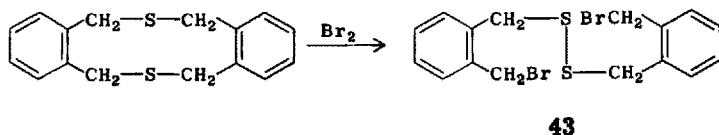
The exact structure of the compound remains obscure; certainly the formulation with two adjacent positively charged sulfur atoms is unreasonable. It has been fairly well demonstrated that halogen adducts of sulfides have the structure $(R_2SX)^+ X^-$,⁵⁴ where *X* is Cl or Br, and it might be reasonable to postulate that the compound is actually the simple bromine adduct (42).



However, the properties of the compound are not in accord with those expected for a bromine adduct. The compound was soluble in benzene,

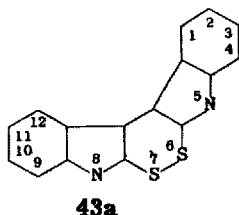
C₄S₂ Ring Systems

acetone, and chloroform, but insoluble in water and alcohol; and bromine was not liberated with hot dilute caustic. A molecular weight determination showed it to be still dimeric, and the possibility of ring bromination was eliminated by showing that it oxidized to the same disulfone as that formed by oxidation of the parent compound. A possible explanation, still unsatisfactory but perhaps better than the formulations above, is that bromine cleaved the ring to give **43**.

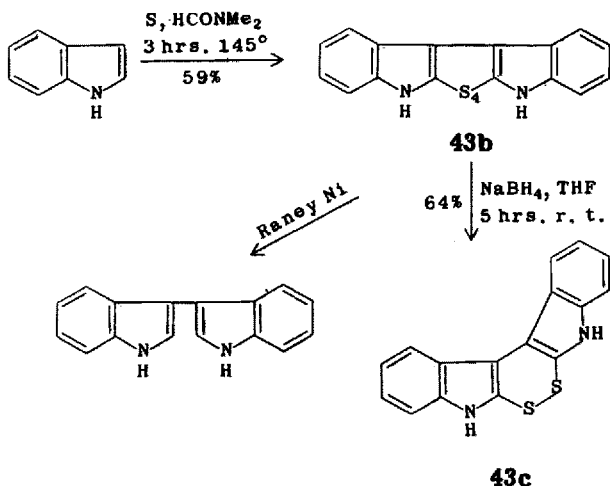


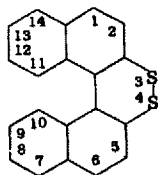
H. C₄N-C₄N-C₄S₂-C₆-C₆ *o*-DITHIINO-[3, 4-*b*: 6, 5-*b'*]-DIINDOLE

(43a)



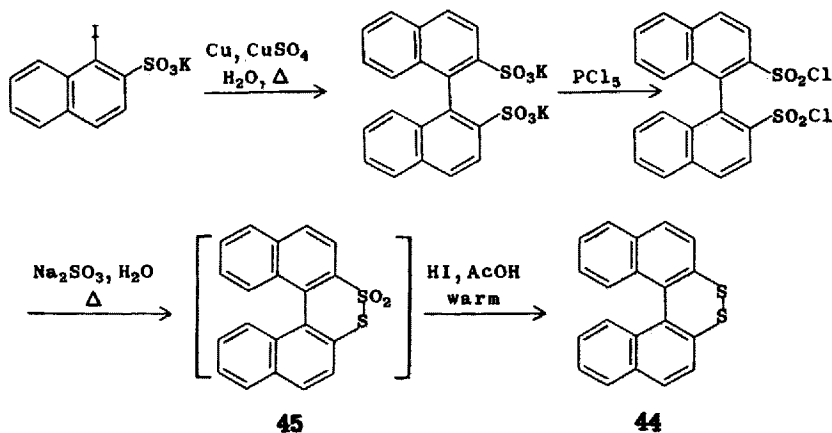
Carpenter, Grant, and Snyder^{93a} formulated the product formed by heating indole with sulfur as 3, 3'-diindolyl-2, 2'-tetrasulfide (**43b**) on the basis of Raney nickel desulfurization to 3, 3'-diindolyl and sodium borohydride reduction to a disulfide, m.p. 205-208°, which they formulated as 5, 8-dihydro-*o*-dithiino[3, 4-*b*: 6, 5-*b'*]diindole (**43c**) and called 3, 3'-diindolyl-2, 2'-disulfide.



I. $C_4S_2-C_6-C_6-C_6-C_6$ 1. Dinaphtho[2,1-*c*:1',2'-*e*]-*o*-dithiin (44)**44**

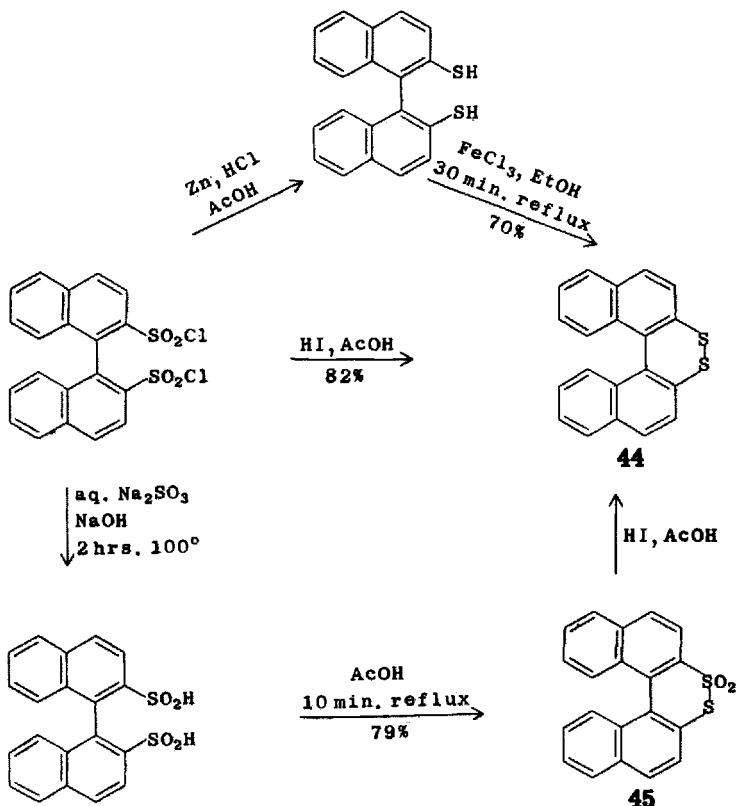
(RRI 6254)

44, isolated as yellow needles melting at 214° , was first prepared by Barber and Smiles³² by a procedure similar to that used for the preparation of dibenzo[*c, e*]-*o*-dithiin (section I F). Barber and Smiles called it 1, 1'-dinaphthalene-2, 2'-disulfide.



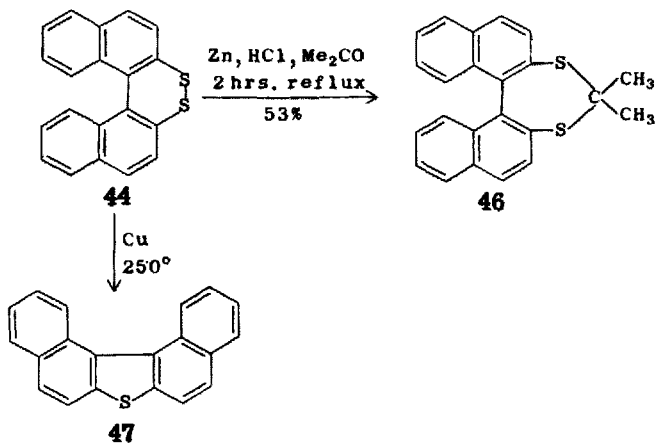
Here, too Armarego and Turner⁹ found that heating the phenyl ester of 1-iodonaphthalene-2-sulfonic acid with copper was superior to the Barber and Smiles procedure for preparing the disulfonic acid. The thiol-sulfonate (**45**), prepared by Barber and Smiles from the disulfonyl chloride and aqueous sulfite but not isolated, was shown by Armarego and Turner to be the disulfonic acid; refluxing in acetic acid converted it smoothly into the 3, 3-dioxide (**45**), m.p. $198-199^\circ$, which could be reduced to **44**. Alternatively, the disulfonyl chloride could be reduced to a dimercaptan, oxidation of which yielded the disulfide (**44**).

C₄S₂ Ring Systems

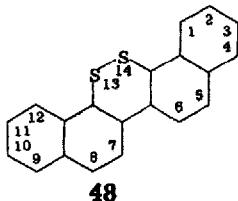


By resolving the disulfonic acid Armarego and Turner were able to prepare optically active **44**, m.p. 262-263°, and **45**, m.p. 162°. Both compounds showed very high optical stability. Fitts, Siegel, and Mislow¹⁷⁹ have concluded that (+)-**44** and -**45** both have the S-configuration, the (-)-isomers having the R-configuration.

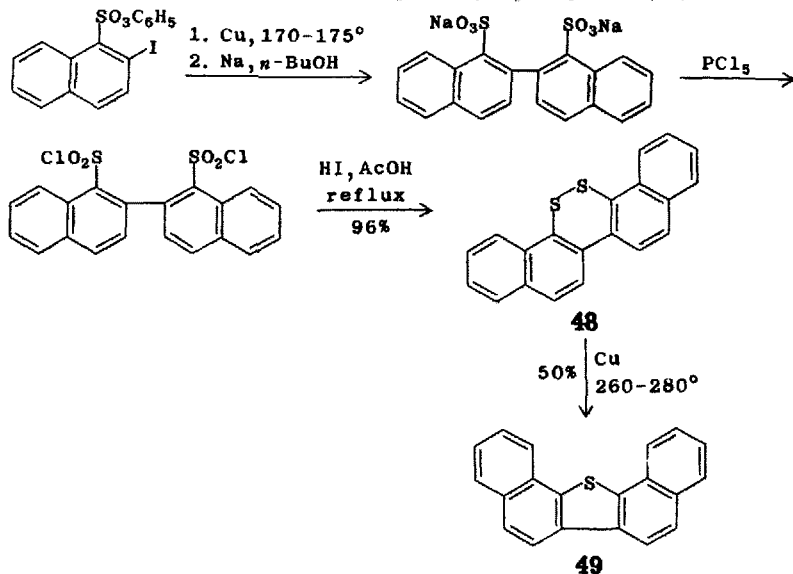
Armarego and Turner reduced the disulfide (**44**) in the presence of acetone and isolated the isopropylidene derivative, 4,4-dimethyldinaphtho[2,1-b:1',2'-a] [1,3] dithiepine (**46**). Barber and Smiles³² desulfurized **44** with copper and isolated dinaphtho[2,1:1',2']thiophene (**47**); the structure was assigned by analogy with other sulfur eliminations and appears reasonable in view of the fact that rearrangements have not been observed in this reaction.⁷⁻⁹



2. Dinaphtho[1,2-c:2',1'-e] [1,2]dithiin (**48**)

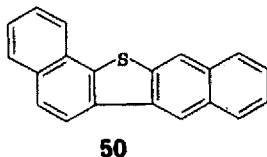


Dinaphtho[1,2-c:2',1'-e] [1,2]dithiin (**48**), m.p. $195.5-196^\circ$, was prepared by Armarego¹⁰ from phenyl 2-iodo-1-naphthalenesulfonate. Heating **48** with copper yielded dinaphtho[1,2:2',1']thiophene (**49**).



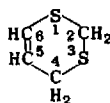
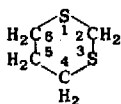
C₄S₂ Ring Systems

The structure of **49** was proved by showing its non-identity with dinaphtho[1,2,2',3']thiophene (**50**), prepared by an unequivocal synthesis.



II. 1,3-DITHIA COMPOUNDS

A. C₄S₂ *m*-DITHIANE (**51**) and *m*-DITHIIN (**52**)



(RRI 266)

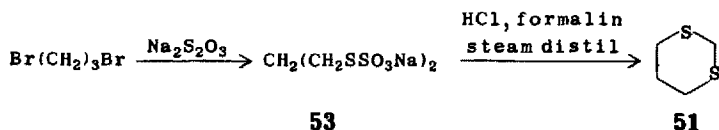
m-Dithiane is indexed as such in Chemical Abstracts. Many authors prefer the name 1,3-dithiane, and some use 1,3-dithiacyclohexane. In the older literature the term tetramethylene 1,3-disulfide is sometimes found. Since a large proportion of compounds of this type are the result of a reaction between an aldehyde or ketone and 1,3-dimercaptopropane, they are frequently named after the carbonyl compound; *e.g.*, acetaldehyde trimethylenemercaptol or acetone trimethylenethioketal. *m*-Dithiin is represented by only a few compounds.

1. *m*-Dithiane

a. Preparation

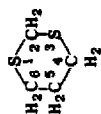
The preparations of the *m*-dithianes closely parallel those of the 1,3-dithiolanes (Chapter 5, section II A-1a). The compounds reported in the literature, other than spiro compounds, are listed in Table 3.

m-Dithiane itself was first prepared by Autenrieth and Wolff¹⁶ by the reaction of 1,3-dimercaptopropane with aqueous formaldehyde in the presence of hydrochloric acid. The yield was poor because of the water present, and the compound was oxidized to *m*-dithiane 1,1,3,3-tetroxide without being isolated. Campaigne and Schaefer⁸⁹ used the same synthesis, but they were able to isolate *m*-dithiane as a crystalline solid, m.p. 54°. Gibson²¹⁴ prepared *m*-dithiane from the bis(Bunte) salt (**53**) and formaldehyde; he was the first to obtain it crystalline.



[For references, see pp. 1252-1271.]

TABLE 3. 1, 3-Dithiane Derivatives



Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
None		54				89, 214
	47	53.3	207-208	760		356
	40		60-62	12		334
1, 1, 3, 3-Tetroxide	100	> 300 (dec.)				16
		287				101
	100	330				214
		307-308				356
2-CH ₃ -			79-80	8-10		16
			66	5		89
2-CH ₃ - 1, 1, 3, 3-tetroxide	100	261-262				16
		264				89
2-C ₂ H ₅ -			85	5		89
2-C ₂ H ₅ - 1, 1, 3, 3-tetroxide	100	209				16, 89
2- <i>n</i> -C ₃ H ₇ -						89
2- <i>n</i> -C ₃ H ₇ - 1, 1, 3, 3-tetroxide		205				89
2-C ₆ H ₅ -		70-71	94	5		16, 89
	99	70.5-72				93
2-C ₆ H ₅ - 1, 1, 3, 3-tetroxide	100	264-265				16, 89

C ₄ H ₈ O ₂ Ring Systems		
2-(3, 4-Methylenedioxyphenyl)-	269-270	93
2-HO ₂ C-	88-89	399
5-HO ₂ C-	115-116	101
4-[-(CH ₂) ₄ CO ₂ H]	146-148	293-296
	70	75
	69	322
	13	75
4-[-(CH ₂) ₄ CO ₂ H] 1, 1, 3, 3-tetroxide	97-98. 5	322
4-[-(CH ₂) ₄ CONH ₂]	166. 2-167. 2	323
2-[HOCH ₂ (CHOH) ₃ -]	131-132	322
2-[HOCH ₂ (CHOH) ₄ -]	150	from Arabinose
2-[2-(1, 3-Dithianyl)-]	130	from Glucose
2-[-CH ₂ -2-(1, 3-Dithianyl 1, 1, 3, 3-tetroxide)]	140-141	
2-(C ₆ H ₅ COCH=)	> 300	310
2-(NCCH=)	52-53	303
2-[HO ₂ CC(CN)=]	32	304
2-[C ₂ H ₅ O ₂ CC(CN)=]	215 (dec.)	304
5-[(CN) ₂ C=]	92	304
5-(O=)	179-180. 5	275
	83	273, 275
	60	347a
	103. 5-104. 5	334
5-(O=) 1, 3-dioxide		275
5-(O=) · H ₂ O 1, 1, 3, 3-tetroxide	260-265 (dec.)	275
5-[H ₂ NCONHN=]	196. 5-198 (dec.)	334
	198 (dec.)	347a

TABLE 3. 1, 3-Dithiane derivatives (contd)

Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
5-(H ₂ NCSNHN=)		168-169				334
5-(C ₆ H ₅ NHN=)		148 (dec.)				347a
5-(HON=)		161-162				334
	69	166-167				275
5-NH ₂	60-70	77-78				334
	52	78-79				275
5-NH ₂ · HCl		202				334
5-OH	60	64	108-110	0.4		334
5-C ₆ H ₅ NHCO ₂ -		168-169				334
5-Br	70-75		76-78	0.3	n _D ²⁰ 1.8307	334
2-(S=)	> 60					361
	76	78			Yellow	423a
	80	80				449a
2-(C ₆ H ₅ NHN=)		76				83
		36				423a
2-(o-CH ₃ O ₂ CC ₆ H ₄ NHN=)		139-140				361
2-(o-HO ₂ CC ₆ H ₄ NHN=)		212				361
2-[(CH ₃) ₂ N=] ⁺ C ₇ H ₇ SO ₃ ⁻	35	136-138				305
2-[C ₂ H ₅) ₂ N=] ⁺ ClO ₄ ⁻	64-69	125.5-127				305
2-[(C ₂ H ₅) ₂ N=] ⁺ (C ₆ H ₅) ₄ B ⁻		184				305

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2-[(n-C ₃ H ₇) ₂ N=] ⁺ ClO ₄ ⁻	53	153-155			305
2-[(C ₆ H ₅ CH ₂) ₂ N=] ⁺ ClO ₄ ⁻	36	134			305
2-( ⁺ ClO ₄ ⁻)	26	142.5-144.5			305
2,2-(CH ₃) ₂			79-81	8-10	16
			65	5	89
	58			<i>d</i> ¹⁸ 1.12	355
2,2-(CH ₃) ₂ 1,1,3,3-tetroxide		246			16, 89
		245			310
	79	246-248			355
5,5-(CH ₃) ₂ 1,1,3,3-tetroxide		201			24
2-CH ₃ -2-C ₂ H ₅ -			92	5	89
	51			<i>d</i> ¹⁸ 1.07	355
	16			<i>n</i> _D ²⁵ 1.5415	135
2-CH ₃ -2-C ₂ H ₅ - 1,1,3,3-tetroxide		204-205			89
	57	204			255
2,2-(C ₂ H ₅) ₂			85	5	89
2,2-(C ₂ H ₅) ₂ 1,1,3,3-tetroxide		200-201			89
		209			310
2-CH ₃ -2- <i>n</i> -C ₃ H ₇ -			95	5	89
2-CH ₃ -2- <i>n</i> -C ₃ H ₇ - 1,1,3,3-tetroxide	100	202-204			16
		208-209			89
2-CH ₃ -2-C ₆ H ₅ CH ₂ - 1,1,3,3-tetroxide		158			16
2-CH ₃ -2-C ₆ H ₅ -			147	5	89

TABLE 3. 1, 3-Dithiane Derivatives (contd)

Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
2-CH ₃ -2-C ₆ H ₅ -1, 1, 3, 3-tetroxide	100	260				16
		229-230				89
2, 2-(C ₆ H ₅) ₂		110				16, 89
2, 2-(C ₆ H ₅) ₂ 1, 1, 3, 3-tetroxide	100	256-257				16
		260				89
5, 5-(<i>p</i> -HOC ₆ H ₄) ₂		109				275
2-CH ₃ -2-(-CH ₂ CO ₂ C ₂ H ₅) 1, 1, 3, 3-tetroxide		157				16
2-CH ₃ -4-[-(CH ₂) ₄ CO ₂ H]	42.5	89-90				75
	35	84-87				322
2-CH ₃ -4-[-(CH ₂) ₄ CO ₂ H] 1, 1, 3, 3-tetroxide	80.4	176.5-177.5			Dimorphic	75
		180-181				
2-CH ₃ -4-[-(CH ₂) ₄ CO ₂ C ₂ H ₅]	54		124-133	0.08		322
2-C ₆ H ₅ -4-[-(CH ₂) ₄ CO ₂ H]	56		175-195	0.6		322
2-C ₆ H ₅ -2-C ₆ H ₅ CO-		99-100				101
2-C ₆ H ₅ -5-OH	100	142-143				469
	87	115				393
	22	141-142			two isomers	1
	56	103-104				
2-C ₆ H ₅ -5-C ₆ H ₅ CO ₂ -	100	111-113			mixt. of isomers	1a
5-CH ₃ -5-OH	90	46	115	12.		334

2-CH ₃ -5-(O=)	39. 5-40	334	
2-CH ₃ -5-(H ₂ NCONHN=)	206-207 (dec.)	334	
2-CH ₃ -5-(H ₂ NCSNHN=)	183-184 (dec.)	334	
2-CH ₃ -2-Br 1, 1, 3, 3-tetroxide	208-210	17	
2-C ₆ H ₅ -2-Br 1, 1, 3, 3-tetroxide	233 (dec.)	16	
2-C ₆ H ₅ -5-Br	86 65-67	393	
2-C ₆ H ₅ -5-SO ₃ H S-benzylthiouronium salt	99-100	393	
2, 2-Br ₂ 1, 1, 3, 3-tetroxide	288	16, 101	
2-(S=)-5-CH ₃ -	50 74	361	Yellow
2-(C ₆ H ₅ NHN=)-5-CH ₃ -	42 89	361	
2-(o-CH ₃ O ₂ CC ₆ H ₄ NHN=)-5-CH ₃ -	64 91. 5-93	361	
2-(o-HO ₂ CC ₆ H ₄ NHN=)-5-CH ₃ -	100 202	361	Canary Yellow
2-(o-HO ₂ CC ₆ H ₄ NHN=) -5-CH ₃ - quinine salt	52-55 184-185	361	
(+)-2-(o-HO ₂ CC ₆ H ₄ NHN=)-5-CH ₃ -	199	361	[α] _D ²⁰ + 12. 3°
2-(o-ClC ₆ H ₄)-5-(O=)	92 140-140. 5	273, 275	
4-(CH ₃ O ₂ C-)-5-(O=)	55	347a	
4-(C ₂ H ₅ O ₂ C-)-5-(O=)	61 62-64	273, 275	
	62	96	
	82 54	334	109-112 0. 2
4-(C ₂ H ₅ O ₂ C-)-5-(O=) Cu complex	139-140	334	
4-(C ₂ H ₅ O ₂ C-)-5-(NH=)	47 122-123. 5	275	
4-(C ₂ H ₅ O ₂ C-)-5-[(NC) ₂ C=]	195-197	275	
4-(CH ₃ O ₂ C-)-5-(H ₂ NCONHN=)	167 (dec.)	347a	
4-(CH ₃ O ₂ C-)-5-(o-H ₂ NC ₆ H ₄ N=)	114	347a	

C₄₀ Ring Systems

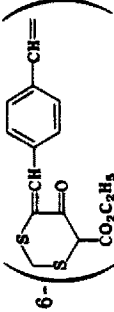
TABLE 3. 1, 3-Dithiane Derivatives (contd)

Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
4-(CH ₃ O ₂ C-)-5-(o-CH ₃ CONHC ₆ H ₄ N=)		186				347a
4-(CH ₃ O ₂ C-)-5-[2, 4-(NO ₂) ₂ C ₆ H ₃ NHN=]		181				347a
4-(C ₂ H ₅ O ₂ C-)-5-[2, 4-(NO ₂) ₂ C ₆ H ₃ NHN=]		147				96
2-(3-CH ₃ O-4-HOC ₆ H ₃ -)-5, 5-(CH ₃ -) ₂		170-171				24
2-(2-Furyl)-5, 5-(CH ₃ -) ₂		62-63.5				24
2-CH ₃ -5, 5-(HOCH ₂ -) ₂	95	122-124				24
2-CH ₃ -5, 5-(HOCH ₂ -) ₂ 1, 1, 3, 3-tetroxide		216-219				24
2-C ₆ H ₅ -5, 5-(HOCH ₂ -) ₂	100	209-211				24
2-C ₆ H ₅ -5, 5-(CH ₃ CO ₂ CH ₂ -) ₂		134-136				24
2-(3-CH ₃ O-4-HOC ₆ H ₃ -)-5, 5-(HOCH ₂ -) ₂	89	186.5-188				24
2, 2-(CH ₃ -) ₂ -4-[-(CH ₂) ₄ CO ₂ H]	63	58.5-59.5	160-161	0.05		75
	70		151-152	0.1		322
2, 2-(CH ₃ -) ₂ -4-[-(CH ₂) ₄ CO ₂ H] 1, 1, 3, 3-tetroxide	89	138.5-140.5				75
2, 2-(C ₆ H ₅ -)-4-[-(CH ₂) ₄ CO ₂ H]					Nondistillable Oil	322
4-(C ₂ H ₅ O ₂ C-)-5, 5-(C ₆ H ₅ S-) ₂					Oil	272
2, 2-(CH ₃ -) ₂ -5-OH	35		117-118	11	n _D ²⁰ 1.5635	1
2, 2-(CH ₃ -) ₂ -5-OH 1, 1, 3, 3-tetroxide	75	258-260				1
2, 2-(CH ₃ -) ₂ -5-C ₆ H ₅ CO ₂ -	20	85-87				1a
2-C ₆ H ₅ -5-CH ₃ -5-OH	20	145-146				1

2, 2-(CH ₃) ₂ -5-(O=)	75	57. 5-59	0. 5	n _D ²⁵ 1. 5540	273, 275
2, 2-(CH ₃) ₂ -5-(H ₂ NCONHN=)	10	106-108	12		334
2, 2-(CH ₃) ₂ -5-(H ₂ NCSNHN=)		196. 5-197. 5 (dec.)			334
2-CH ₃ -4-(C ₂ H ₅ O ₂ C-)-5-(O=)	77-80	177-178			334
2-(o-ClC ₆ H ₄ -)-4-(C ₂ H ₅ O ₂ C-)-5-(O=)	55	48-49	0. 3		334
2-[(C ₂ H ₅ O ₂ C) ₂ C=]-4-(C ₂ H ₅ O ₂ C-)-5-(O=)		87	220-260		272, 273, 275
2-CH ₃ -2-C ₆ H ₅ -5-SO ₃ H S-benzythiuronium salt	150		15		304
5-(O=)-4, 6-(C ₆ H ₅ CH=) ₂	78	147-148. 5		Yellow	274, 275
5-(O=)-4, 6-(p-ClC ₆ H ₄ CH=) ₂	73	234-235			275
5-(O=)-4, 6-[p-(CH ₃) ₂ NC ₆ H ₄ CH=] ₂	43	252-255		Red	274, 275
5-(O=)-4, 6-[p-(CH ₃) ₂ NC ₆ H ₄ CH=CH-CH=] ₂	76	198-200		Black	274
5-(O=)-4, 6-[p-(NCCH ₂ CH ₂) ₂ NC ₆ H ₄ CH=] ₂	44	206-207		Red	274, 275
5-(O=)-4, 6-(2-furyl-CH=) ₂	76	149-150. 5		Gold	274, 275
5-(O=)-4, 6-(1-naphthyl-CH=) ₂	71	153. 5-155		Orange-yellow	274, 275
4-(C ₂ H ₅ O ₂ C-)-5-(O=)-6-(C ₆ H ₅ CH=)	80	70-71		Yellow	274, 275
4-(C ₂ H ₅ O ₂ C-)-5-(O=)-6-(p-ClC ₆ H ₄ CH=)	44	115. 8-117			275
4-(C ₂ H ₅ O ₂ C-)-5-(O=)-6-[p-(CH ₃) ₂ NC ₆ H ₄ CH=]	10	132-133		Red	274, 275
4-(C ₂ H ₅ O ₂ C-)-5-(O=)-6-[p-(CH ₃) ₂ NC ₆ H ₄ CH=CH-CH=]	59	152-153			274, 275
4-(C ₂ H ₅ O ₂ C-)-5-(O=)-6-[p-(NCCH ₂ CH ₂) ₂ NC ₆ H ₄ CH=]	46	159-160. 5		Yellow-orange	274, 275
4-(C ₂ H ₅ O ₂ C-)-5-(O=)-6-(3, 4-Cl ₂ C ₆ H ₃ CH=)	44	133-134. 5			275
4-(C ₂ H ₅ O ₂ C-)-5-(O=)-					

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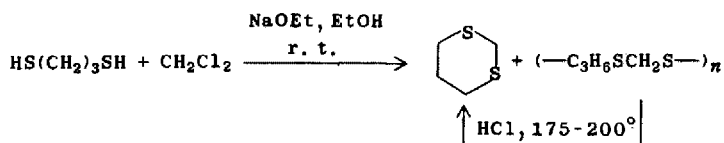
TABLE 3. 1, 3-Dithiane Derivatives (contd)

Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
	64	180-181				274
2, 2, 5, 5-(CH ₃) ₄		57.5-58.5				24
2, 2, 5, 5-(CH ₃) ₄ 1, 1, 3, 3-tetroxide	100	263.5-264.5				24
2-C ₆ H ₅ -2, 5, 5-(CH ₃) ₃		59-60				24
2, 2-(C ₆ H ₅) ₂ -5, 5-(CH ₃) ₂		89.5-90.5				24
2, 2-(CH ₃) ₂ -5, 5-(HOCH ₂) ₂	92	199.5-200.5				24
	62	198-200				51
2, 2-(CH ₃) ₂ -5, 5-(CH ₃ CO ₂ CH ₂) ₂		71-72				51
2, 2-(CH ₃) ₂ -5, 5-(CH ₃ SO ₃ CH ₂) ₂		123-125				51
2-CH ₃ -2-C ₆ H ₅ -5, 5-(HOCH ₂) ₂	90	164-165				24
2-CH ₃ -2-C ₆ H ₅ -5, 5-(HOCH ₂) ₂ 1, 1, 3, 3-tetroxide	85	ca. 290 (dec.)				24
2, 2-(C ₆ H ₅) ₂ -5, 5-(HOCH ₂) ₂	52	169-170				24
2, 5-(CH ₃ CO-) ₂ -2, 5-(C ₂ H ₅ O ₂ C-) ₂			100-110	14		72
2, 2-(CH ₃) ₂ -4-(C ₂ H ₅ O ₂ C-)-5-(O=)	80		128-130	1.5		334
2-(<i>o</i> -ClC ₆ H ₄)-4-(C ₂ H ₅ O ₂ C-)-5-(O=)-6-[<i>p</i> -(CH ₃) ₂ NC ₆ H ₄ CH=]	50	155-157				275
2, 2-(CH ₃) ₂ -5-(O=)-4, 6-[<i>p</i> -(CH ₃) ₂ NC ₆ H ₄ CH=] ₂	45	225-227				275

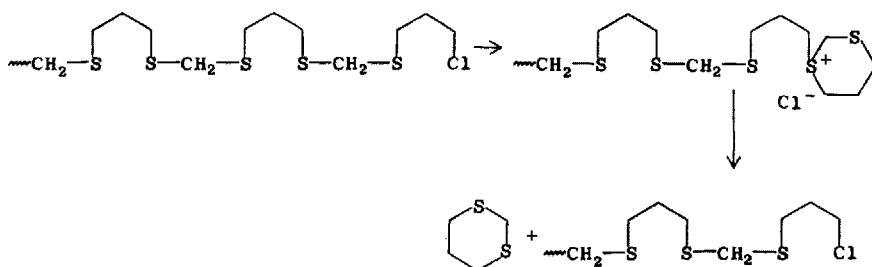
Furostane derivatives (see Table 4)

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Meadow and Reid³⁵⁶ were the only ones to report a yield in the synthesis of *m*-dithiane. Treatment of a mixture of 1,3-dimercaptopropane and methylene chloride with alcoholic sodium ethoxide gave a 15% yield of *m*-dithiane and a large amount of polymer. Heating the polymer in a current of dry hydrogen chloride gave an additional 32% of *m*-dithiane.

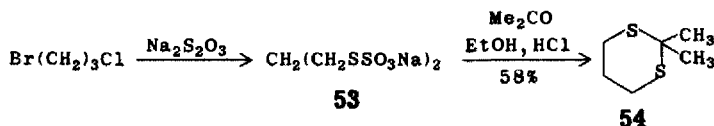


According to these authors the polymer did not cyclize in the absence of halogen, indicating a ring closure such as the following:



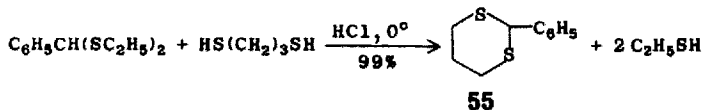
Autenrieth and Wolff¹⁶ and Campaigne and Schaefer⁸⁹ prepared a number of 2-alkyl- and 2-aryl-*m*-dithianes by the now standard procedure of passing dry hydrogen chloride into a mixture of 1,3-dimercaptopropane and carbonyl compound, generally in the cold. Condensations have been carried out with a variety of aliphatic aldehydes and ketones, benzaldehyde, acetophenone, benzophenone, acetoacetic ester, and the like. Yields are generally good, especially with aromatic aldehydes, where self-condensation is not a problem. Lawrence³²³ obtained crystalline derivatives from glucose and arabinose, while galactose and xylose yielded syrups. The use of *p*-toluenesulfonic acid in refluxing benzene has been suggested.³⁹⁹

Several other syntheses have been reported. Mazover³⁵⁵ used a modification of Gibson's Bunte salt procedure to prepare 2,2-dimethyl-*m*-dithiane (54) from acetone and 2-methyl-2-ethyl-*m*-dithiane from methyl ethyl ketone.



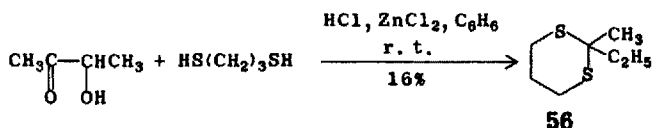
However, he reported the compounds to be non-distillable, even *in vacuo*, so they must have been quite impure. Campos and Hauptmann⁹³ prepared 2-phenyl-*m*-dithiane (55) by an exchange reaction between benzaldehyde diethylmercaptal and 1,3-dimercaptopropane.

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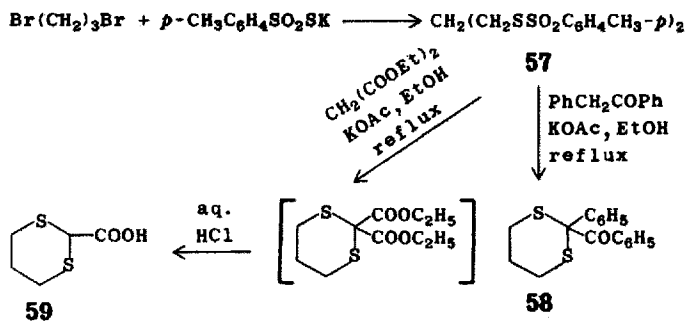
Benzaldehyde dibenzylmercaptan and bis(thiophenyl)mercaptan also exchanged, although in somewhat lower yield, showing the considerable tendency for ring formation. This was also indicated by the fact that 2-phenyl-*m*-dithiane would not exchange with ethyl mercaptan, benzyl mercaptan, or thiophenol.

Cram and Cordon¹³⁵ discovered that acyloins react with 1,3-dimercaptopropane to form *m*-dithianes, acetoin yielding 2-methyl-2-ethyl-*m*-dithiane (56).



This reaction is discussed in greater detail in the section on spiro compounds (section II A-2).

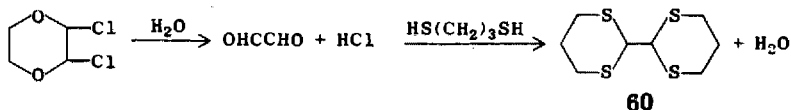
Chivers and Smiles¹⁰¹ prepared several *m*-dithianes from 1, 3-propanebis(toluenethiolsulfonate) (57), desoxybenzoin yielding 2-phenyl-2-benzoyl-*m*-dithiane (58) and diethyl malonate *m*-dithiane-2-carboxylic acid (59) after hydrolysis and decarboxylation.



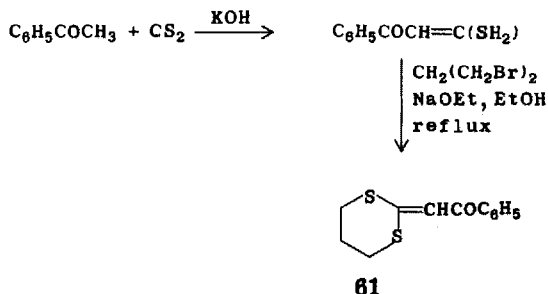
The reactions undoubtedly take place because of the active hydrogens on the methylene groups, *p*-toluenesulfinic acid being eliminated.

Proštenik and Balenović⁴⁰⁰ treated 1, 3-dimercaptopropane with 2, 3-dichlorodioxane in hot benzene. Two structures for the product are possible, 2, 2'-bis(*m*-dithiane) (60) or a condensed tetrathio compound with two seven-membered rings. Inasmuch as it has been proved that 1, 2-dimercaptoethane yields 2, 2'-bis(1, 3-dithiolane) and not the condensed compound (see Chapter 5, section II A-1a), it is reasonable to assume that the reaction product here is 2, 2'-bis(*m*-dithiane) (60); the reaction is probably initiated by a trace of water.

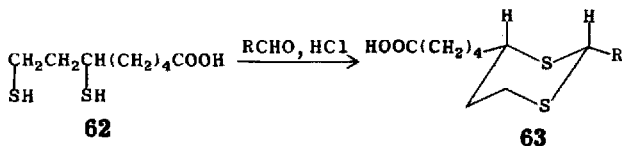
C₄S₂ Ring Systems



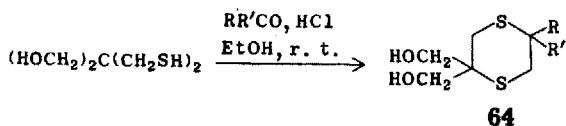
Kelber and Schwarz³⁰³ prepared 2-phenacylidene-*m*-dithiane (**61**) by still another route, which involved the condensation of acetophenone with carbon disulfide followed by reaction with 1, 3-dibromopropane.



A number of 1, 3-dimercaptans other than 1, 3-dimercaptopropane have been converted into substituted *m*-dithianes by reaction with aldehydes or ketones. Thus, Latham, Todd, and Wayne³²² and Brockman and Fabio⁷⁵ reduced α -lipoic acid to 6, 8-dimercaptooctanoic acid (**62**) (see Chapter 5, section I A-1b) and reacted it with formaldehyde, acetaldehyde, acetone, benzaldehyde, and benzophenone. Two isomers are possible with acetaldehyde and with benzaldehyde, but only one was reported. However, yields were rather low, and two isomers may have been formed. It is reasonable to assume that the most stable isomer would be *cis* (**63**), since this would allow the two substituents to be equatorial.

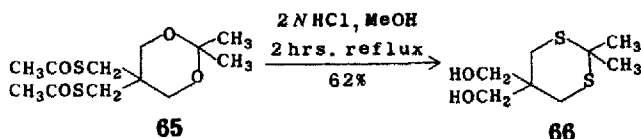


Baker and Tamsma²⁴ prepared a number of substituted 5, 5-dimethanol (**66**) but by a different route. 2, 2-Dimethyl-5, 5-bis(acetylthio)- and ketones with 2, 2-dimethyl-1, 3-dimercaptopropane and with 2, 2-dimercaptomethyl-1, 3-propanediol. Formation of spiro derivatives was avoided in the latter instance by carrying out the reactions at room temperature.



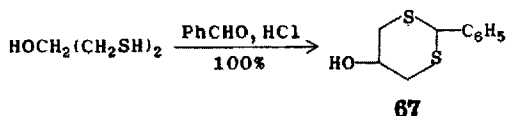
Bladon and Owen⁵¹ also prepared 2, 2-dimethyl-*m*-dithiane-5, 5-di-methanol (**66**) but by a different route. 2, 2-Dimethyl-5, 5-bis(acetylthio)-

methyl)-*m*-dioxane (65), on treatment with methanolic hydrogen chloride, rearranged to the *m*-dithiane derivative, either by hydrolysis to the free dimercapto-glycol or perhaps *via* the formation of a *m*-oxathiane. The inference is that a *m*-dithiane ring is more stable to acid than a *m*-dioxane ring.



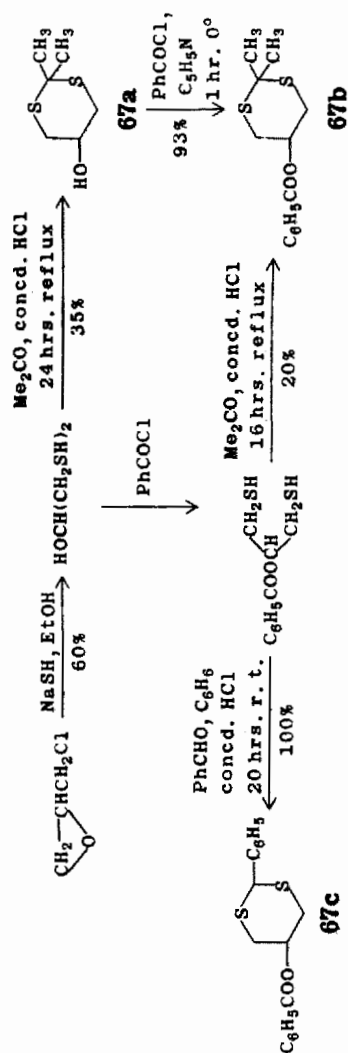
Bladon and Owen reported that methanolic potassium hydroxide also yielded 66, but Fitt and Owen¹⁷⁸ showed subsequently that 66 was formed because the reaction mixture had been made acid during the work-up.

Stocken⁴⁶⁹ obtained 2-phenyl-5-*m*-dithianol (67) from 1,3-dimercapto-2-hydroxypropane and benzaldehyde. Here, too, two isomers are possible, but Stocken obtained only one isomer, and that in quantitative yield. It is interesting that the *m*-dithiane ring was formed to the exclusion of the 1,3-oxathiolane ring.



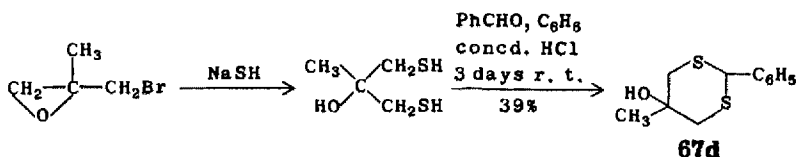
It is rather strange that Adams, Doyle, and co-workers,¹ using only a slight modification of Stocken's conditions, isolated both isomers of 67, with Stocken's isomer as the minor product. The geometry of the two isomers is not known. Petrun'kin and Lysenko³⁹³ also prepared 67; apparently they obtained a mixture of the two isomers.

Adams, Doyle, and co-workers,¹ used the formation of 67 and of other *m*-dithianes to prove that epihalohydrins open the epoxide ring normally with sodium hydrosulfide. Thus, the reaction product from epichlorohydrin and sodium hydrosulfide reacted with acetone to give 2,2-dimethyl-5-*m*-dithianol (67a), different from the known 2,2-dimethyl-1,3-dithiolane-4-methanol (see Chapter 5, section II A-1a). Therefore, the dimercaptan is 1,3-dimercapto-2-propanol and not 2,3-dimercapto-1-propanol. The corresponding benzoate (67b) was prepared both by esterifying 67a and by the reaction of 1,3-dimercapto-2-propyl benzoate with acetone. Reaction of the latter with benzaldehyde gave an inseparable mixture of *cis*- and *trans*-2-phenyl-5-*m*-dithianyl benzoate (67c).^{1a}

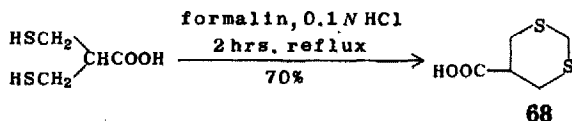


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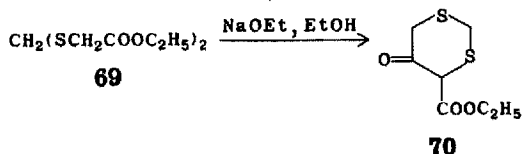
Similarly, 1, 3-dimercapto-2-methyl-2-propanol, prepared from the epibromohydrin, yielded 2-phenyl-5-methyl-5-*m*-dithianol (**67d**), only one isomer of which was isolated pure.



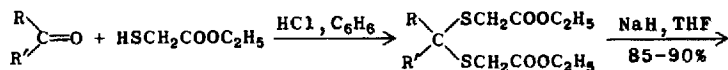
Jansen²⁹³⁻²⁹⁶ prepared *m*-dithiane-5-carboxylic acid (**68**) from 2, 2'-dimercaptoisobutyric acid and formaldehyde; the dimercaptan was isolated from asparagus.



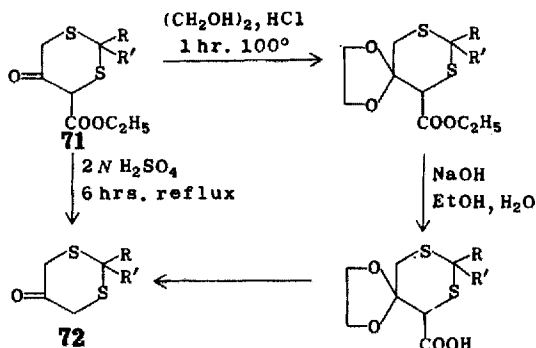
Challenger and Miller⁹⁶ applied the Dieckmann cyclization to the synthesis of *m*-dithianes. Treatment of diethyl 3, 5-dithiapimelate (**69**) with sodium ethoxide yielded ethyl 5-oxo-*m*-dithiane-4-carboxylate (**70**).



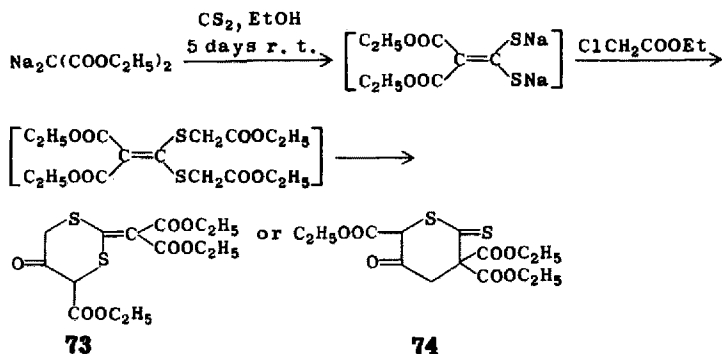
Martani^{347a} prepared the corresponding methyl ester by the same procedure. This reaction was extended by Howard and Lindsey^{272,273,275} and by Lüttringhaus and Prinzbach³³⁴ to the synthesis of a number of 2-substituted analogs (**71**), the substituted pimelates being readily available from the condensation of aldehydes or ketones with ethyl mercaptoacetate. Lüttringhaus and Prinzbach found that the cyclization to form **70** and **71** was best carried out with sodium hydride in tetrahydrofuran. Howard and Lindsey²⁷⁵ found that **70** could be isolated in two forms, a liquid and a solid. Infrared and proton magnetic resonance spectra showed that the liquid is the keto form and the solid the enol form. The acid strength of **70** is surprisingly high; it has a pK_A value of 9.2, comparable to phenol, while 2-carbethoxycyclohexanone is too weak to be measured under the same conditions. Lüttringhaus and Prinzbach, as well as Martani, succeeded in hydrolyzing and decarboxylating **70** and **71** to the 5-ketone (**72**), although some decomposition took place. A better synthesis of **72** is that of Howard and Lindsey, who protected the carbonyl group by dioxolane formation. By this means they obtained an 83% yield of *m*-dithian-5-one (**72**, $\text{R} = \text{R}' = \text{H}$) from **70**.



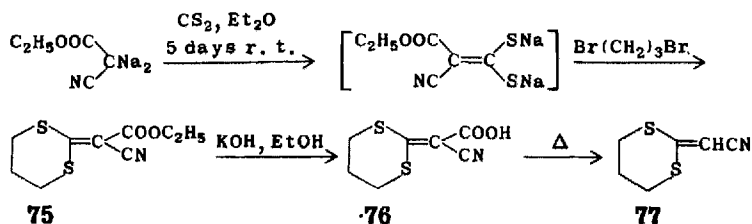
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Kendall and Edwards³⁰⁴ carried out what also appears to be a Dieckmann cyclization to form presumably ethyl 2-dicarbethoxymethylene-5-oxo-*m*-dithiane-4-carboxylate (**73**). The structure of the compound was not proved, however, and an alternative structure, triethyl 5,6-dihydro-5-oxo-2-thioxo-1,2*H*-thiapyran-3,3,6(4*H*)-tricarboxylate (**74**), was considered.

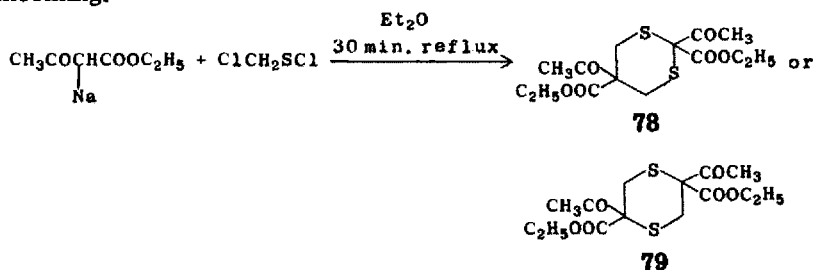


Kendall and Edwards used still another synthesis for a more unequivocal preparation of *m*-dithiane derivatives. Reaction of cyanoacetic ester with carbon disulfide, followed by alkylation with 1,3-dibromopropane, yielded ethyl Δ^2 , α -*m*-dithiane-2-cyanoacetate (**75**). Hydrolysis gave the corresponding acid (**76**), which was decarboxylated to 2-cyano-methylene-*m*-dithiane (**77**).

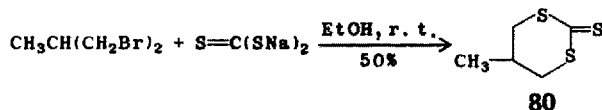


Brintzinger and Schmah⁷² condensed sodioacetoacetic ester with chloromethylsulfenyl chloride and isolated a compound which they formulated as either diethyl 2,5-diacetyl-*m*-dithiane-2,5-dicarboxylate

(78) or the corresponding *p*-isomer (79). No structure proof has been forthcoming.

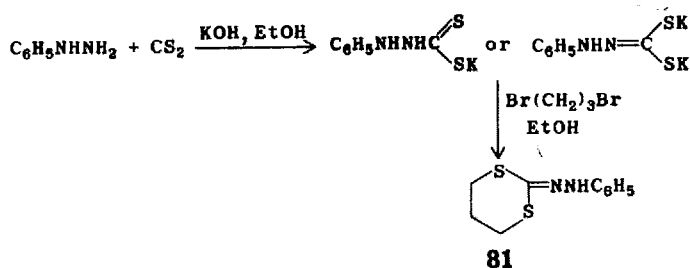


Very few cyclic esters of trithiocarbonic acid containing six-membered rings are known, in contrast to the considerable body of literature available on five-membered ring compounds (see Chapter 5, section II A-5). Mills and Saunders³⁶¹ prepared *m*-dithiane-2-thione and 5-methyl-*m*-dithiane-2-thione (80) from sodium trithiocarbonate and the corresponding 1,3-dibromopropanes. Runge and co-workers^{423a} prepared the former in 76% yield by the same procedure.



Iqbal and Owen^{287a} were unsuccessful in their attempts to prepare *m*-dithiane-2-thione from either oxetane or thietane and xanthate, the reaction used so successfully for the preparation of 1,3-dithiolane-2-thiones. The failure is undoubtedly attributable to the greater stability of the four-membered heterocyclic ring as compared to the three.

Busch and Lingenbrink⁸³ had previously prepared *m*-dithiane-2-phenylhydrazone (81) from 1, 3-dibromopropane and the potassium salt of phenylhydrazinedithiocarbonic acid.

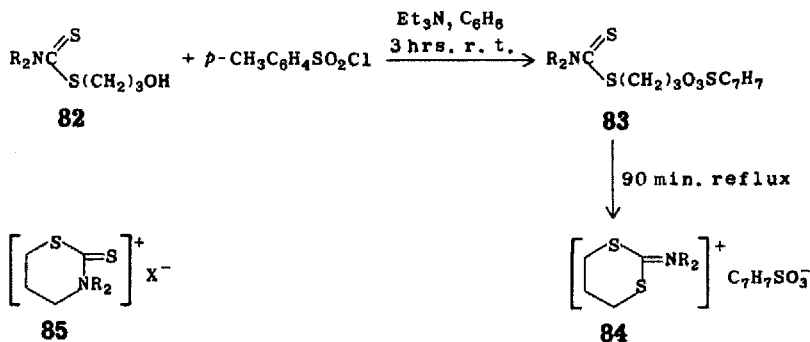


The structural assignment is reasonable in view of the fact that the reaction product with 1,2-dibromoethane was shown to be 1,3-dithiolane-2-phenylhydrazine (see Chapter 5, section A-5a). However, Runge and co-workers^{423a} obtained a compound with a different melting point from *m*-dithiane-2-thione and phenylhydrazine. Although

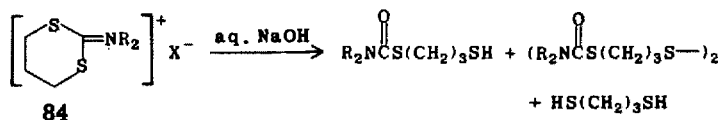
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they did not analyze their derivative, a number of trithiocarbonates reacted in the same manner, and it is difficult to believe that *m*-dithiane-2-phenylhydrazone was not formed. This question remains to be resolved.

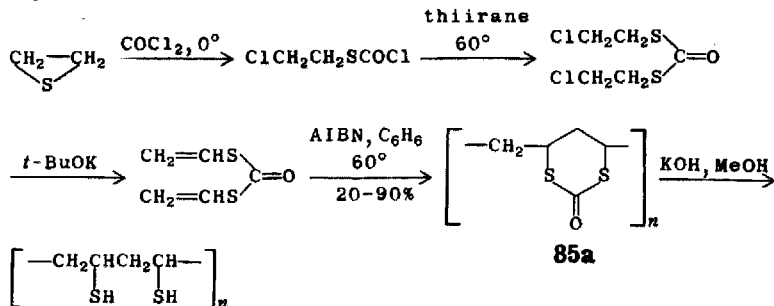
Kennard and VanAllan³⁰⁵ found that 3-hydroxypropyl dialkyldithiocarbamates (**82**) yield tosylates (**83**), which cyclized spontaneously on heating to form *m*-dithiane-2-dialkylimmonium salts (**84**), isolated as tosylates, perchlorates, or tetraphenylboron salts. The reaction could also be effected without isolation of the tosylate.



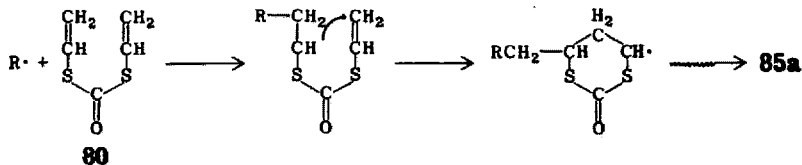
That cyclization proceeded as indicated, and not to form the isomeric compound (**85**), was shown by hydrolysis. None of the dialkyl 3-mercapto-propylamine expected from **85** was formed.



Ringsdorf and Overberger^{416a} polymerized *S, S'*-divinyl dithiocarbonate, prepared from thiirane and phosgene. With azobis(isobutyronitrile) as catalyst, a mixture of soluble and insoluble polymer was formed. By analogy with other intramolecular-intermolecular polymerizations, the soluble polymer was formulated as **85a**; its infrared spectrum showed only a trace of vinyl unsaturation and hydrolysis yielded poly(vinyl mercaptan).

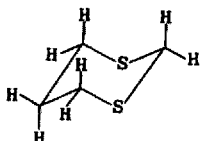


The polymer (85a) is presumably formed in the following manner:



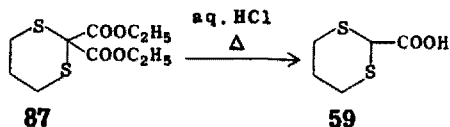
b. Properties and Reactions

Although a crystallographic determination of the structure of a *m*-dithiane derivative has not been reported, there appears to be no good reason for not assuming that the ring is staggered, with the chair form being the more stable configuration, as in **86**.

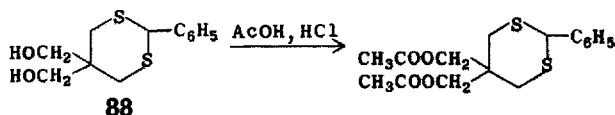


m-Dithianes are generally colorless liquids or solids, distillable *in vacuo*, with not unpleasant odors.¹⁶ Campaigne and Schaefer⁸⁹ have determined the ultraviolet absorption spectra of *m*-dithiane and of a number of 2-alkyl and 2-aryl derivatives. *m*-Dithiane itself and the 2-alkyl derivatives have absorption maxima at about 250 mμ. According to Iqbal and Owen^{287a} *m*-dithiane-2-thione has bands at 1081 and 1033 cm⁻¹. The 1081 cm⁻¹ band is at the same place as the C=S stretching vibration in 1,3-dithiolane-2-thione.

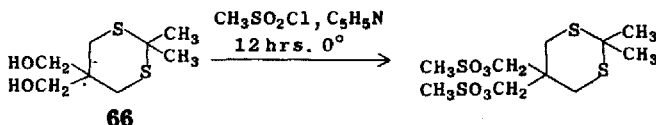
The *m*-dithiane ring is quite stable, both thermally and in the presence of a number of reagents. The fact that Chivers and Smiles¹⁰¹ were able to prepare *m*-dithiane-2-carboxylic acid (**59**) by acid hydrolysis of the 2,2-dicarbethoxy derivative (**87**) indicates the stability of the ring under acidic conditions.



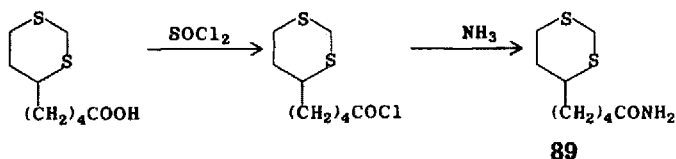
Similarly, the sequence of reactions carried out by Kendall and Edwards³⁰⁴ (see section II A-1a) showed the ring to be stable under alkaline conditions. Backer and Tamsma²⁴ and Bladon and Owen⁵¹ were able to esterify 2-phenyl-*m*-dithiane-5,5-dimethanol (**88**) and 2,2-dimethyl-*m*-dithiane-5,5-dimethanol (**66**) without affecting the ring.



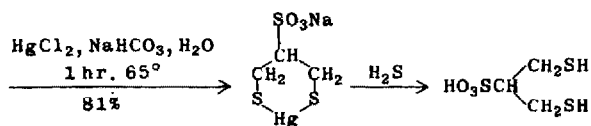
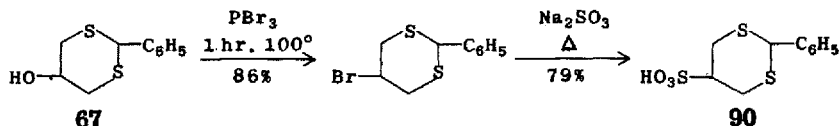
C₄S₂ Ring Systems



Latham, Todd, and Wayne³²² prepared the amide of 5-(*m*-dithian-4-yl)-pentanoic acid (**89**).

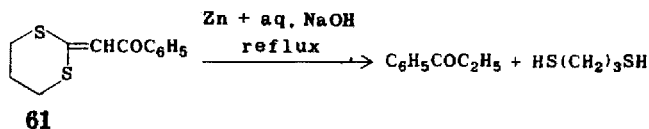


Petrun'kin and Lysenko³⁹³ converted 2-phenyl-5-*m*-dithianol (**67**) into 2-phenyl-*m*-dithiane-5-sulfonic acid (**90**); 2-methyl-2-phenyl-*m*-dithiane-5-sulfonic acid was prepared similarly. From the narrow melting ranges reported for the S-benzylthiuronium salts, it may be inferred that these authors were dealing with one isomer. **90** was cleaved by mercuric chloride to 1, 3-dimercaptopropane-2-sulfonic acid.



According to Chivers and Smiles¹⁰¹ *m*-dithiane-2-carboxylic acid forms an unstable dibromide and diiodide, which decompose to a polymeric sulfide. Runge and co-workers^{423a} reported that *m*-dithiane-2-thione forms an amorphous adduct with three molecules of mercuric chloride.

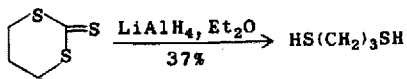
Although no reductions of simple *m*-dithianes have been reported, the reactions would be expected to follow the same course as for 1, 3-dithiolanes (see Chapter 5, section II A-1b). Thus, Kelber and Schwarz³⁰³ reduced 2-phenacylidene-*m*-dithiane (**61**) to propiophenone and 1, 3-dimercaptopropane.



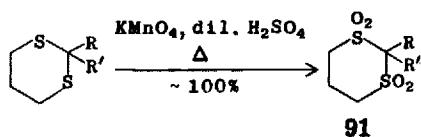
Iqbal and Owen^{287a} reduced *m*-dithiane-2-thione to 1, 3-dimercapto-

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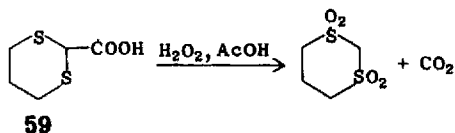
propane with lithium aluminum hydride; the yield was much lower than with 1, 3-dithiolane-2-thione.



A variety of *m*-dithianes have been oxidized to the corresponding disulfones, *m*-dithiane 1, 1, 3, 3-tetroxides (**91**), as shown in Table 3. Yields are excellent with acid permanganate, first utilized by Autenrieth and Wolff,¹⁶ or with hydrogen peroxide in acetic acid.

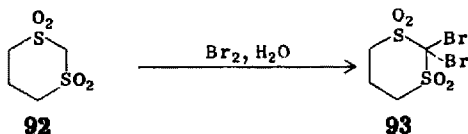


Not unexpectedly, oxidation of *m*-dithiane-2-carboxylic acid (**59**) led to spontaneous elimination of carbon dioxide.¹⁰¹

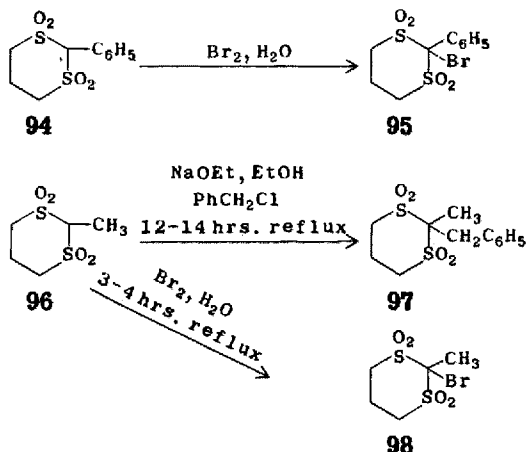


The disulfones are very stable; they can be dissolved in concentrated sulfuric acid and recovered unchanged.¹⁶ According to Stuffer's rule⁴⁷³ the disulfones should also be stable to alkaline hydrolysis, since they do not contain sulfone groups on adjacent carbons. Autenrieth and Wolff¹⁶ claimed that 2-methyl-*m*-dithiane 1, 1, 3, 3-tetroxide (**96**) could be hydrolyzed with aqueous alkali, in contradiction to Stuffer's rule, but they were unable to isolate any discrete products from the hydrolysis. Both Baumann and Walter³⁴ and Kötze³¹⁰ disagreed, and Autenrieth and Wolff's claim is probably in error.

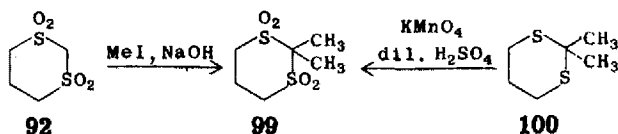
The disulfones are generally high melting, relatively insoluble solids. Autenrieth and Wolff¹⁶ found that the compounds derived from aldehydes could be alkylated, and also brominated. Thus, *m*-dithiane 1, 1, 3, 3-tetroxide (**92**) yielded, presumably, 2, 2-dibromo-*m*-dithiane 1, 1, 3, 3-tetroxide (**93**); 2-phenyl-*m*-dithiane 1, 1, 3, 3-tetroxide (**94**) yielded 2-bromo-2-phenyl-*m*-dithiane 1, 1, 3, 3-tetroxide (**95**); and 2-methyl-*m*-dithiane 1, 1, 3, 3-tetroxide (**96**) could be alkylated to 2-methyl-2-benzyl-*m*-dithiane 1, 1, 3, 3-tetroxide (**97**), or brominated to the 2-bromo derivative (**98**).¹⁷



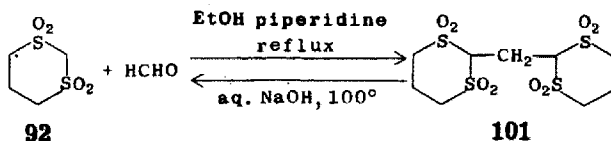
C₄S₂ Ring Systems



Since 2,2-disubstituted-*m*-dithiane 1,1,3,3-tetroxides (**91**) did not show these reactions, there can be little doubt that substitution takes place in the 2-position. This was verified by Kötzt,³¹⁰ who succeeded in alkylating *m*-dithiane 1,1,3,3-tetroxide (**92**) to 2,2-dimethyl-*m*-dithiane 1,1,3,3-tetroxide (**99**), the product being identical with that formed by oxidizing 2,2-dimethyl-*m*-dithiane (**100**) prepared from acetone;¹⁶ the 2,2-diethyl derivative was also synthesized.



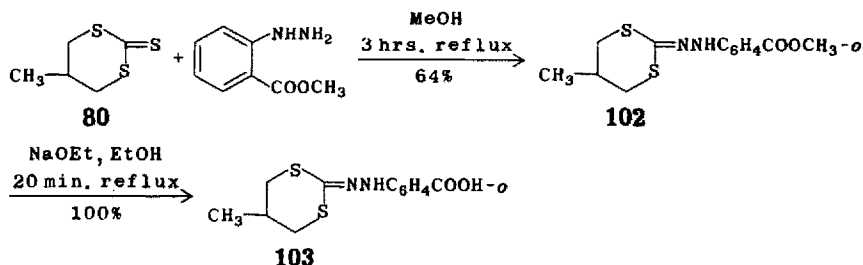
Kötzt also reacted *m*-dithiane 1,1,3,3-tetroxide with formaldehyde, and isolated a product to which he assigned the structure methylenebis(2,2'-*m*-dithiane) 1,1,3,3,1',1',3',3'-octaoxide (**101**); the reaction was reversed by alkaline hydrolysis.



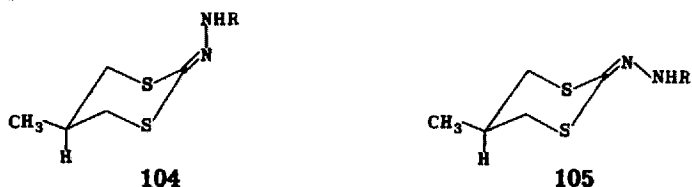
Other aldehydes did not react. Nitrous acid and diazonium salts were without effect on **92**, indicating that the methylene group is relatively unreactive. It is surprising, nevertheless, that Campaigne and Schaefer⁸⁹ found no spectroscopic evidence for the formation of an anion; 2-phenyl-*m*-dithiane 1,1,3,3-tetroxide (**94**) had the same ultraviolet absorption spectrum in 0.01 *M* sodium ethoxide as in pure ethanol.

Mills and Saunders³⁶¹ prepared phenylhydrazones (**102** and **103**) from 5-methyl-*m*-dithiane-2-thione (**80**) in order to prove that the nitrogen valences are not planar.

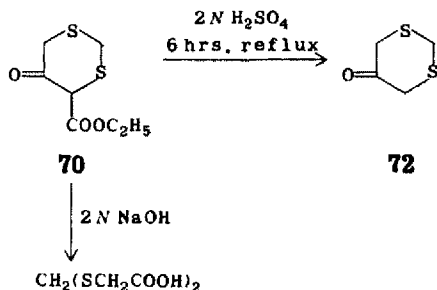
Chapter 12



103 was resolved *via* its quinine salt. The compound was quite stable in neutral organic solvents, but it racemized slowly in hot dilute base and rapidly in hot acetic acid. The two diastereoisomers can be represented by **104** and **105**.



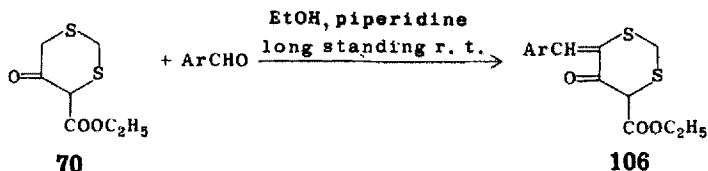
The chemistry of ethyl 5-oxo-*m*-dithiane-4-carboxylate (**70**) and of *m*-dithian-5-one (**72**), as well as 2-substituted derivatives, has recently been investigated by Howard and Lindsey,²⁷²⁻²⁷⁵ by Lüttringhaus and Prinzbach,³³⁴ and by Martani.^{374a} As already mentioned, Lüttringhaus and Prinzbach and Martani prepared **72** by acid hydrolysis of **70**; Lüttringhaus and Prinzbach claimed that relatively little ring cleavage occurred with **70**, although it was extensive with the 2, 2-dimethyl derivative. Challenger and Miller⁹⁶ showed that alkaline hydrolysis of **70** led exclusively to ring cleavage, and it is an interesting question why ketonic cleavage of this β -keto ester is so difficult to effect. Lüttringhaus and Prinzbach felt that the extensive decomposition with ethyl 2, 2-dimethyl-5-oxo-*m*-dithiane-4-carboxylate might be attributable to the axial methyl group adjacent to the bulky sulfur atoms.



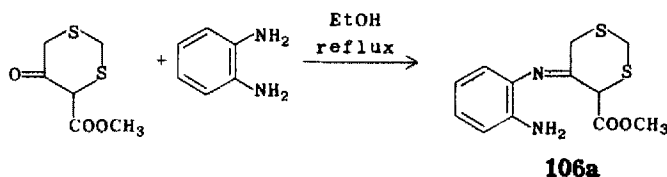
Howard and Lindsey showed, as already described, that excellent yields of **72** could be obtained by blocking the carbonyl group in **70** with ethylene glycol; the chemistry of the resulting 1, 4-dioxa-7, 9-dithiaspiro-[4.5]decanes is described in section II A-2.

C₄S₂ Ring Systems

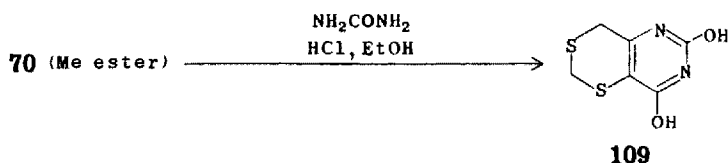
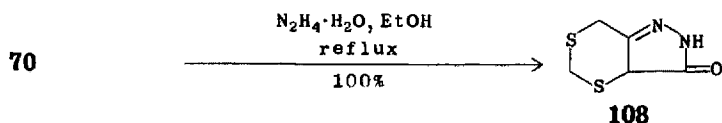
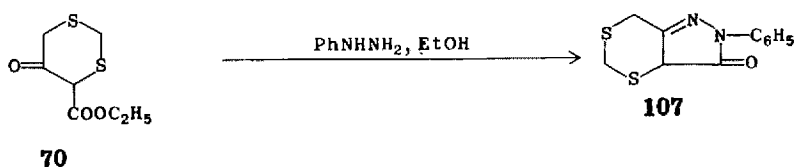
Howard and Lindsey^{274, 275} found that **70** and its 2-substituted derivatives reacted with a variety of predominantly aromatic aldehydes in the presence of piperidine to give colored ethyl 5-oxo-6-benzylidene-*m*-dithiane-4-carboxylate compounds (**106**).



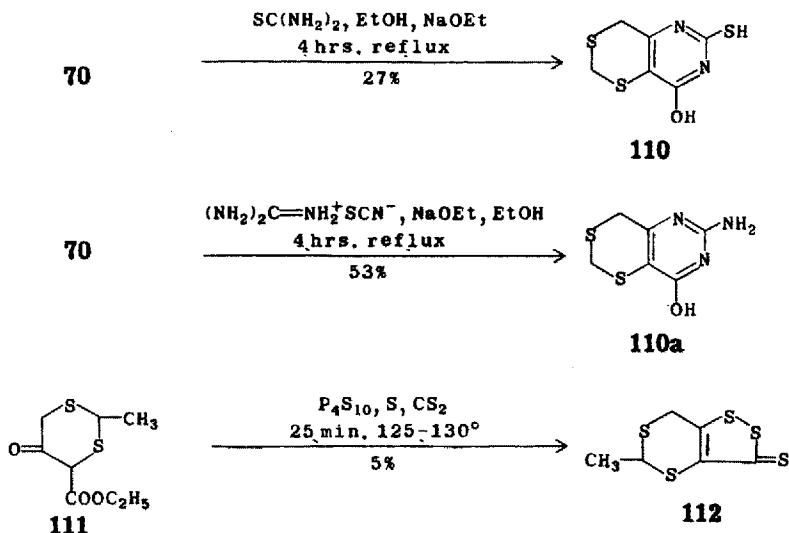
Martani reported the formation of methyl 5-(*o*-aminophenylimino)-*m*-dithiane-4-carboxylate (**106a**) from the methyl ester and *o*-phenylenediamine.



Martani,^{347a} Lüttringhaus and Prinzbach,³³⁴ and Howard and Lindsey²⁷⁵ prepared a number of condensed heterocyclic compounds from **70** or the corresponding methyl ester. Thus, phenylhydrazine and hydrazine gave the expected pyrazolones (**107** and **108**), although Challenger and Miller⁹⁶ and Martani reported the formation of a 2,4-dinitrophenylhydrazone, and Martani reported the formation of a semicarbazone. Urea, thiourea, and guanidine gave pyrimidines (**109**, **110**, **110a**), while phosphorus pentasulfide with ethyl 2-methyl-5-oxo-*m*-dithiane-4-carboxylate (**111**) gave a 1,2-dithiole-3-thione (**112**).

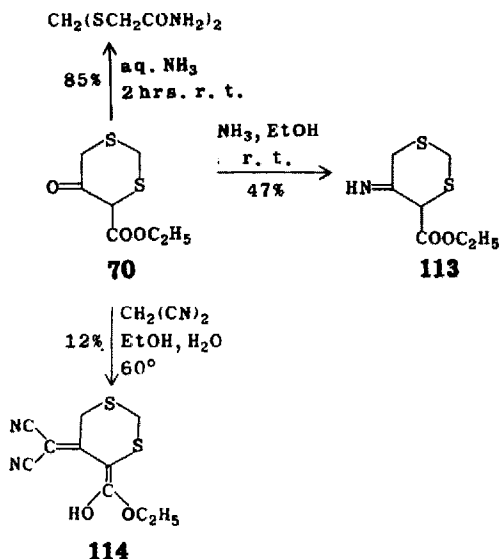


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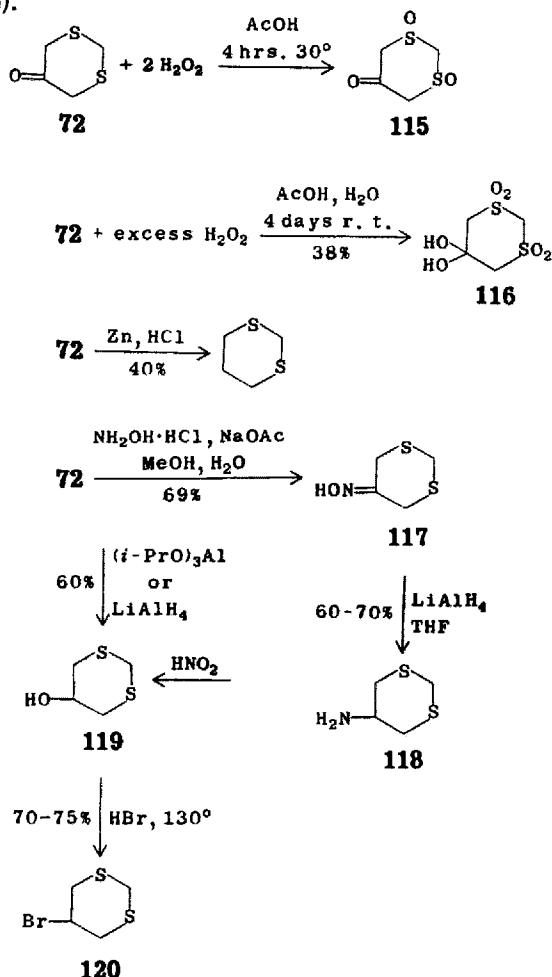
It should be noted that either Martani drew incorrect structures for **107** and **109** or Chemical Abstracts transcribed them incorrectly.

Howard and Lindsey²⁷⁵ found that **70** reacted with anhydrous ammonia to yield ethyl 5-imino-*m*-dithiane-4-carboxylate (**113**), while aqueous ammonia gave 3,5-dithiapimelamide by ring opening, in agreement with Challenger and Miller.⁹⁶ Malononitrile gave ethyl 5-dicyanomethylene-*m*-dithiane-4-carboxylate (**114**), which, because of the absence of carbonyl absorption in the infrared, was considered to exist in the enol form.

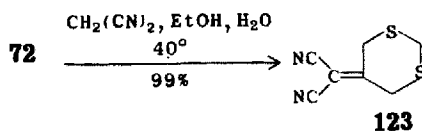
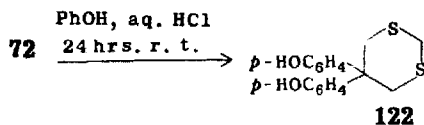
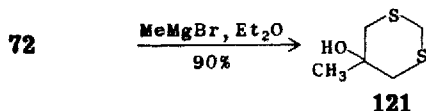


C₄S₂ Ring Systems

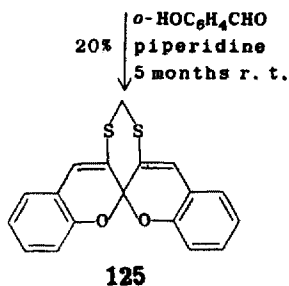
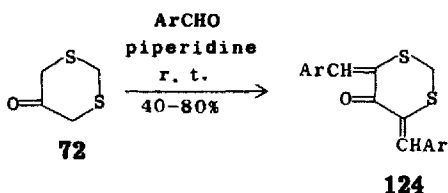
Numerous reactions of *m*-dithian-5-one (**72**) and its 2-substituted derivatives were investigated by Howard and Lindsey^{274,275} and by Lüttringhaus and Prinzbach.³³⁴ Thus, **72** was oxidized to *m*-dithian-5-one 1,3-dioxide (**115**) and 1,1,3,3-tetroxide (**116**) by hydrogen peroxide; **116** was isolated as its hydrate, formulated as a dihydroxy compound because of the very weak carbonyl absorption. Clemmenson reduction of **72** yielded *m*-dithiane. **72** formed an oxime (**117**), which was reduced to *m*-dithian-5-amine (**118**). This in turn with nitrous acid gave *m*-dithian-5-ol (**119**), also prepared by reduction of **72**. Treatment of **119** with hydrogen bromide yielded 5-bromo-*m*-dithiane (**120**). Treatment of **72** with a methyl Grignard gave 5-methyl-*m*-dithian-5-ol (**121**). **72** reacted with phenol in the presence of an acid catalyst to form 5,5-bis(*p*-hydroxyphenyl)-*m*-dithiane (**122**). **72** reacted quantitatively with malononitrile without a catalyst to give 5-dicyanomethylene-*m*-dithiane (**123**).



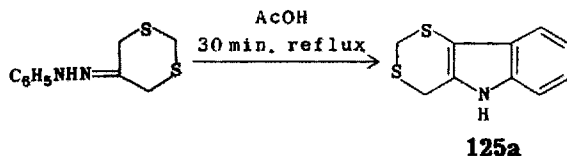
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Howard and Lindsey found, as expected, that **72** reacted with benzaldehyde, and similar aldehydes, to yield colored 4, 6-dibenzylidene derivatives (**124**). Salicylaldehyde, however, gave a product formulated as **125**, because the infrared spectrum showed the absence of both carbonyl and hydroxyl groups.

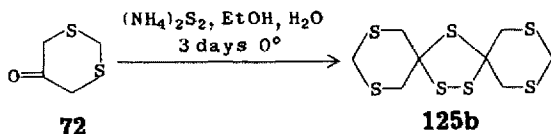


Martani^{347a} applied the Fischer indole synthesis to *m*-dithiane-5-phenylhydrazone to prepare a *m*-dithiaindoindole (**125a**).



C₄S₂ Ring Systems

According to Magnusson³⁴⁰ *m*-dithian-5-one reacts with ammonium polysulfide to form 2, 4, 7, 8, 11, 13, 15-heptathiadispiro [5. 2. 5. 1]penta decane (**125b**), but neither the details of the preparation nor the properties of the compound have been reported.



c. Uses

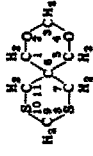
Few uses for *m*-dithiane derivatives have been reported. Hentrich and Grundmann²⁵⁵ patented *m*-dithian-2-one as an insecticide, and Seipold and co-workers^{449a} patented *m*-dithiane-2-thione as a fungicide and insecticide. Prill, Hartzell, and Arthur³⁹⁹ claimed that 2-(3,4-methylenedioxyphenyl)-*m*-dithiane showed some effectiveness against the housefly. Latham, Todd, and Wayne³²² stated that *m*-dithianes derived from 6,8-dimercaptooctanoic acid are useful as antioxidants in vegetable oils, while Salzberg⁴²⁴ patented the same type of compound as corrosion inhibitors for iron in the presence of acid. Howard²⁷³ claimed that certain *m*-dithian-5-ones are useful antioxidants, while the 4,6-dibenzylidene-*m*-dithian-5-ones appear to have some use as dyes.^{274,275} According to Lincoln and Byrkit³²⁸ 2,2-dimethyl-*m*-dithiane is useful as a lubricating oil additive.

2. Spiro Derivatives

There is little basic difference between the chemistry of *m*-dithianes and spiro-*m*-dithianes. The compounds which have been reported are listed in Table 4. Chemical Abstracts indexes the compounds using the usual spiro nomenclature, but here, as with the 1,3-dithiolanes, it is more convenient to name the steroid derivatives as cyclic trimethylene mercaptoles or trimethylenethioketals of the parent compounds.

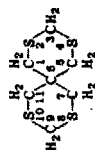
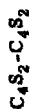
Howard and Lindsey^{272,273,275} prepared ethyl 1,4-dioxo-7,9-dithiaspiro[4.5]decane-6-carboxylate (**126**) by reacting ethyl 5-oxo-*m*-dithiane-4-carboxylate (**70**) with ethylene glycol; blocking the carbonyl group prevented ring cleavage during conversion of **70** to *m*-dithian-5-one (**72**). Alkaline hydrolysis of the ester (**126**) gave the corresponding acid (**127**), which was converted into the amide (**129**) *via* the acid chloride (**128**). Acid hydrolysis of the acid (**127**) gave *m*-dithian-5-one (**72**), while pyrolysis yielded 1,4-dioxo-7,9-dithiaspiro[4.5]decane (**130**), prepared also from the ketone (**72**) and ethylene glycol. **130** was oxidized with hydrogen peroxide to the corresponding disulfone (**131**).

TABLE 4. Spiro *m*-Dithiane Derivatives

Compound	Yield (%)	M.p. (°C)	Other properties	Ref.
$C_3O_2-C_4S_2$				
				
1,4-Dioxo-7,9-dithiaspiro[4.5]decane	94	105-105.5		272, 275
7,7,9,9-Tetroxide		330		275
8- $C_2H_5O_2C$ -	92	59-60		272, 273, 275
8- HO_2C -	90	200-201 (dec.)		272, 273, 275
8-COCl	97	91-91.5		272, 275
8- $CONH_2$		179.5-181		272, 275
8- $C_2H_5O_2C$ -8-(<i>o</i> - ClC_6H_4 -)	55	120-121		272, 273, 275
8- HO_2C -8-(<i>o</i> - ClC_6H_4 -)		190-192 (dec.)		272, 273, 275
8- NaO_2C -8-(<i>o</i> - ClC_6H_4 -)		269-272.5 (dec.)		272, 273, 275
8-(<i>o</i> - ClC_6H_4 -)	37	123-124		272, 275
8- $C_2H_5O_2C$ -8,8-(CH_3 -) ₂	68	76-77		272, 273, 275
8- $C_2H_5O_2C$ -8,8-(CH_3 -) ₂ 7,7,9,9-tetroxide	73	153-154		275
8- HO_2C -8,8-(CH_3 -) ₂	89	114-115		272, 273, 275
8,8-(CH_3 -) ₂	97	76.5-77.5		272, 275
$C_4O_2-C_4S_2$				
				

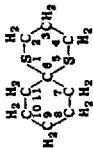
C_4S_2 Ring Systems

2, 4-Dioxo-8, 10-dithiaspiro[5. 5]undecane (RRI 1650)			
3, 9-(C_6H_5) ₂	87	171. 5-173. 5	24
3- C_6H_5 -9- CH_3 -	100	132-133	24
3- C_6H_5 -9- CH_3 - 8, 8, 10, 10-tetroxide	72	226-231	24
3- CH_3 -9- C_6H_5 -	100	156-158	24
3, 3, 9, 9-(CH_3) ₄	30	127-128	24
3, 9-(CH_3) ₂ -3, 9-(C_6H_5) ₂		135-137	24



2, 4, 8, 10-Tetrathiospiro[5. 5]undecane (RRI 1672)			
3, 9-(CH_3) ₂		110	23
3, 9-(CH_3) ₂ -3, 9-(CH_3CO) ₂		164-165. 5	23
3, 9-(2-Furyl) ₂	95	132. 5-133	23
3, 3, 9, 9-(CH_3) ₄	100	192-193	23
3, 3, 9, 9-(CH_3) ₄ 2, 2, 4, 4, 8, 8, 10, 10-octaoxide		>350	23
3, 9-(CH_3) ₂ -3, 9-(C_2H_5) ₂		143-143. 5	23
3, 9-(CH_3) ₂ -3, 9-(C_2H_5) ₂ 2, 2, 4, 4, 8, 8, 10, 10-octaoxide		>300	23
3, 3, 9, 9-(C_2H_5) ₄		118-118. 5	23
3, 9-(CH_3) ₂ -3, 9-(i - C_4H_9) ₂		165-167	23
3, 9-(C_2H_5) ₂ -3, 9-(i - C_4H_9) ₂		177-178	23
3, 9-(C_6H_5) ₂		233-234	23
3, 9-(β - $CH_2C_6H_4$) ₂		244-245	23
3, 9-(3- CH_3O -4-HOC $_6H_3$) ₂		269-271	23
3, 9-(3, 4-Methylenedioxyphenyl) ₂		265-267	23

TABLE 4. Spiro *m*-Dithiane Derivatives (contd)

Compound	Yield (%)	M.p. (°C)	Other properties	Ref.
3, 9-(C ₆ H ₅ CH=CH-) ₂		225-226		23
3, 9-(CH ₃ -) ₂ -3, 9-(C ₆ H ₅ -) ₂		184-185		23
3, 3, 9, 9-(C ₆ H ₅ -) ₄		222-223		23
C ₄ S ₂ -C ₆				
				
1, 5-Dithiaspiro[5. 5]undecane (RRI 1876)	79	40. 5-41. 5	b.p. 148-148. 5° at 17 mm.	253
1, 1, 5, 5-Tetroxide	61			355
10-CH ₃ -7-[(CH ₃) ₂ CH-]	47	200-201		355
	58	41-42	b.p. 152-155° at 3 mm.	253
3, 3-(CH ₃ -) ₂ 1, 1, 5, 5-tetroxide	79	235. 5-237		24
3, 3-(HOCH ₂ -) ₂	100	186. 5-187. 5		24
3, 3-(HOCH ₂ -) ₂ -8-CH ₃ -	100	182		24
3, 3-(HOCH ₂ -) ₂ -8-Cl	100	194-196		24
4-[-(CH ₂) ₄ CO ₂ H]	63. 5	104-106		322
2-C ₂ H ₅ O ₂ C-3-(O=)	80-83		b.p. 130-133° at 4 mm.	334
3-(O=)	80		b.p. 146-147° at 12 mm.	334
3-(H ₂ NCONHN=)		211-212 (dec.)		334

C_4S_2 Ring Systems

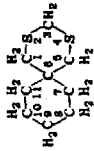
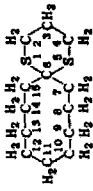
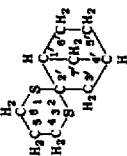
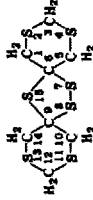
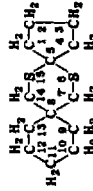
3-($H_2NCSNH=$)				334
				
2, 4-Dithiaspiro[5.5]undecane (RRI 1677)				
3- CH_3 - 2, 2, 4, 4-tetroxide	68	220-221		24
3- C_6H_5 -		162		24
3-(3- CH_3O -4-HOC H_3 -)		191-192		24
3-(2-Furyl)		103		24
3, 3-(CH_3 -) $_2$		76-77		24
3, 3-(CH_3 -) $_2$ 2, 2, 4, 4-tetroxide	94	268, 5-269, 5 (dec.)		24
3- CH_3 -3- C_2H_5 -	95	37-37, 5		24
3, 3-(n - $C_{21}H_{43}$ -) $_2$		83-84		24
3- CH_3 -3- C_6H_5 -	82	293 (dec.)		24
3, 3-(C_6H_5 -) $_2$		125		24
<u>C_4S_2-C_{10}</u>				
				
1, 5-Dithiaspiro[5.9]pentadecane (RRI 1930)	34		n_D^{25} 1. 5640	135
			n_D^{25} 1. 5570	135a

TABLE 4. Spiro *m*-Dithiane Derivative (contd)

Compound	Yield (%)	M.p. (°C)	Other properties	Ref.
<u>C₃-C₃-C₄S₂</u>				
				
Spiro[<i>m</i> -dithiane-2, 2'-norbornane] (RRI 2544)				
<i>anti</i> -7'-Cl	70	81.5-83		418
<i>sym</i> -7'-Cl		54-55.5		418
1', 7', 7'-(CH ₃) ₃ or Spiro [camphane-2, 2'- <i>m</i> -dithiane]	50		b.p. 140-143° at 4 mm.	253
5, 5-(HOCH ₂) ₂ -1', 7', 7'-(CH ₃) ₃ or Spiro[camphane-2, 2'- <i>m</i> -dithiane]-5, 5-dimethanol	100	155-157		24
<u>C₂S₂-C₄S₂-C₄S₂</u>				
				
2, 4, 7, 8, 11, 13, 15-Heptathiadispiro[5.2.5.1]pentadecane				340
<u>C₃-C₄S₂-C₆</u>				
				

C_4S_2 Ring Systems

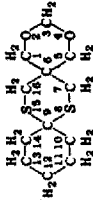
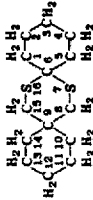
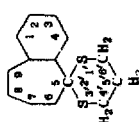
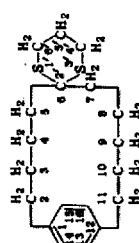
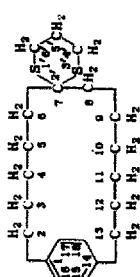
6, 15-Dithiadispiro[4. 2. 5. 2]pentadecane (RRI 3087)					
$C_4O_2-C_4S_2-C_6$	68-68. 5	34			
					
2, 4-Dioxo-8, 15-dithiadispiro[5. 2. 5. 2]hexadecane (RRI 3423)					
3-C ₆ H ₅ -12-CH ₃ -	123-125, 158-160	<i>cis-trans isomers</i>	24		
$C_4S_2-C_6-C_6$					
7, 16-Dithiadispiro[5. 2. 5. 2]hexadecane (RRI 3452)	106-106. 5		24		
					
					
Spiro[m-dithiane-2, 2'(3'H)-naphthalene]					
1', 4', 4'α, 5', 6', 7', 8', 8'αβ-H ₈ -6'β-HO-	45		125		
1', 4', 4'α, 5', 6', 7', 8', 8'αβ-H ₈ -3'-(O=)	78		204a		
1', 4', 4'α, 5', 6', 7', 8', 8'αβ-H ₈ -3'-(O=)-4', 4'-(CH ₃) ₂	70		204a		
<i>cis</i> -H ₈ -6', 6', 8'a-(CH ₃) ₃ -3'-(O=)	44		461a		
					

TABLE 4. Spiro *m*-Dithiane Derivatives (contd)

Compound	Yield (%)	M.p. (°C)	Other properties	Ref.
Spiro[<i>m</i> -dithiane-2, 2'(4' <i>aH</i>)-naphthalene] 3', 4', 7, 8'-H ₄ -4'-a-CH ₃ -5'-CH ₃ CO-	75	119.5-120		373a
<u>C₄S₂-C₆-C₇</u> 				
Spiro[5 <i>H</i> -benzocycloheptene-5, 2'-(<i>m</i>)dithiane] 8, 9-H ₂ -6'(1 <i>H</i>)-(O=)	71	96-97.5		127b
<u>C₄S₂-C₈-C₁₄</u> 				
Spiro[bicyclo[10.2.2]hexadeca-12,14,15-triene-6, 2'- <i>m</i> -dithiane] (RRI 3838)	83	88-89.5		135
<u>C₄S₂-C₆-C₁₆</u> 				

C_4S_2 Ring Systems

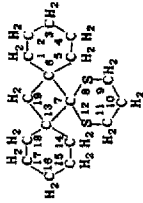
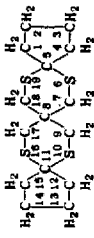
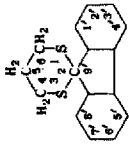
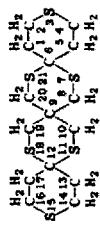
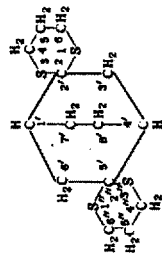
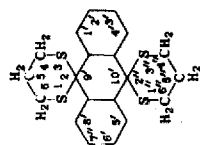
Spiro[bicyclo[12.2.2]octadeca-14,16,17-triene-7,2'- <i>m</i> -dithiane] (RRI 3854)	72	56-59	135
$C_4-C_4S_2-C_6-C_6$			
8,12-Dithiatripiro[5.0.5.0.5.1]nonadecane (RRI 4028)	71	112.5-113	502, 503
19-(O=)			
$C_5-C_5-C_4S_2-C_4S_2$			
6,10,16,19-Tetrathiatripiro[4.2.2.4.2.2]nonadecane (RRI 4317) 6,6,10,10,16,16,19,19-Octaoxide	90	212.5-213 >300	23 23
$C_5-C_4S_2-C_6-C_6$			
Spiro[<i>m</i> -dithiane-2,9'-fluorene] (RRI 4723) 5,5-(CH_3) ₂ 5,5-($HOCH_2$) ₂	64	144.5-145 244-245	24 24

TABLE 4. Spiro *m*-Dithiane Derivatives (contd)

Compound	Yield (%)	M.p. (°C)	Other properties	Ref.
$C_4S_2-C_4S_2-C_3S-C_3S$ 				
3, 7, 11, 15, 21-Hexathiatripiro[5. 2. 2. 5. 2. 2]heneicosane (RRI 5043)		273		23
$C_4S_2-C_4S_2-C_6-C_6$ 				
7, 11, 18, 21-Tetrathiatripiro[5. 2. 5. 2. 2]heneicosane (RRI 5045)		206-207		23
7, 7, 11, 11, 18, 18, 21, 21-Octaoxide		> 300		23
3, 15-(HO ₂ C-) ₂				23
				
Dispiro[<i>m</i> -dithiane-2, 2'-bicyclo[2. 2. 2]octane-5', 2''- <i>m</i> -dithiane] (RRI 5046)				
1', 4'-(C ₂ H ₃ O ₂ C-) ₂	81	119-120		417

C_4S_2 Ring Systems



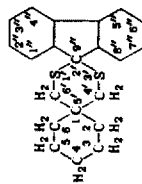
Dispiro[m-dithiane-2,9'(9'H)-anthracene-10'(10'H), 2''-m-dithiane]
1',4',4'aα,5',8',8'aβ,9'aα,10'aβ-H₈

124

306-311

67

$C_5-C_4S_2-C_6-C_6-C_6$



Dispiro[cyclohexane-1,5'-m-dithiane-2',9''-fluorene] (RRI 6011)

24

172-173

90

17β-Acetoxy-3-methoxy-1,3,5(10)-estratrien-16-one cyclic
trimethylene mercaptole

452

158-159

18

3α-Hydroxy-11,12-dioxocholanic acid 12-(cyclic trimethylene
mercaptole)

6

209-212

82

Methyl 3α-Hydroxy-11,12-dioxocholanate 12-(cyclic trimethylene
mercaptole)

5, 6

163-164

$[\alpha]_D^{25} - 30.4^\circ$

Methyl 3α-Formoxy-11,12-dioxocholanate 12-(cyclic trimethylene
mercaptole)

5, 6

172-174

$[\alpha]_D^{25} - 23.9^\circ$

Methyl 3α-Acetoxy-11,12-dioxocholanate 12-(cyclic trimethylene
mercaptole)

5, 6

221-222

$[\alpha]_D^{25} - 22.4^\circ$

Methyl 3α-Carboethoxy-11,12-dioxocholanate 12-(cyclic
trimethylene mercaptole)

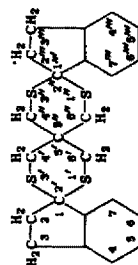
5, 6

161-163, 5

$[\alpha]_D^{25} - 8^\circ$

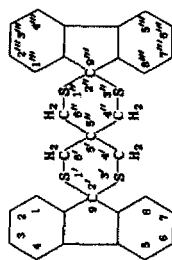
TABLE 4. Spiro π -Dithiane Derivatives (contd)

Compound	Yield (%)	M. p. (°C)	Other properties	Ref.
5 α -Cholestane-2, 3-dione 2-(cyclic trimethylene mercaptole)	60	182-183	$[\alpha]_D + 114^\circ$	49
4 α -Methylcholestane-2, 3-dione 2-(cyclic trimethylene mercaptole)	48	160-161	$[\alpha]_D + 70^\circ$	49
4 β -Methylenecholestane-2, 3-dione 2-(cyclic trimethylene mercaptole)	8	161-162	$[\alpha]_D + 89^\circ$	49
4, 4-Dimethylcholestane-2, 3-dione 2-(cyclic trimethylene mercaptole)	17	128-129	$[\alpha]_D - 16^\circ$	49
4-Cholestene-2, 3-dione 2-(cyclic trimethylene mercaptole)	64	179-180		512
4, 4-Dimethyl-6-cholestene-2, 3-dione 2-(cyclic trimethylene mercaptole)	33	178-179		512
C ₃ -C ₅ -C ₄ S ₂ -C ₆ -C ₆ -C ₆				
2-Oxo-24-demethylcycloeucaleanone 2-(cyclic trimethylene mercaptole)	72		$[\alpha]_D + 160^\circ$	127a
2-Oxo-4-methyl-24-demethylcycloeucaleanone 2-(cyclic trimethylene mercaptole)	22	168-170	$[\alpha]_D + 107^\circ$	127a
C ₅ -C ₅ -C ₄ S ₂ -C ₄ S ₂ -C ₅ -C ₆				
Trispiro[indane-1, 2'- <i>m</i> -dithiane-5', 5''- <i>m</i> -dithiane-2'', 1'''-indane]		258-259		23
C ₄ O-C ₅ -C ₄ S ₂ -C ₆ -C ₆ -C ₆				
3 β -Acetoxy-5 α -furostane 26-(cyclic trimethylene mercaptole)	38	130, 5-132	$[\alpha]_D - 10^\circ$	160
3 β -Acetoxy-5 α -furostane 12, 26-bis(cyclic trimethylene mercaptole)	60	226-227, 5	$[\alpha]_D + 24^\circ$	160

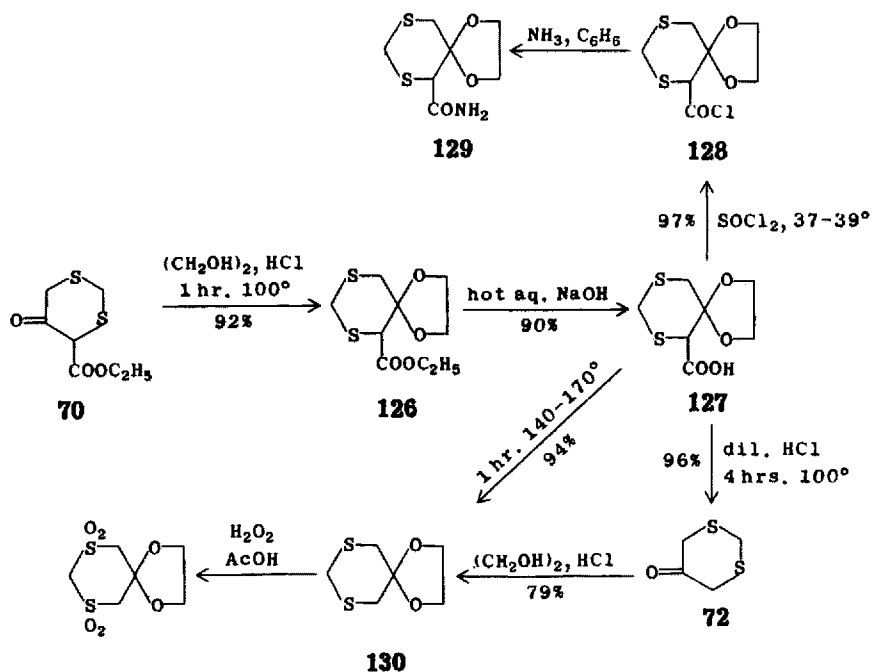


C₄S₂ Ring Systems

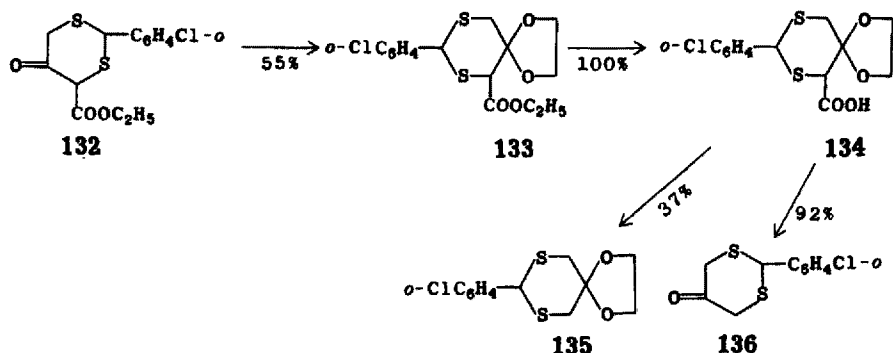
C ₅ -C ₄ S ₂ -C ₄ S ₂ -C ₆ -C ₆ -C ₆				
Cholestane-3, 6-dione 3, 6-bis(cyclic trimethylene mercaptole)	85	180-181	[σ] _D + 80°	177b
C ₅ -C ₄ S ₂ -C ₄ S ₂ -C ₄ S ₂ -C ₆ -C ₆ -C ₆				
Ethyl 3, 7, 12-trioxocholanate 3, 7, 12-tris(cyclic trimethylene mercaptole)	96	208-209		93
C ₅ -C ₅ -C ₄ S ₂ -C ₄ S ₂ -C ₆ -C ₆ -C ₆ -C ₆				
Trispiro[fluorene-9, 2'-m-dithiane-5', 5''-m-dithiane-2'', 9''-fluorene]		>300		23



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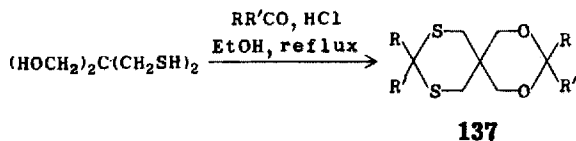
The same sequence was carried out with ethyl 2-(*o*-chlorophenyl)-5-oxo-*m*-dithiane-4-carboxylate (**132**) and with the corresponding 2,2-dimethyl derivative. The β -keto ester (**132**) would not be expected to exist as isolatable stereoisomers, but ethyl 8-(*o*-chlorophenyl)-1,4-dioxo-7,9-dithiaspiro[4.5]decane (**133**) should exist in two isomeric forms. Although Howard and Lindsey²⁷⁵ isolated only one sharp-melting compound, hydrolysis to the corresponding acid (**134**) gave a material with a broad melting range, which the authors attributed to the existence of stereoisomeric forms. It is surprising, however, that the broad melting point persisted in the decarboxylated product, 8-(*o*-chlorophenyl)-1,4-dioxo-7,9-dithiaspiro[4.5]decane (**135**), although not in the hydrolysis product, 2-(*o*-chlorophenyl)-*m*-dithian-5-one (**136**).



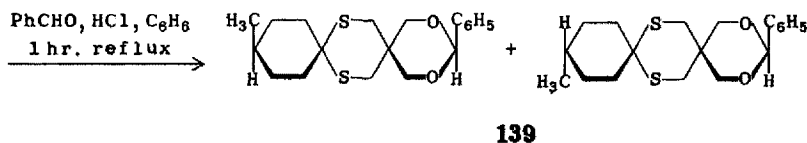
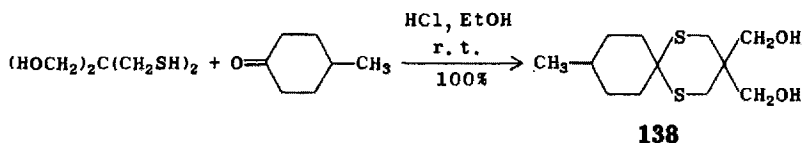
C₄S₂ Ring Systems

The compounds were reported to be useful for inhibiting the development of rancidity in vegetable oils.

Backer and Tamsma²⁴ prepared a number of derivatives of 2,4-dioxo-8,10-dithiaspiro[5.5]undecane (**137**, R = R' = H) in excellent yields by reacting 2,2-bis(mercaptomethyl)-1,3-propanediol with aldehydes and ketones. Dry hydrogen chloride was used as catalyst and the mixtures were heated; as already mentioned, at room temperature only the *m*-dithiane ring was formed.



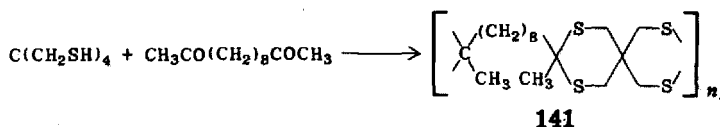
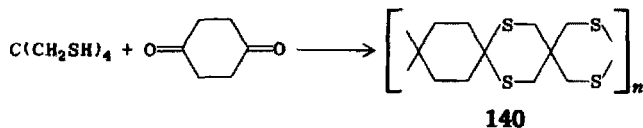
By forming the *m*-dithiane ring first, they were able to prepare mixed compounds. For example, 4-methylcyclohexanone was reacted to give 9-methyl-1,5-dithiaspiro[5.5]undecane-3,3-dimethanol (**138**), which was then reacted with benzaldehyde to form 3-phenyl-12-methyl-2,4-dioxo-8,15-dithiadispiro[5.2.5.2]hexadecane (**139**). The latter was isolated in two forms, presumably *cis-trans* isomers.



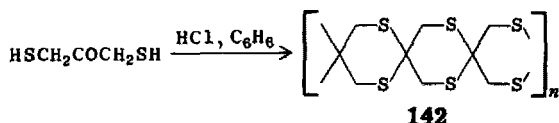
Backer and Evenhuis²³ prepared a variety of spiro compounds from 2,2-bis(mercaptomethyl)-1,3-dimercaptopropane (tetrathio-pentaerythritol) and aldehydes or ketones, and Backer and Tamsma²⁴ used 1,1-bis(mercaptomethyl)cyclohexane and 2,2-dimethyl-1,3-dimercaptopropane, as well as 2,2-bis(mercaptomethyl)-1,3-propanediol described above. The reactions were carried out in excellent yields using hydrogen chloride as the catalyst without solvent, or in ethanol, chloroform, or benzene. Several of the derivatives were oxidized to the corresponding sulfones with hydrogen peroxide in acetic acid. The compounds are listed in Table 4.

2,2-Bis(mercaptomethyl)-1,3-dimercaptopropane can be reacted with diketones to form spiro polymers. Thus, 1,4-cyclohexanedione gave a polymer (**140**) melting at 314-318° but of rather low molecular weight, 613, while 2,11-dodecanedione gave a polymer (**141**) melting at 153-167°. ²⁸⁷

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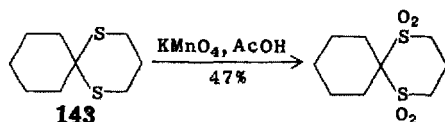
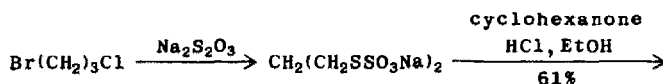


Schotte⁴⁴² prepared what appear to be spiro-polymers (**142**) by a different route, treatment of 1, 3-dimercaptoacetone with acid (see section III A-1j).



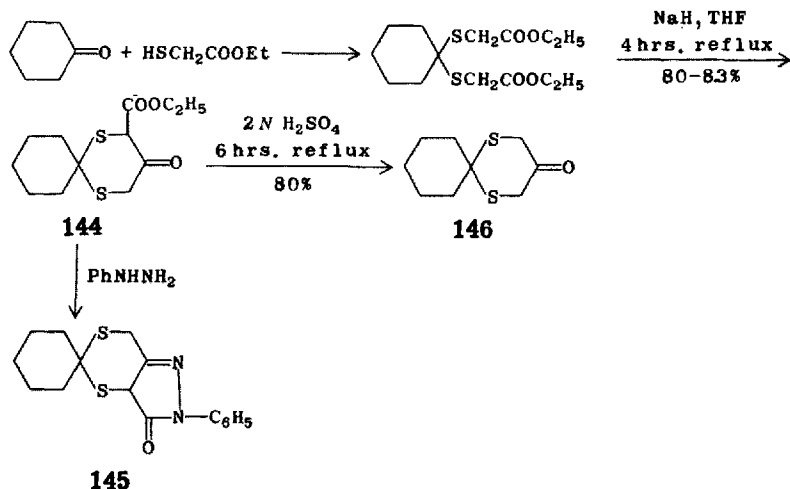
Hauptmann and Campos²⁵³ applied their zinc chloride-sodium sulfate catalyst combination to the formation of spiro compounds from 1, 3-dimercaptopropane and cyclohexanone, menthone, and camphor. The lack of reactivity of camphor with simple mercaptans and the reasons for the difference have already been discussed (see Chapter 5, section II A-4a).

Mazover³⁵⁵ used the Bunte salt procedure to prepare 1, 5-dithiaspiro[5. 5]undecane (**143**), probably impure, which he oxidized to the pure disulfone.

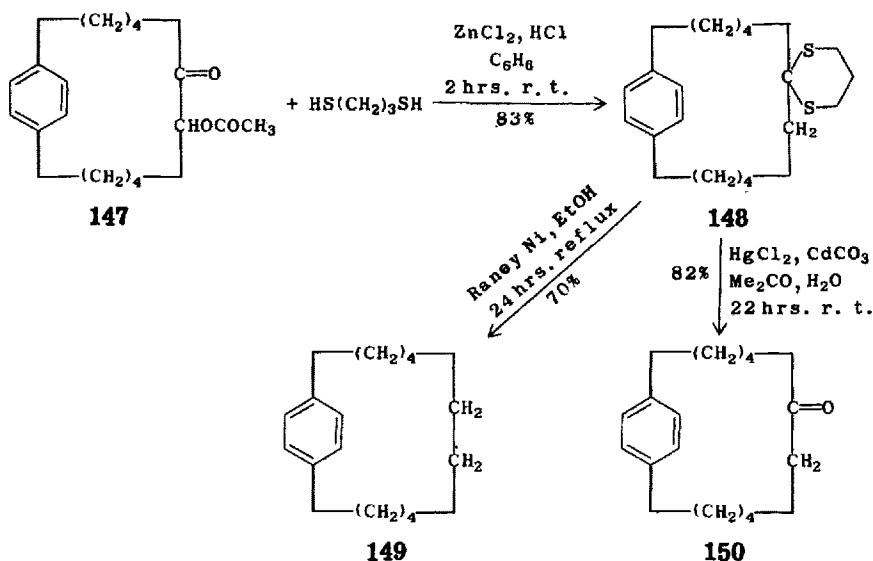


Lüttringhaus and Prinzbach³³⁴ applied the Dieckmann cyclization procedure to the synthesis of ethyl 3-oxo-1, 5-dithiaspiro[5. 5]undecane-2-carboxylate (**144**), starting with cyclohexanone. As with the nonspiro analogs, phenylhydrazine yielded a pyrazolone (**145**) and acid hydrolysis yielded 1, 5-dithiaspiro[5. 5]undecan-3-one (**146**), in this case in excellent yield.

C_4S_2 Ring Systems



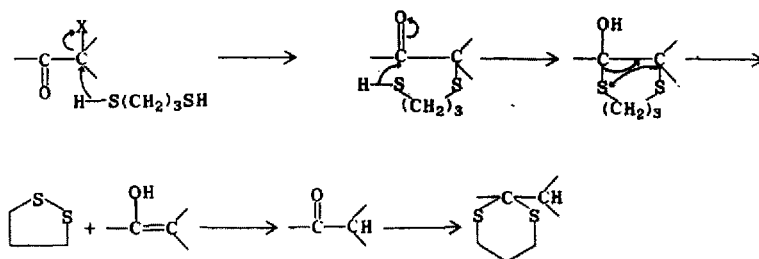
Cram and Cordon¹³⁵ discovered a new synthesis of m -dithianes. Treatment of 5-acetoxy-[10]paracyclophan-6-one (**147**) with 1, 3-dimercaptopropane under acidic conditions led to the formation of spiro[bicyclo[10. 2. 2]hexadeca-12, 14, 15-triene-6, 2'- m -dithiane] (**148**), the acetoxy group being reduced during the reaction. Raney nickel desulfurization gave the saturated [10]paracyclophane (**149**), while cleavage with mercuric chloride and cadmium carbonate gave [10]paracyclophan-5-one (**150**).



The acyloin itself gave slightly lower yields. The generality of the reaction was shown by its application to the [12]paracyclophane, to se-

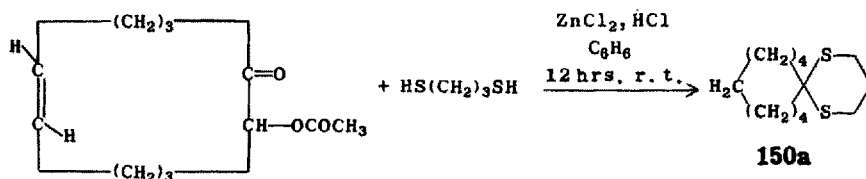
Chapter 12

bacoin acetate, and to acetoin, although there is an example in the steroid field⁴⁵² that the reaction is not completely general. The authors postulated the following course for the reaction:

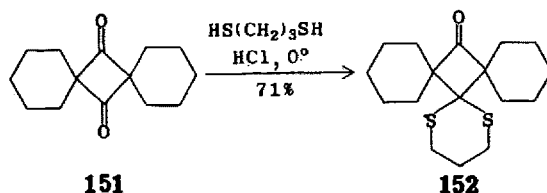


As evidence, they cited the isolation of trimethylene disulfide dimer, presumably formed from 1,2-dithiolane.

Cram and Gaston^{135a} obtained an even more unusual result with 6-acetoxy-*trans*-cyclodecen-7-one, which reacted with 1,3-dimercaptopropane to form 1,5-dithiaspiro[5.9]pentadecane (**150a**). Since the reduction of an isolated double bond by a mercaptan is unprecedented, the authors attributed the reduction to some sort of transannular reaction involving both the double bond and the acyloin group.

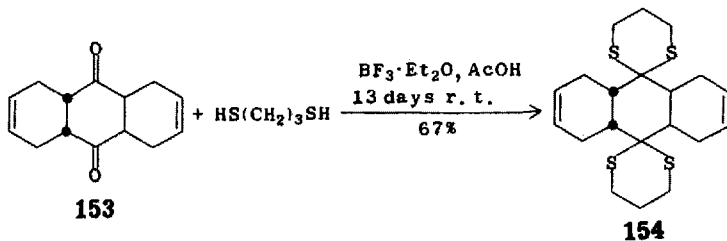


Walborsky^{502,503} reacted dispiro[5.1.5.1]tetradecane-7,14-dione (**151**) with 1,3-dimercaptopropane, and isolated 8,12-dithiatrispiro[5.0.5.0.5.1]nonadecan-19-one (**152**). Only one carbonyl group reacted, in agreement with the general difficulty of synthesizing compounds with two 1,3-dithia rings in close proximity.



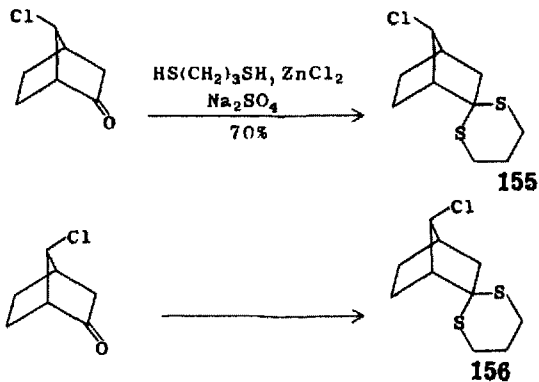
When the carbonyl groups are somewhat further apart, however, a bis-mercaptole can be formed, as shown by Clarke and Johnson,¹²⁴ who prepared the bis(cyclic trimethylene mercaptole) (**154**) from the Diels-Alder condensation product of benzoquinone with butadiene (**153**).

C₄S₂ Ring Systems

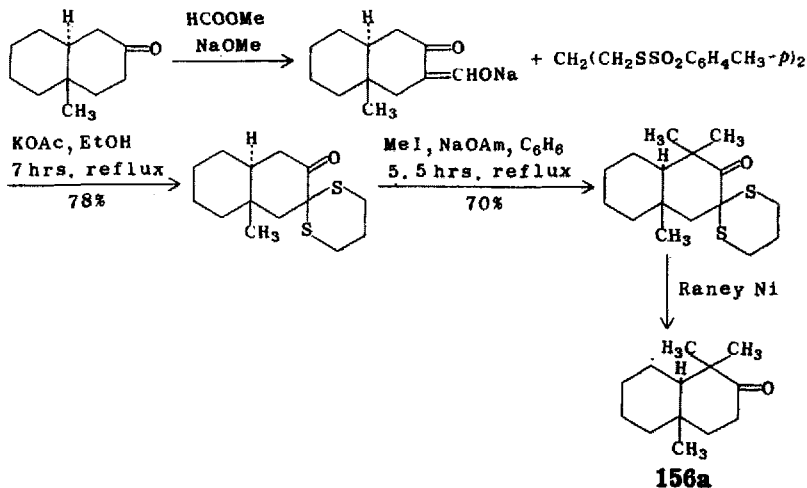


It is interesting, however, that a trimethylene mercaptole could not be isolated from the perhydro compound derived from **153**, although a bis (cyclic ethylene mercaptole) was (see Chapter 5, section II A-4a).

Roberts, Johnson, and Carboni⁴¹⁸ synthesized *anti*-7'-chlorospiro[*m*-dithiane-2, 2'-norcamphane] (155) and the corresponding *syn* isomer (156) from the two 7-chloronorcamphor isomers.

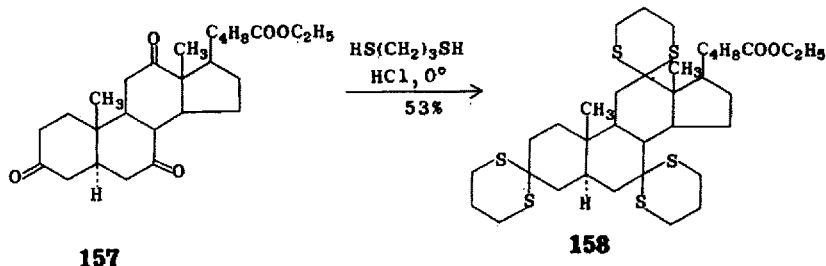


Gaspert, Halsall, and Willis^{204a} applied the Woodward procedure (*vide infra*) to the synthesis of 1, 1, 10-trimethyl-*trans*-2-decalone (156a).

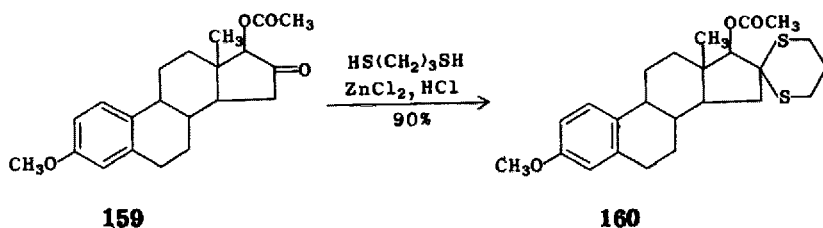


Sondheimer and Wolfe^{461a} used the same procedure on 7, 7, 10-trimethyl-*cis*-2-decalone, while Crabb and Schofield^{127b} applied it to a benzocycloheptanone.

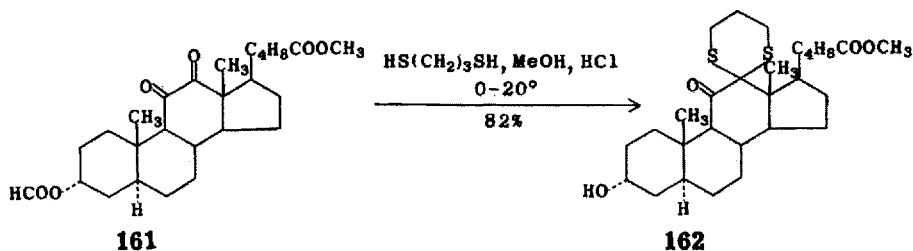
Few examples of the reaction of steroids with 1, 3-dimercaptopropane have been reported, in marked contrast to the use of 1, 2-dimercaptoethane (see Chapter 5, section II A-4b). Campos and Hauptmann⁹³ demonstrated with ethyl dehydrocholate (157) that carbonyl groups in positions 3, 7, and 12 would react (158).



It is interesting that the 3, 3-bis(ethylthio) derivative gave the same compound in almost quantitative yield. Sheehan, Coderre, and Cruickshank⁴⁵² demonstrated with 3-methoxy-17 β -acetoxy-1, 3, 5(10)-estratrien-16-one (159) that a carbonyl group in the 16-position would react (160).

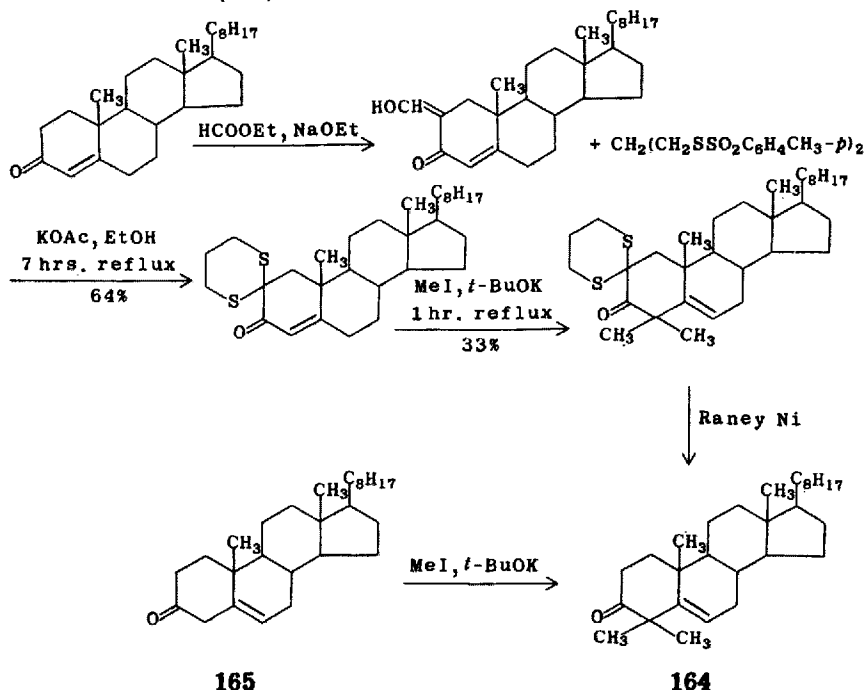


In spite of the fact that 159 is an acyloin acetate, the acetoxy group was unaffected, in contrast to the results obtained by Cram and Cordon¹³⁵ with other acyloin acetates. Archer, Lewis, and co-workers,^{5,6} found with methyl 3 α -formoxy-11, 12-dioxocholanoate (161), as expected, that a 12-oxo group would react but not an 11-oxo (162).

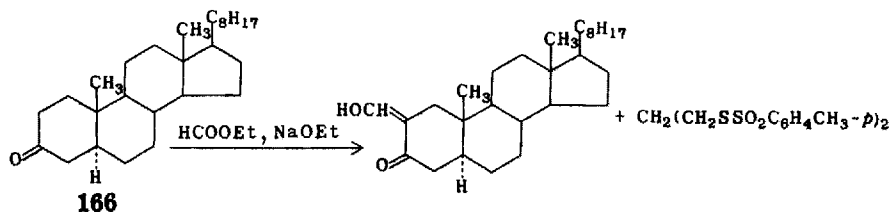


C₄S₂ Ring Systems

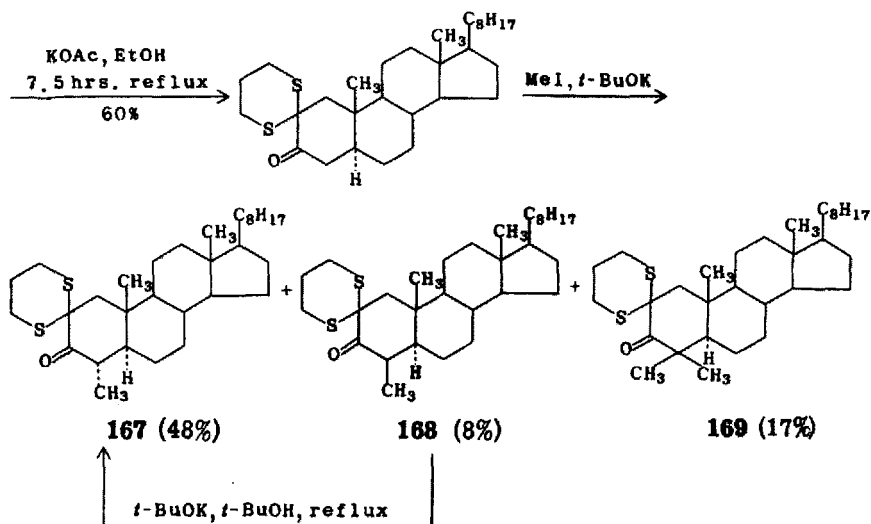
Woodward and co-workers⁵¹² developed a synthesis of spiro *m*-dithianes containing a carbonyl group adjacent to the ring junction. The synthesis involved reaction of a 2-hydroxymethylene ketone with 1, 3-propanebis(*p*-toluenethiolsulfonate). It was applied by these authors to the synthesis of 4, 4-dimethylcholestenone (**164**) from 4-cholesten-3-one (**163**); the structure of **164** was proved by its synthesis directly from 5-cholesten-3-one (**165**).



Beton, Halsall, and co-workers,⁴⁹ used the same procedure to methylate cholestanone (**166**), the thioketal being used to block the 2-position. By controlling the amount of methyl iodide used they were able to prepare and separate a mixture of 4 α -methylcholestane-2, 3-dione 2-(cyclic trimethylene mercaptole) (**167**), the 4 β -methyl isomer (**168**), and the 4, 4-dimethyl derivative (**169**). The basis for the structural assignments was the base-catalyzed isomerization of the 4 β -methyl derivative (axial) to the 4 α -methyl derivative (equatorial).



Chapter 12

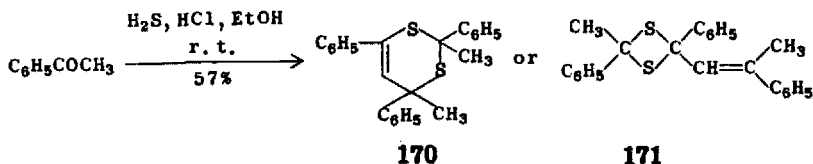


Djerassi and co-workers¹⁵⁹ carried out optical rotatory dispersion studies on the Woodward and Beton compounds.

Djerassi, Halpern, Pettit, and Thomas¹⁶⁰ investigated the effect of different catalysts on the reaction between steriodal sapogenins and 1,2-dimercaptoethane or 1,3-dimercaptopropane. The two mercaptans showed identical reactions (see Chapter 5, section II A-4b), and the fact that differences in reactivity of the two mercaptans are rare accounts for the limited use of 1,3-dimercaptopropane.

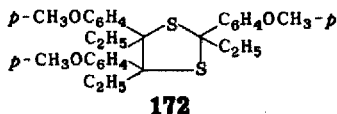
3. *m*-Dithiin

In 1895 Baumann and Fromm³⁵ reacted acetophenone with hydrogen sulfide and hydrochloric acid. In addition to 2,4,6-trimethyl-2,4,6-triphenyl-*s*-trithiane (Chapter 10, section II A-1), they isolated a crystalline compound, $\text{C}_{24}\text{H}_{22}\text{S}_2$, m.p. 107-108°, which they called "anhydro-triacetophenone disulfide", and which they formulated as 2,4-dimethyl-2,4,6-triphenyl-*m*-dithiin (**170**) or as **171**; **170** was preferred. Campaigne⁸⁷ confirmed the preparation in 1944, but he too offered no proof of structure.

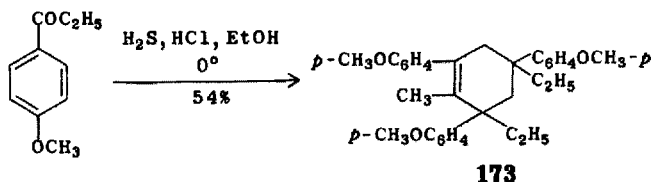


Linnell and Sharma^{88,329} carried out the same reaction on *p*-methoxypropiophenone and assigned the structure 2,4,5-tri-*p*-methoxyphenyl-2,4,5-triethyl-1,3-dithiolane (**172**) to the product, again without any proof.

C₄S₂ Ring Systems



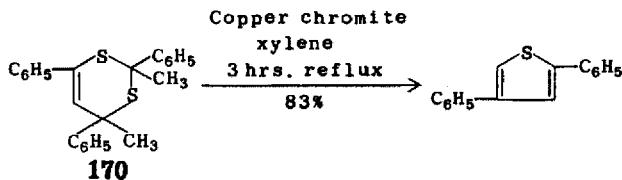
Campaigne⁸⁷ carried out the same reaction, but believed the product to be "anhydro-*p*-methoxypropiophenone disulfide", or 2, 4-diethyl-5-methyl-2, 4, 6-tri-*p*-methoxyphenyl-*m*-dithiin (**173**), m.p. 158. 1-158. 6°.⁸⁸



Campaigne, Reid, and Pera⁹⁰ found that the amount of "anhydro compound" increased as the condensation temperature was raised with certain *p*-substituted acetophenones. The compounds which have been reported are listed in Table 4a.

Recently, Pasto and Servé confirmed the *m*-dithiin structure (**170**) for 'anhydroacetophenone disulfide'. The proton magnetic resonance spectrum agreed with **170** but not with **171**. Furthermore, ozonolysis yielded benzoic acid and not acetophenone; the latter would have been expected from **171**. Other degradation reactions are in agreement with the assigned structure.

According to Baumann and Fromm a blue liquid, presumably thioacetophenone, was formed on heating the phenyl derivative (**170**) to 180°, while further heating yielded styrene, hydrogen sulfide, and 2, 4-diphenylthiophene. Campaigne⁸⁷ was unable to confirm this, isolating only a trace of thiophene derivative under these conditions. When the decomposition was carried out in refluxing xylene in the presence of copper chromite, however, an excellent yield of 2, 4-diphenylthiophene was isolated.



Similarly, the *p*-methoxypropiophenone derivative (**173**) yielded 2, 4-dimethyl-3, 5-di-*p*-methoxyphenylthiophene rather than the 2, 3, 5, 6-tetra-*p*-methoxyphenyl-2, 3, 5, 6-tetraethyl-*p*-dithiane (**174**) postulated by Linnell and Sharma.^{88, 329}

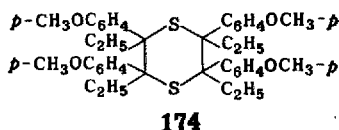
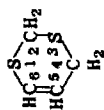
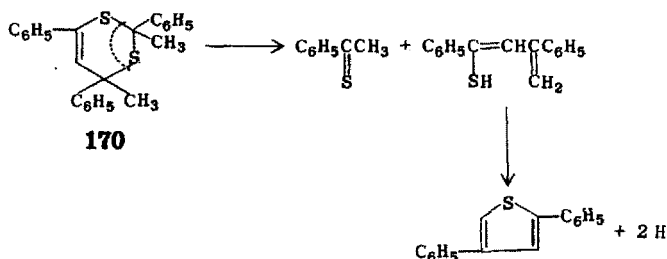


TABLE 4a. *m*-Dithiin Derivatives

Substituents	Yield (%)	M.p. (°C)	Ref.
2, 4-(CH ₃) ₂ -2, 4, 6-(C ₆ H ₅) ₃	57	107-108	35, 87
2, 4-(CH ₃) ₂ -2, 4, 6-(<i>p</i> -FC ₆ H ₄) ₃	43	132-133.5	90
2, 4-(CH ₃) ₂ -2, 4, 6-(<i>p</i> -ClC ₆ H ₄) ₃	21	161.5-162.5	90
2, 4-(CH ₃) ₂ -2, 4, 6-(<i>p</i> -BrC ₆ H ₄) ₃	17	166.5-167.5	90
2, 4-(CH ₃) ₂ -2, 4, 6-(<i>p</i> -IC ₆ H ₄) ₃	10	163-165	90
2, 4-(CH ₃) ₂ -2, 4, 6-(<i>p</i> -C ₆ H ₅ C ₆ H ₄) ₃	81	172 (dec.)	90
2, 4-(C ₂ H ₅) ₂ -5-CH ₃ -2, 4, 6-(<i>p</i> -CH ₃ OC ₆ H ₄) ₃	54	158.1-158.6	87, 88

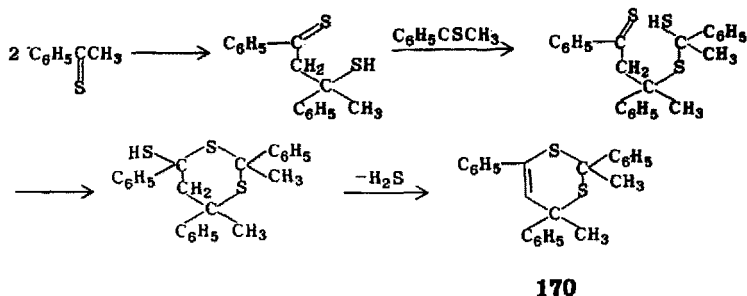
C₄S₂ Ring Systems

Campaigne found that the reaction goes in two steps by the following suggested course:

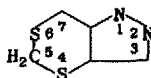


Evidence for this was found with the *p*-methoxypropiophenone derivative (**173**) which, when refluxed in xylene, gave an unsaturated oil and no thiophene derivative. The oil gave the thiophene compound when refluxed with copper chromite in ethanol, whereas **173** was unchanged in hot ethanol, either in the presence or absence of copper chromite.

It is reasonable to assume that **170** could be formed in the following way from thioacetophenone:

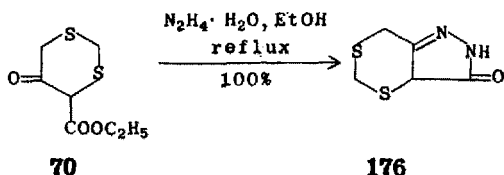


B. C₃N₂-C₄S₂ *m*-DITHINO[5, 4-*c*]PYRAZOLE (**175**)



175

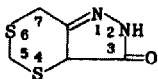
This ring system is represented by the pyrazolones of 5-oxo-*m*-dithianecarboxylic esters (section II A-1b). Thus, Howard and Lindsey²⁷⁵ prepared 2, 7-dihydro-*m*-dithino[5, 4-*c*]-pyrazol-3(3*aH*)-one (**176**) from ethyl 5-oxo-*m*-dithiane-4-carboxylate (**70**) and hydrazine hydrate.



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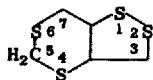
Similarly, Lüttringhaus and Prinzbach³³⁴ and Martani^{247a} prepared the 2-phenyl analog with phenylhydrazine. The compounds which have been reported are listed in Table 5.

TABLE 5. Pyrazolones from *m*-Dithiane Derivatives



Substituents	Yield (%)	M.p. (°C)	Ref.
None	100	233-236 (dec.)	275
5-(<i>p</i> -ClC ₆ H ₄ -)	100	234-238 (dec.)	275
2-C ₆ H ₅ -		205-208 (dec.)	334
		210 (dec.)	347a
2-C ₆ H ₅ -5-CH ₃ -		226-228 (dec.)	334
2-(<i>p</i> -HO ₃ SC ₆ H ₄ -)-5-CH ₃ -		>270 (dec.)	334
2-C ₆ H ₅ -5-pentamethylene		196-197	334

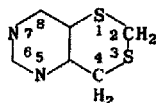
C. C₃S₂-C₄S₂ 1,2-DITHIOLO[4,3-*d*]-*m*-DITHIIN (177)



177

The only compound containing this ring system is a 1,2-dithiole-3-thione analog (see Chapter 5, section I D).

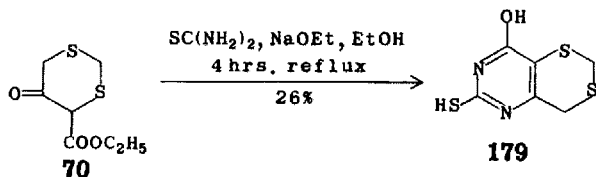
D. C₄N₂-C₄S₂ 4*H*-*m*-DITHIINO[5,4-*d*]pyrimidine (178)



178

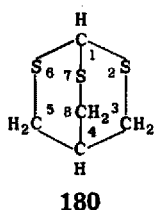
Howard and Lindsey²⁷⁵ prepared 6-mercapto-4*H*-*m*-dithiino[5,4-*d*]pyrimidin-8-ol (179) from ethyl 5-oxo-*m*-dithiane-4-carboxylate (70) and thiourea.

C₄S₂ Ring Systems



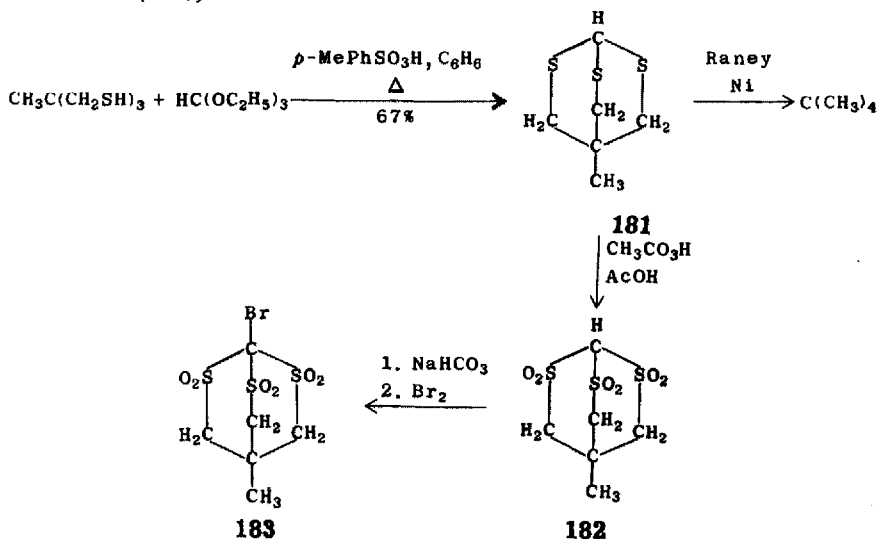
179 could not be melted. Guanidinium thiocyanate similarly gave the 6-amino derivative. Martani^{347a} prepared the analogous 6,8-dihydroxy compound, m.p. 298° (dec.), by an acid-catalyzed condensation of the methyl ester corresponding to **70** with urea.

E. C₄S₂-C₄S₂ 2,6,7-TRITHIABICYCLO[2.2.2]OCTANE (**180**)



(RRI 1670)

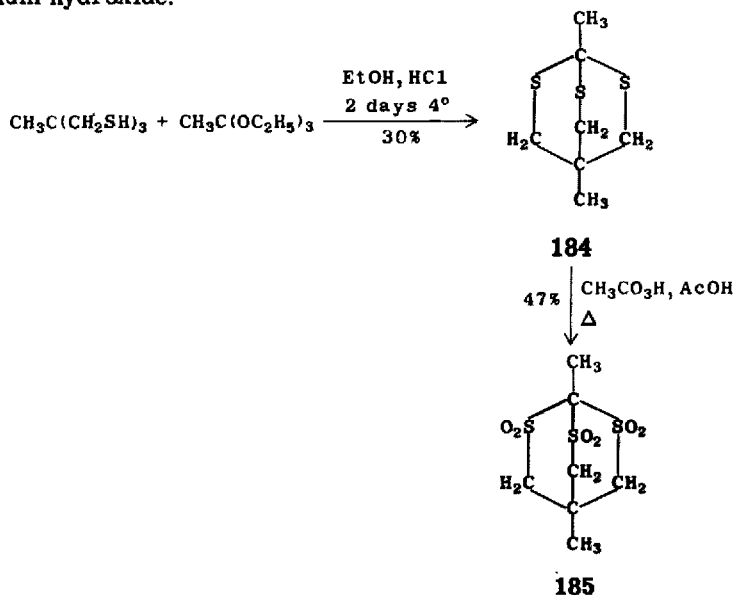
Doering and Levy¹⁶¹ prepared this ring system in connection with their very interesting study of d-orbital resonance in sulfur compounds. Reaction of 2-methyl-2-mercaptomethyl-1,3-dimercaptopropane with ethyl orthoformate gave 4-methyl-2,6,7-trithiabicyclo[2.2.2]octane (**181**), m.p. 130.5-131; its structure was proved by Raney nickel desulfurization to neopentane. Peroxide oxidation yielded the trisulfone, 4-methyl-2,6,7-trithiabicyclo[2.2.2]octane 2,2,6,6,7,7-hexasulfide (**182**), dec. 357-360°, whose sodium salt, on treatment with bromine in water, gave 1-bromo-4-methyl-2,6,7-trithiabicyclo[2.2.2]octane 2,2,6,6,7,7-hexasulfide (**183**), dec. 269-273°.



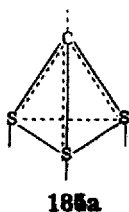
[For references, see pp. 1252-1271.]

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The trisulfone (**182**) is strongly acidic, pK_a 3.30, but somewhat less acidic than the corresponding non-cyclic compound, $HC(SO_2C_2H_5)_3$. That the acidity is due to the C-1 hydrogen was shown by preparation of 1,4-dimethyl-2,6,7-trithiabicyclo[2.2.2]octane (**184**), m.p. 133-135°, and conversion to the hexaoxide (**185**), which is insoluble in aqueous sodium hydroxide.

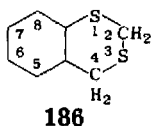


Oae, Tagaki, and Ohno^{374a} studied the alkoxide-catalyzed deuterium-hydrogen exchange of the 1-deutero analog of 4-methyl-2,6,7-trithiabicyclo[2.2.2]octane (**181**). Exchange was a thousand times faster than with the non-cyclic compound, $DC(SC_2H_5)_3$, corresponding to a difference in free energy of activation of 4.6 kcal/mole. This unexpected result, in view of the finding of Doering and Levy that the non-cyclic sulfone is more acidic than **182**, was explained by the authors in two ways. One possible explanation is that constraining the sulfur atoms in a fixed position as in **181** leads to effective 2p-3d overlap. A second alternative is that each of the close-packed sulfur atoms in the cyclic compound has a pair of electrons available for 3p-3d overlap involving the negative charge and the three sulfur atoms, as in **185a**. The sulfone, having no unbonded 3p orbitals, cannot interact in this fashion.



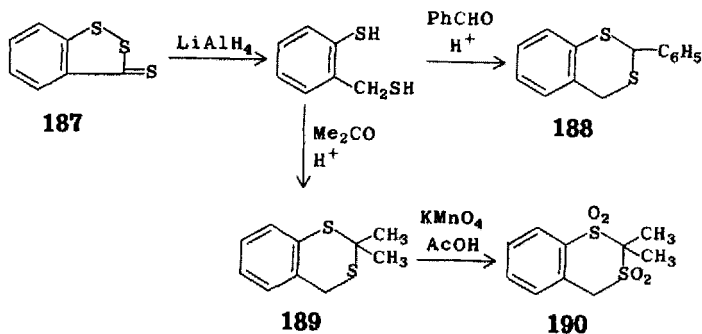
C₄S₂ Ring Systems

F. C₄S₂-C₆ 1, 3-BENZODITHIIN (186)

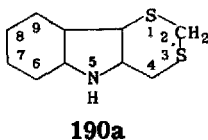


(RRI 1673)

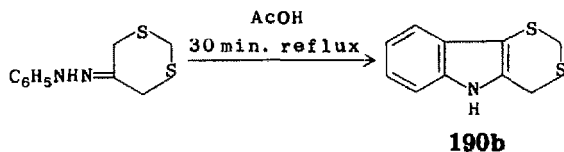
Lüttringhaus and Hägele³³³ prepared 2-phenyl-1, 3-benzodithiin (**188**), m.p. 113-114°, from *o*-mercaptomethylthiophenol and benzaldehyde. Acetone yielded the corresponding 2, 2-dimethyl derivative (**189**), b.p. 140-141° at 12 mm. The dimercaptan was prepared by reduction of 1, 2-benzodithiole-3-thione (**187**). The 2, 2-dimethyl derivative was oxidized to the corresponding disulfone (**190**), m.p. 145-146°, but no other properties of these compounds have been described.

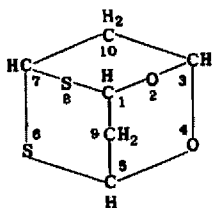


G. C₄N-C₄S₂-C₆ *m*-DITHIINO[5, 4-*b*]INDOLE (190a)



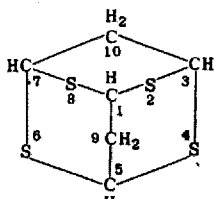
Martani^{347a} prepared the 4, 5-dihydro derivative (**190b**), m.p. 156°, by applying the Fischer indole synthesis to *m*-dithiane-5-phenylhydrazone.



H. $C_4O_2-C_4OS-C_4S_2$ 2, 4-DIOXA-6, 8-DITHIAADAMANTANE (191)

191

Brändström⁶⁰ prepared a compound, m.p. 138.2-138.4°, from acetylacetone and hydrogen sulfide, to which he assigned the structure 1, 3, 5, 7-tetramethyl-2, 4-dioxo-6, 8-dithiaadamantane. For a discussion of this ring system see Chapter 11, section II C.

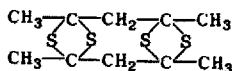
I. $C_4S_2-C_4S_2-C_4S_2$ 2, 4, 6, 8-TETRATHIAADAMANTANE (192)

192

This ring system was named 2, 4, 6, 8-tetrathiaadamantane by Stetter,⁴⁶⁶ who has reviewed this class of compounds. It has also been called 2, 4, 6, 8-tetrathiatricyclo[3. 3. 1.^{13.7}]decane.

In 1901 Leteur³²⁶ reacted a solution of acetylacetone in concentrated hydrochloric acid with hydrogen sulfide and isolated a compound, m.p. 162-163.5°, with the empirical formula $C_5H_8S_2$. A molecular weight determination showed it to be dimeric, $C_{10}H_{16}S_4$, and Leteur correctly considered it to be a dimer of dithioacetylacetone, although he assigned no structure to the compound.

Several years later Fromm and Ziersch¹⁹⁸ carried out the same reaction, treating acetylacetone in cold alcohol with hydrogen sulfide in the presence of a small amount of hydrogen chloride. The same product was obtained; the water insoluble, organosoluble compound was very stable both to strong bases and strong acids, and was decomposed by bromine. By analogy with tetraethenyl hexasulfide (see Chapter 10, section II B), they formulated the compound as duploacetylacetone tetrasulfide (193).

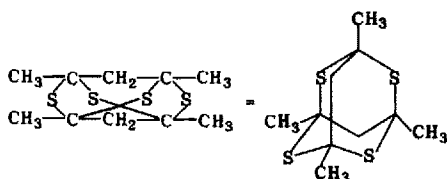


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C₄S₂ Ring Systems

Dimethylacetylacetone reacted similarly, but methylacetylacetone gave a compound, C₁₂H₁₈S₃, m.p. 193°, whose structure has not been elucidated. The compound from dimethylacetylacetone was oxidized with acid permanganate to a disulfone, whereas the compound from acetylacetone gave ill-defined oxidation products.

Fredga and Brändström^{187,188} assigned reasonable structures to these compounds in 1948-9. If Fromm and Ziersch's four-membered rings are written as six-membered rings, a strainless adamantane-like structure is arrived at which consists of four six-membered rings, each containing two sulfur atoms. The compound from acetylacetone would therefore be 1, 3, 5, 7-tetramethyl-2, 4, 6, 8-tetrathiaadamantane (194).



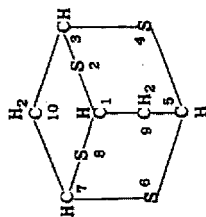
194

Similarly, the compound from dimethylacetylacetone would be 1, 3, 5, 7, 9, 9, 10, 10-octamethyl-2, 4, 6, 8-tetrathiaadamantane, and it is reasonable to assume that the disulfone would be the 2, 2, 6, 6-tetroxide.

Fredga and Bränström^{187,188} improved the synthesis considerably by carrying out the reaction of the β -diketone with hydrogen sulfide in concentrated alcoholic hydrogen chloride at low temperature. In this way they were able to prepare derivatives from a variety of β -diketones, including methylacetylacetone, in yields of 70-100%. β -Ketoaldehydes were also reacted, although in somewhat lower yields. Compounds with a phenyl group adjacent to the carbonyl group failed to yield the tricyclic compound; here, too, a parallel exists between these compounds and the hexathiaadamantane derivatives (Chapter 10, section II B). The compounds prepared are listed in Table 6.

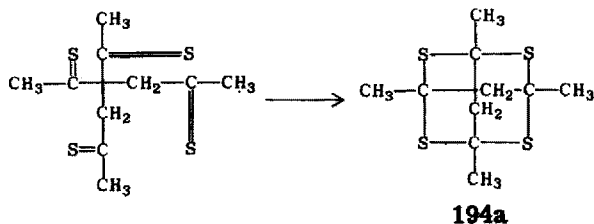
The only real basis for the assignment of this structure to these compounds is the fact that unsymmetrical β -diketones, RCOCH₂COR', gave excellent yields of only one compound, whereas two isomers might be expected. The adamantane structure fulfills this requirement of predicting only one structure from unsymmetrical diketones. Inasmuch as the adamantane structure has been proved quite definitely for the hexathiaadamantanes and the two types of compounds have similar properties, this structure assignment would seem to be a very reasonable one. Furthermore, Stetter⁴⁶⁶ has postulated a reasonable mechanism for the formation of this ring system.

TABLE 6. Derivatives of 2, 4, 6, 8-Tetrathiaadamantane



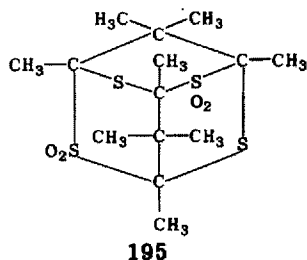
Substituents	β -Dicarbonyl Compound	Yield (%)	M.p. ($^{\circ}\text{C}$)	Ref.
1, 3, 5, 7-(CH_3) ₄	Acetylacetone		162-163.5 161	326 198
1, 3, 5, 7, 9, 10-(CH_3) ₆				
1, 3, 5, 7, 9, 10-(CH_3) ₆ 2, 2, 4, 4, 6, 6-hexaoxide	Methylacetylacetone	85	162.5-163	187
1, 3, 5, 7, 9, 9, 10, 10-(CH_3) ₈		70	128	187
1, 3, 5, 7, 9, 9, 10, 10-(CH_3) ₈ 2, 2, 6, 6-tetroxide	Dimethylacetylacetone		<i>ca.</i> 260 (dec.) 227	60 198
1, 3-(CH_3) ₂ -5, 7-(C_2H_5) ₂	Propionylacetone		350 (dec.)	198
1, 3, 5, 7-(C_2H_5) ₄	Dipropionylmethane	85	136-136.5	187
1, 3-(CH_3) ₂ -5, 7-($n\text{-C}_3\text{H}_7$) ₂	Butyrylacetone	85	164.5-165	187
1, 3, 5, 7-($n\text{-C}_3\text{H}_7$) ₄	Dibutyrylmethane	90	113	188
1, 3-(CH_3) ₂ -5, 7-($n\text{-C}_6\text{H}_{11}$) ₂	Heptoylacetone	100	136.5	188
1, 3, 5, 7-($n\text{-C}_6\text{H}_{11}$) ₄	Diheptoylmethane	75	71	188
1, 3-($t\text{-C}_4\text{H}_9$) ₂	Pivaloylacetalddehyde	50	92-93	188
1, 3-(CH_3) ₂ -5, 7-($t\text{-C}_4\text{H}_9$) ₂	Pivaloylacetone	85	176	188
1, 3-(CH_3) ₂ -5, 7-($\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$) ₂	β -Phenylpropionylacetone	75	164 110-110.5	188 188

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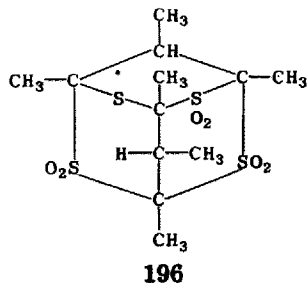


194a is another projection of the adamantane ring system, and the dimerization is quite analogous to the trimerization of a thioketone to an *s*-trithiane.

The oxidation of these compounds raises some puzzling points. As already mentioned, Fromm and Ziersch¹⁹⁸ oxidized the derivative from dimethylacetylacetone to a disulfone with acid permanganate. In the hexathiaadamantane system oxidation stops at the disulfone stage, and an examination of molecular models shows that conversion of the sulfurs in the 2- and 6-positions to sulfones effectively blocks the other sulfur atoms. By analogy, therefore, it is reasonable to assume that the disulfone from the dimethylacetylacetone compound is 1, 3, 5, 7, 9, 9, 10, 10-octamethyl-2, 4, 6, 8-tetrathiaadamantane 2, 2, 6, 6-tetroxide (**195**).



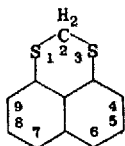
By contrast, oxidation of the acetylacetone derivative (**194**) led to the evolution of carbon dioxide, and Bränström⁶⁰ was able to isolate a trisulfone from the methylacetylacetone derivative, 1, 3, 5, 7, 9, 10-hexamethyl-2, 4, 6, 8-tetrathiaadamantane 2, 2, 4, 4, 6, 6-hexaoxide (**196**).



The difference between the results with the methylacetylacetone and the dimethylacetylacetone derivatives can be ascribed to steric hindrance,

but it must be inferred that the acetylacetone derivative is not as stable as other compounds with the adamantane-type structure.

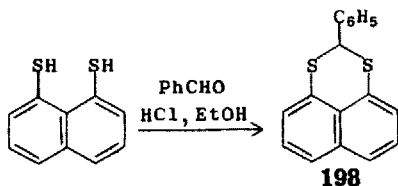
J. $C_4S_2-C_6-C_6$ NAPHTHO[1,8-*de*]-*m*-DITHIIN (197)



197

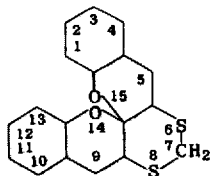
(RRI 3451)

This ring system was prepared by Price and Smiles³⁹⁸, who called it *peri*-naphtha-1,3-dithiane. Reaction of 1,8-dimercaptonaphthalene with benzaldehyde yielded 2-phenylnaphtho[1,8-*de*]-*m*-dithiin (198), m.p. 116°.



198

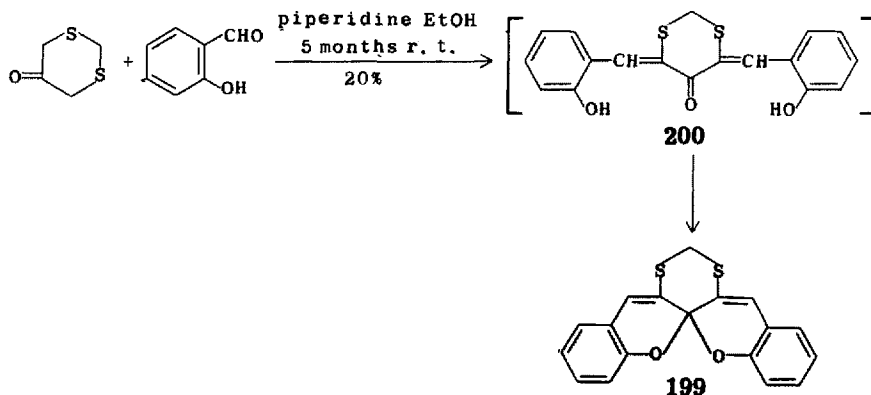
K. $C_4S_2-C_5O-C_5O-C_6-C_6$ *m*-DITHIINOBIS[5,4-*b*:5,6-*b'*] [1]
BENZOPYRAN (199)



199

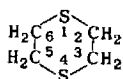
Howard and Lindsey²⁷⁵ reacted *m*-dithian-5-one with salicylaldehyde and isolated a compound, $C_{18}H_{12}O_2S_2$, m.p. 224-225°, which they formulated as **199** because of the absence of hydroxyl and carbonyl bands in the infrared spectrum. Its formation from the expected intermediate, 4,6-bis(salicylidene)-*m*-dithian-5-one (**200**) (see section II A-1b), is reasonable under acidic conditions, but appears rather unlikely in the absence of acid.

C₄S₂ Ring Systems

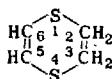


III. 1,4-DITHIA COMPOUNDS

A. C₄S₂ *p*-DITHIANE (201) and *p*-DITHIIN (202)



201



202

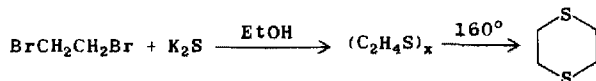
(RRI 267)

These compounds are indexed in Chemical Abstracts under the names shown above. *p*-Dithiane is frequently called 1,4-dithiane. In the early literature it was called diethylene sulfide, then diethylene disulfide; an alternative name would be 1,4-dithiacyclohexane. *p*-Dithiin has been known under a variety of names. It was first called biophene, but this name was soon discarded. In more recent times it has been known as divinylene disulfide, *p*-dithiene, 1,4-dithiene, and 1,4-dithiin. Present writers seem to prefer the name 1,4-dithiadene.

1. *p*-Dithiane

a. Preparation of *p*-Dithiane

In 1840 Löwig and Weidmann³³⁰ reacted ethylene chloride with potassium sulfide and isolated a solid, now known to be polymeric, which analyzed as C₂H₄S. Crafts^{129,130,133} in 1862 was apparently the first to prepare *p*-dithiane; he repeated Löwig and Weidmann's preparation, but with ethylene bromide, and found that the polymer on heating yielded a volatile crystalline solid, which melted at 112° and boiled at 199-220°; apparently a small amount of *p*-dithiane was also formed directly.

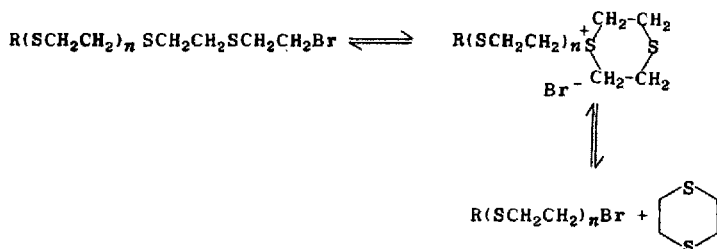


[For references, see pp. 1252-1271.]

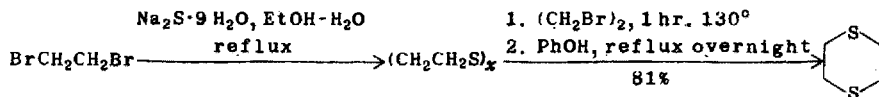
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Crafts formulated *p*-dithiane as C_2H_4S , but in the following year Husemann,²⁸⁶ who repeated the preparation and investigated *p*-dithiane more thoroughly, determined the molecular weight and correctly formulated *p*-dithiane as $C_4H_8S_2$. Werner⁵⁰⁵ obtained essentially the same results as Crafts.

Numerous variations of this synthesis have been reported. Mansfield³⁴⁵ showed that, although heating the polymer alone gave a poor yield of *p*-dithiane, it cleaved smoothly when heated in phenol. V. Meyer³⁵⁸ found that the polymer existed in two forms; when ethylene bromide was added to an alcoholic solution of potassium sulfide, a polymer was formed, in an exothermic reaction, which could be decomposed to *p*-dithiane. However, long refluxing of ethylene bromide with a concentrated aqueous solution of potassium sulfide gave a polymer which could not be converted into *p*-dithiane on heating. Bell, Bennett, and Hock³⁹ explained this phenomenon in a very reasonable fashion. According to these authors the cleavable polymer has a terminal halogen and *p*-dithiane is formed from it *via* reversible sulfonium salt formation.



The non-cleavable polymer has a hydroxyl or vinyl end group and therefore cannot cleave. The evidence for this hypothesis is convincing. Sulfonium salts of *p*-dithiane are well known (see section III A-1g), and the authors were able to explain a number of other syntheses and reactions of *p*-dithiane by assuming reversible sulfonium salt formation (*vide infra*). Most conclusive was the fact that refluxing the non-cleavable polymer with a saturated solution of hydrogen bromide in phenol gave a 33% yield of *p*-dithiane; substitution of ethylene bromide for the hydrogen bromide gave a 22% yield. By combining these facts, Fuson and co-workers²⁰² were able to prepare *p*-dithiane in a yield of 73% by the following route:

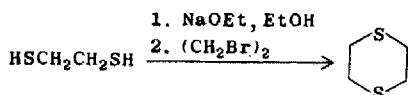


Many closely related syntheses have been reported. Masson³⁵² found that, if the reaction between ethylene bromide and potassium sulfide was carried out in concentrated alcoholic solutions, some *p*-dithiane was formed directly; by cleaving the polymer he obtained an overall yield of *p*-dithiane of 37%. Gavrilov and Tischenko²⁰⁵ used only enough ethanol to moisten the sodium sulfide, reacted this with ethylene bromide, and

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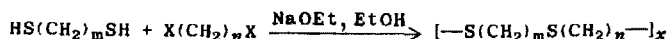
claimed an 86% yield of *p*-dithiane; confirmation of this would make it the simplest synthesis of *p*-dithiane. According to Gomberg²²⁸ the chloride cannot be substituted for the bromide.

V. Meyer³⁵⁸ prepared *p*-dithiane from the sodium salt of 1,2-dimer-captoethane and ethylene bromide.



Addition of the dibromide to a dilute solution of the sodium salt with cooling yielded *p*-dithiane, whereas if it was added to a concentrated solution all at once, only a cleavable polymer was obtained, presumably identical with that formed from the dibromide and potassium sulfide. Rây and Bose-Rây⁴⁰⁸ and Mohler and Sorge³⁶⁷ used the Meyer synthesis for the preparation of *p*-dithiane. A 55-60% yield of *p*-dithiane by this procedure is reported in *Organic Syntheses*.^{214a} Tucker and Reid⁴⁹⁷ investigated the quantitative aspects of the synthesis and obtained a 46% yield of *p*-dithiane and a 51% yield of polymer. Heating the polymer with ethylene bromide gave a 65% yield of *p*-dithiane, for an overall yield of 79%. If the Fuson procedure²⁰² were to be used on the polymer, the attractive overall yield of 87% should be obtainable.

Reid and co-workers^{356,497} prepared a number of polymers from dimercaptans and dihalides. Heating any polymer containing two sulfur



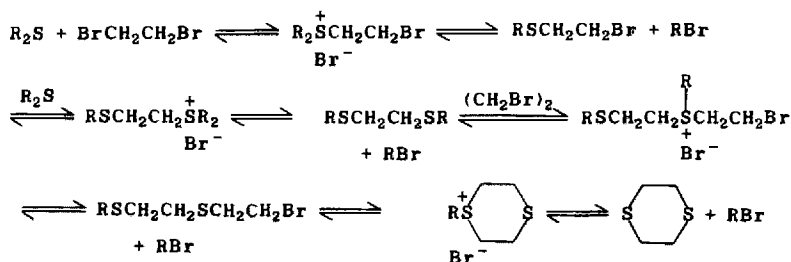
atoms separated by a $-\text{CH}_2\text{CH}_2-$ group with dry hydrogen chloride or with ethylene bromide yielded some *p*-dithiane. Here, too, Bell, Bennett, and Hock's reversible sulfonium salt formation³⁹ can be used to explain these results.

Bouknight and Smith⁵⁹ prepared *p*-dithiane by a procedure which appears to be a modification of that used by Meyer. These authors added ethylene bromide and sodium hydroxide to an alcoholic solution of sodium hydrogen sulfide. The best yield obtainable was 45%; this was confirmed by Schroyer and Jackman.⁴⁴⁸ Rây and co-workers⁴⁰⁴⁻⁴¹⁰ prepared *p*-dithiane similarly, omitting the sodium hydroxide. Although they described their compound as triethylene trisulfide, $(\text{C}_2\text{H}_4)_3\text{S}_3$, Bennett and Berry^{42,43} identified it unequivocally as *p*-dithiane.

Dehn^{151,152,353} found that *p*-dithiane could be formed by heating dimethyl or diethyl sulfide with ethylene bromide, the alkyl bromide being formed as a by-product. Meadow and Reid³⁵⁶ obtained the same

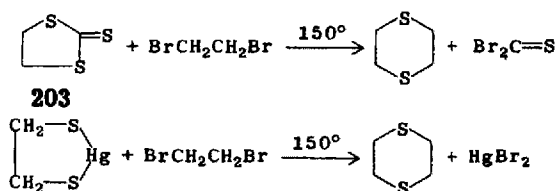
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results with di-*n*-butyl sulfide. The reaction can be formulated as follows:



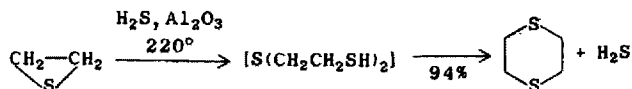
As evidence for this scheme, Tucker and Reid⁴⁹⁷ isolated a 48% yield of *p*-dithiane by heating 1,2-ethylenebis(*n*-butyl sulfide) with ethylene bromide.

Husemann,²⁸⁶ who apparently discovered *p*-dithiane independently, prepared it by heating 1,3-dithiolane-2-thione (**203**) or the mercury salt of 1,2-dimercaptoethane with ethylene bromide.

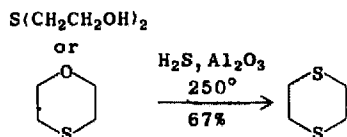


Some *p*-dithiane was also formed by heating the mercury compound with ethyl iodide.

Yur'ev and German⁵²⁰ prepared *p*-dithiane in high yield by passing thiirane and hydrogen sulfide over alumina. If thiirane were readily available, this would be an excellent synthesis of *p*-dithiane. The authors considered bis(2-mercaptoethyl) sulfide to be an intermediate.

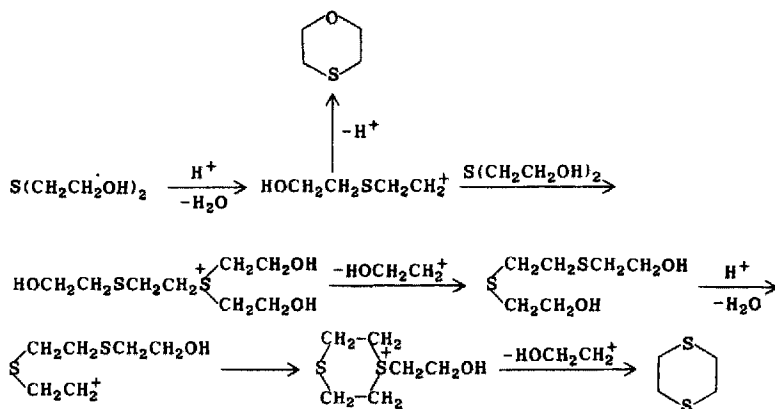
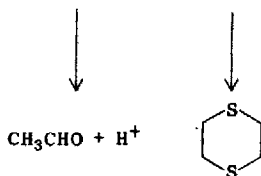


In the absence of hydrogen sulfide the yield dropped to 41%. 1,2-Dimercaptoethane, passed over alumina in a nitrogen atmosphere at 300°, gave a 51% yield of *p*-dithiane; by simple distillation Meadow and Reid³⁵⁶ obtained a yield of only 5-6%. Yur'ev and Novitski⁵¹⁶ obtained a 67% yield of *p*-dithiane by passing either bis(2-hydroxyethyl) sulfide or *p*-oxathiane over alumina in the presence of hydrogen sulfide.



4

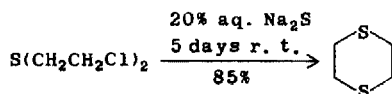
There have been numerous references to the formation of *p*-dithiane by the reaction of bis(2-hydroxyethyl) sulfide (thiodiglycol) with acidic dehydrating agents—hydrogen bromide,³⁹ phosgene,⁹⁸ potassium bisulfate,^{199,200} zinc chloride,²⁰⁰ phosphoric acid,^{200,322a} and sulfuric acid.³⁵⁷ These syntheses are of little preparative value, the major product being *p*-oxathiane or, with phosgene, bis(2-chloroethyl) sulfide. Richter, Augustine, and co-workers,⁴¹⁶ obtained small amounts of *p*-dithiane by treating bis(2-hydroxyethyl) sulfide with glycols and an acid. The formation of *p*-dithiane in these reactions can be formulated as taking place *via* sulfonium salt formation:


$$\text{HOCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2^+ \longrightarrow \text{HOCH}_2\text{CH}_2^+ + ^-\text{SCH}_2\text{CH}_2^+$$


[For references, see pp. 1252-1271.]

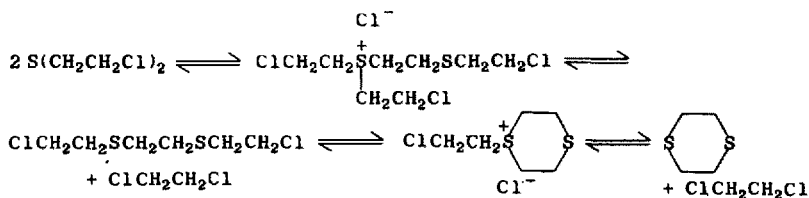
Even mercaptoethanol has been reported to give *p*-dithiane. Thus, Bennett⁴¹ found that some *p*-dithiane was formed when mercaptoethanol was allowed to stand in dilute hydrochloric acid. Refluxing mercaptoethanol with 50% sulfuric acid gave two polymers, one of which yielded *p*-dithiane on distillation; yields with phosphorus pentoxide were lower.⁴² Backer and Wiggerink²⁵ obtained a polymer from mercaptoethanol or 1, 3-oxathiolan-2-one by treatment with a trace of sulfuric acid; sublimation of the polymer gave *p*-dithiane.

A readily available starting material for *p*-dithiane formation is bis(2-chloroethyl) sulfide or mustard gas. Although the chemistry of this compound has been investigated extensively, it has not been much used synthetically, probably because of its vesicant action. Gomberg²²⁸ reported an 85% yield of *p*-dithiane with dilute aqueous sodium sulfide; the yield decreased as the concentration increased, presumably because of the competing hydrolysis reaction.



Mohler³⁶⁶ carried out the preparation in hot ethanol but reported no yield. The formation of *p*-dithiane by reaction with sodium sulfide has been suggested as a qualitative test for mustard gas.⁴⁶²

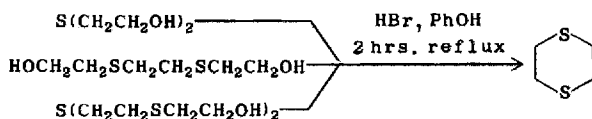
Chang⁹⁷ reported a 76% crude yield of *p*-dithiane by heating mustard gas with sulfur at 200°. This is rather surprising, in view of the fact that numerous thermal reactions have been reported to give *p*-dithiane in only low yield. Thus, although Bell, Bennett, and Hock³⁹ reported a 50% yield of *p*-dithiane by heating bis(2-chloroethyl) sulfide in a sealed tube at 180°, Williams⁵⁰⁸ obtained only a 10% yield under the same conditions. In an open vessel the maximum yield was 3.3% at 220°. Fuson and co-workers²⁰² also obtained only a low yield, as did Mann and Pope,³⁴³ from mustard gas and sulfur dichloride. Actually, Davies¹⁴⁸ found that *p*-dithiane is an impurity in mustard gas; this was confirmed by Price and Nullitt.³⁹⁷ Bell, Bennett, and Hock³⁹ showed that the amount increases on standing, indicating that it is formed from mustard gas rather than as a by-product during preparation. These authors formulated *p*-dithiane formation as follows:



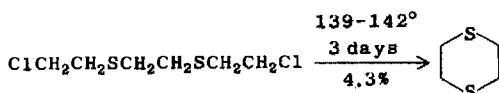
Evidence for this was the isolation of ethylene chloride from the reaction and the formation of bis(2-chloroethyl) sulfide by heating *p*-dithiane with ethylene chloride. Furthermore, these same authors prepared *p*-dithiane by heating thiodiglycol, ethylene bis(2-hydroxyethyl sulfide), and

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bis(2-hydroxyethylthioethyl) sulfide with hydrogen bromide in phenol.

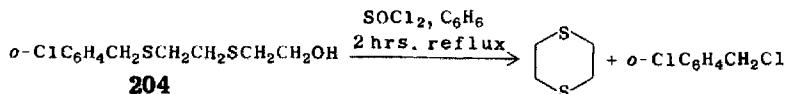


In addition, Fuson and co-workers²⁰² isolated *p*-dithiane by heating ethylene bis(2-chloroethyl sulfide).

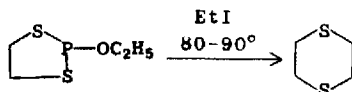


The same explanation can be used to rationalize the formation of *p*-dithiane by heating 2-chloroethyl 2-hydroxyethyl sulfide, $\text{ClCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{OH}$.²⁰¹ Williams⁵⁰⁸ attributed the low yields to the formation of open-chain sulfonium polymers.

The formation of *p*-dithiane from 2-hydroxyethyl 2-mercaptoethyl sulfide, $\text{HOCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{SH}$, with hydrochloric acid by Miles and Owen³⁶⁰ is straightforward. Reversible sulfonium salt formation can also be used to explain the isolation of *p*-dithiane from 7-*o*(or *p*)-chlorophenyl-3, 6-dithiaheptanol (**204**) by Kulka.³²⁰



A few additional syntheses of *p*-dithiane of little preparative importance have been reported. Bennett⁴¹ found that impure *p*-dithiane is formed when ethylene chlorohydrin is treated with sodium disulfide and the product heated with hydrochloric acid. Similarly bis(2-chloroethyl) sulfide with sodium sulfide also forms *p*-dithiane. Charnock and Mogridge⁹⁹ isolated some *p*-dithiane from the pyrolysis of bis(2-methylthioethyl) sulfide, $\text{S(CH}_2\text{CH}_2\text{SCH}_3)_2$, at 260°. Williams and Woodward⁵⁰⁹ treated bis(2-chloroethyl) sulfide with the sodium salt of 3-mercapto-propionitrile and formed some *p*-dithiane. Arbuzov and Zoroastrova⁴ found that some *p*-dithiane is formed on treatment of 2-ethoxy-1, 3, 2-dithiaphospholane (**205**) with ethyl iodide.



Harman and Vaughan²⁴⁵ suggested the synthesis of *p*-dithiane by the radical-catalyzed addition of hydrogen sulfide to divinyl sulfide, but no experimental details are available.

In Table 7 are summarized the syntheses of *p*-dithiane which appear to be of preparative value, as well as certain physical constants.

TABLE 7. *p*-Dithiane Syntheses

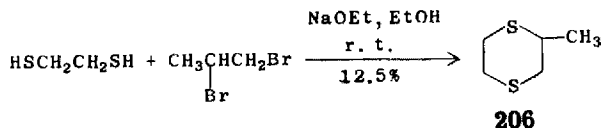
Method of synthesis	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Ref.
Heating $(\text{CH}_2\text{CH}_2\text{S})_x$ formed from $\text{C}_2\text{H}_4\text{Br}_2 + \text{Na}_2\text{S}$	73	111-111.5			202
$\text{C}_2\text{H}_4\text{Br}_2 + \text{Na}_2\text{S}$	86	110			205
	45	110-111			59, 448
$(\text{CH}_2\text{SNa})_2 + \text{C}_2\text{H}_4\text{Br}_2$	55-60	112-113			214a
$(\text{CH}_2\text{SNa})_2 + \text{C}_2\text{H}_4\text{Br}_2$ plus pyrolysis of polymer	79	111			497
Thiirane + H_2S over Al_2O_3	94	110.5			520
$(\text{CH}_2\text{SH})_2$ over Al_2O_3	51	110			520
$\text{S}(\text{C}_2\text{H}_4\text{OH})_2 + \text{H}_2\text{S}$ over Al_2O_3	67	110.5			516
$\text{S}(\text{C}_2\text{H}_4\text{OH})_2 + \text{P}_2\text{S}_5$	50	110			127
$\text{S}(\text{C}_2\text{H}_4\text{Cl})_2 + \text{Na}_2\text{S}$	85				228
$\text{S}(\text{C}_2\text{H}_4\text{Cl})_2 + \text{S}$	76	112	140-150	28	97
		111-112	199-200	760	129, 286
			115.6	60	297
			133.2	119	297
			144.3	170	297
			154.7	232	297
			158.0	252	297
			163.7	306	297

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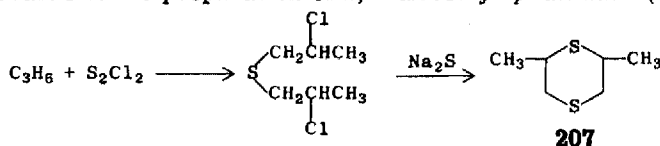
b. Alkyl and Aryl Derivatives

In this section are discussed alkyl- and aryl-substituted *p*-dithianes; the compounds which have been reported are listed in Table 8. Although compounds possessing functional groups on the side chains are described in this section, those compounds in which functional groups are attached directly to the ring are discussed in later sections.

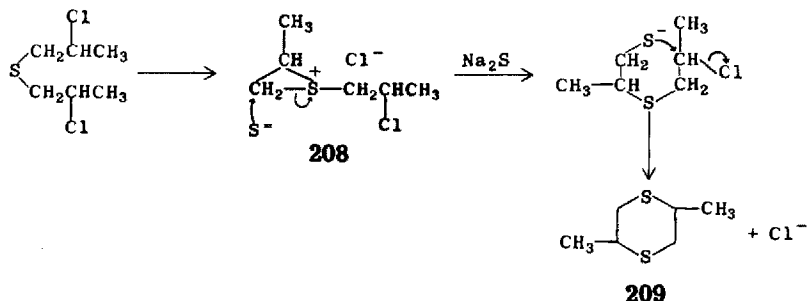
Meadow and Reid³⁵⁶ prepared 2-methyl-*p*-dithiane (**206**) from 1, 2-dibromopropane and 1, 2-dimercaptoethane.



However, because of the unsymmetrical nature of the starting materials, difficulty was encountered in the application of other *p*-dithiane syntheses to the preparation of alkyl-substituted *p*-dithianes. Thus, Glavis, Ryden, and Marvel²²⁷ sought to apply the mustard gas-sodium sulfide procedure to the preparation of 2, 6-dimethyl-*p*-dithiane (**207**).



Marvel and Weil³⁵¹ discovered, however, that a rearrangement takes place during the sodium sulfide reaction, and the compound isolated was actually 2, 5-dimethyl-*p*-dithiane (**209**). The rearrangement may be pictured as follows; on steric grounds the sulfide ion would be expected to attack the unsubstituted carbon atom in the intermediate sulfonium ion (**208**).



The structure of **209** was proved by an unequivocal synthesis of the 2, 6-dimethyl isomer (**207**) via the base-catalyzed addition of hydrogen sulfide to diallyl sulfide.³⁵¹

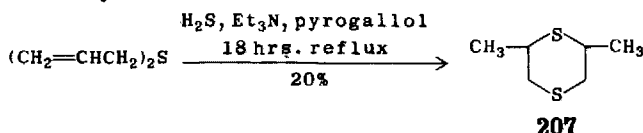


TABLE 8. Alkyl- and Aryl-substituted *p*-Dithianes

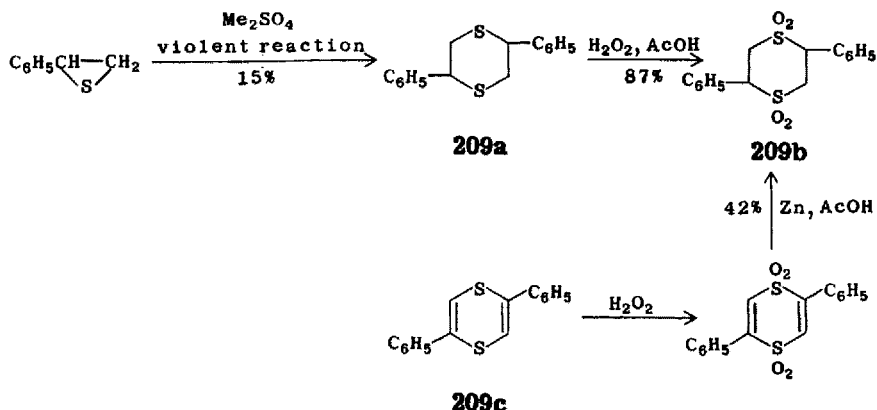
Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	B.p. (mm)	Other properties	Ref.
2-CH ₃ -	12.5	20	209-210			356
		20-22				203
2,5-(CH ₃) ₂	14		85-87	12	n_D^{20} 1.5420 d_4^{20} 1.080	227, 351
	49		108-114	38	Impure	413
2,6-(CH ₃) ₂	20		80-100	15	n_D^{20} 1.5324	245, 351
2,6(?)-(CH ₃) ₂	72				Steam distillable oil	205
2,5-(<i>n</i> -C ₃ H ₇) ₂	9		145-155	20	n_D^{20} 1.5255 d_4^{20} 1.002	227
2,5-(<i>n</i> -C ₁₀ H ₂₁) ₂	83		245-255	2.4	n_D^{20} 1.4919	414
2,5-(C ₆ H ₅) ₂	11		190-195	30	n_D^{20} 1.6060 d_4^{20} 1.143	227
	15	206.5-207.5				373b
2,3,5,6-(CH ₃) ₄			145-150	35		395
	31.2					205
2,2,6,6(?)-(CH ₃) ₄	28.1					205, 245
2-ClCH ₂ -	75		80-82	0.3	n_D^{20} 1.5884 d_4^{20} 1.315	204

2-HOCH ₂ -	41		103-105	0.4	n_D^{20} 1.5935	n_D^{25} 1.5910	204
2-C ₆ H ₅ CO ₂ CH ₂ -		47.5-48.5	77	0.5			204
2-(<i>p</i> -O ₂ NC ₆ H ₄ CO ₂ CH ₂ -)		96-97					204
2,5-[-(CH ₂) ₈ CO ₂ H] ₂	1		90-100	10-12	n_D^{20} 1.4417	d_{20}^{20} 0.842	349
2,3-(CH ₃ CO ₂ CH ₂ -) ₂	45		156	1	n_D^{20} 1.5252		51a
2,5-(C ₆ H ₅ SO ₂ CH ₂ -) ₂		157-158					141, 494
2,5-(<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ CH ₂ -) ₂	47	189-190					141
		180-181					494
2,5-(CH ₃ -) ₂ -4,6-(HO ₂ CCH ₂ -) ₂		275					496

Chapter 12

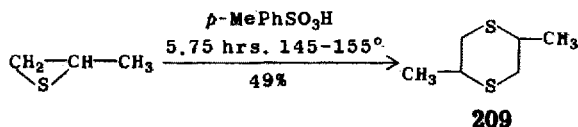
The non-identity of the two isomers was shown by oxidation to the disulfones (see section III A-1f).

Marvel, Davis, and Glavis³⁴⁹ used the mustard gas-sodium sulfide procedure to prepare the di-*n*-propyl derivative from 1-pentene, the diphenyl derivative from styrene, and the bis(8-carboxyoctyl) derivative from 10-undecenoic acid. These compounds, listed in the literature as 2, 6-derivatives, are probably either 2, 5-derivatives or mixtures. A recent preparation of 2, 5-diphenyl-*p*-dithiane (**209a**) by Noshay and Price^{373b} favors the latter interpretation. Noshay and Price proved the structure of the dithiane by oxidation to the disulfone (**209b**) and comparison of it with an unequivocal sample prepared from 2, 5-diphenyl-*p*-dithiin (**209c**) (see section III A-2).

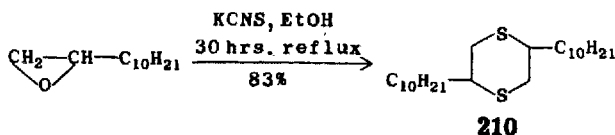


The identity of the disulfone from the two preparations was proved by identical infrared and X-ray diffraction spectra.

Remes and Krewer⁴¹³ prepared a dimethyl-*p*-dithiane by heating 2-methylthiirane in the presence of an acid catalyst. Although they formulated the product as 2, 5-dimethyl-*p*-dithiane (**209**), they adduced no proof for this structure. The material isolated was undoubtedly impure and may have consisted of a mixture of the 2, 5-dimethyl and 2, 6-dimethyl compounds.

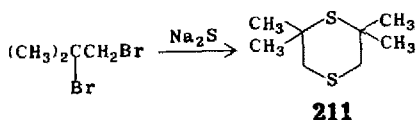
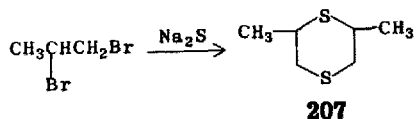


The same authors⁴¹⁴ prepared a compound formulated as 2, 5-di-*n*-decyl-*p*-dithiane (**210**) from 2-*n*-decyloxirane and potassium thiocyanate. Here, too, however, the structure was not characterized.

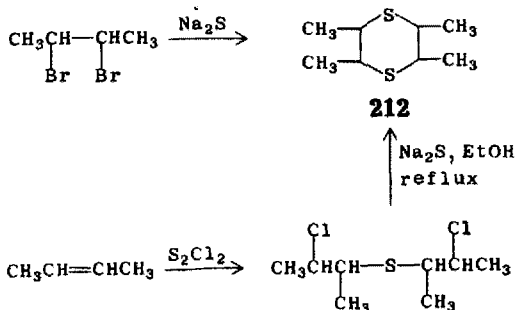


C₄S₂ Ring Systems

Gavrilov and Tischenko²⁰⁵ prepared alkyl-*p*-dithianes from the dibromides and sodium sulfide. According to these authors 1,2-dibromopropane and 1,2-dibromo-2-methylpropane react to give 2,6-dimethyl- and 2,2,6,6-tetramethyl-*p*-dithiane (**211**), respectively. The compounds were not characterized and no reason for the assignment of the unsymmetrical structures was given. In view of the results of Marvel and Weil,³⁵¹ it would probably be more reasonable to assign a 2,5-structure to these compounds. However, the formation of 2,3,5,6-tetramethyl-*p*-dithiane (**212**) from the symmetrical compound, 2,3-dibromobutane, appears reasonable. **212** had been prepared previously by Pope and Smith³⁹⁵ from bis(1-methyl-2-chloropropyl) sulfide.

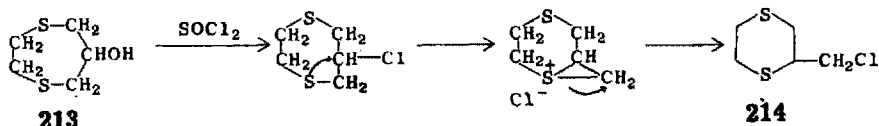


ture to these compounds. However, the formation of 2,3,5,6-tetramethyl-*p*-dithiane (**212**) from the symmetrical compound, 2,3-dibromobutane, appears reasonable. **212** had been prepared previously by Pope and Smith³⁹⁵ from bis(1-methyl-2-chloropropyl) sulfide.



Harman and Vaughan²⁴⁵ suggested the preparation of the 2,2,6,6-tetramethyl isomer (**211**) by the addition of hydrogen sulfide to dimethylallyl sulfide, but no example was given.

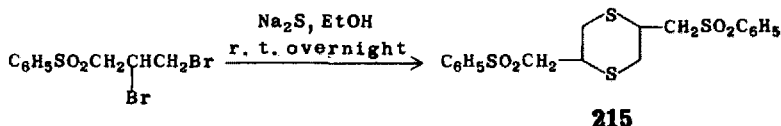
Fuson and Speziale²⁰⁴ prepared 2-chloromethyl-*p*-dithiane (**214**) by an unusual reaction, treatment of 6-hydroxy-1,4-dithiacycloheptane (**213**) with thionyl chloride. They postulated the reaction as taking the following course:



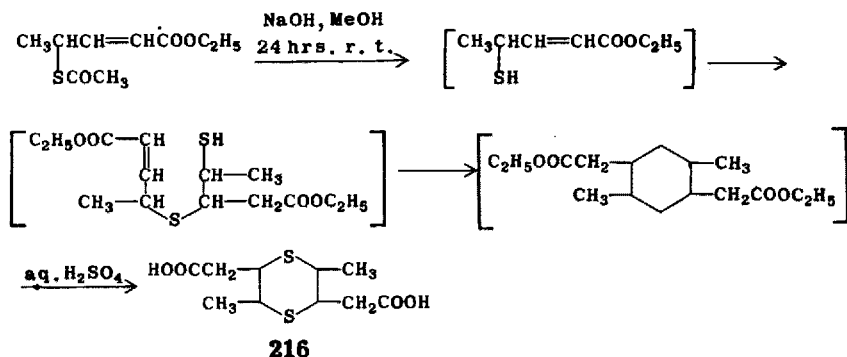
The compound could be hydrolyzed to the hydroxymethyl derivative.

Chapter 12

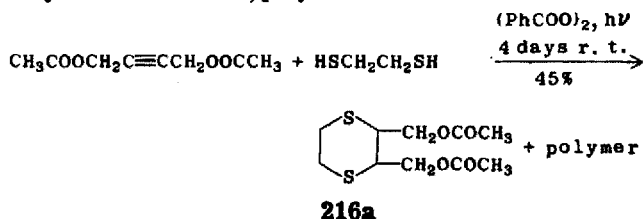
Troeger and Hornung⁴⁹⁴ reacted 1-phenylsulfonyl-2, 3-dibromopropane with potassium sulfide and isolated a compound which they formulated as a thirane derivative. Culvenor, Davies, and Savige¹⁴¹ repeated the work and showed the compound to be 2, 5-bis(phenylsulfonylmethyl)-*p*-dithiane (**215**); the *p*-tolyl derivative reacted similarly. Actually, the 2, 6-structure was not eliminated as a possibility.



Tschesche, Barkemeyer, and Heuschkel⁴⁹⁶ treated ethyl 4-acetylthio-2-pentenoate with base, hydrolyzed the product, and isolated a compound to which they assigned the structure 2, 5-dimethyl-*p*-dithiane-3, 6-diacetic acid (**216**) on the basis of its analysis, its molecular weight, and the absence of double bonds and of disulfide links. A reasonable course for the reaction would involve the base-catalyzed addition of a mercaptan to an activated double bond.



Blomquist and Wolinsky^{51a} prepared 2, 3-bis(acetoxymethyl)-*p*-dithiane (**216a**) by the photochemical addition of 1, 2-dimercaptoethane to 1, 4-butynediol diacetate; polymer was formed as well.



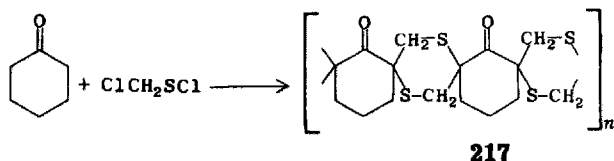
The structure of **216a** was assigned by analogy with the addition of simple mercaptans to a variety of acetylenic compounds.

There have been no reports of the isolation of *cis-trans* isomers of *p*-dithianes containing substituents of the types discussed in this section.

C₄S₂ Ring Systems

Kaufmann and co-workers²⁹⁹ reacted unsaturated fatty acids with thiocyanogen, hydrolyzed the products with alcoholic potassium hydroxide, and isolated crystalline materials from elaidic, brassidic, and erucic acids, which they formulated as tetrasubstituted *p*-dithianes. These compounds underwent ring cleavage during acid-catalyzed esterification of the carboxyl groups, and did not give the expected reactions with halogens. Inasmuch as the *p*-dithiane ring is very stable towards acidic reagents, the designation of these compounds as *p*-dithianes is suspect. The authors attributed the instability to the tetrasubstituted nature of the ring, but this does not seem reasonable if Tschesche and co-workers⁴⁹⁶ are correct in their assignment. A more detailed investigation utilizing modern instrumental techniques would be required to settle this point, which is of considerable importance in light of the suggestion by Kaufmann and co-workers that dithiane rings are present in factice prepared from fats and sulfur or sulfur monochloride, and also in vulcanized rubber.

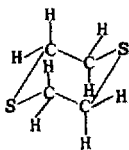
Brintzinger, Schmahl, and Witte⁷¹ treated cyclohexanone with chloromethylsulfenyl chloride. A vigorous reaction ensued, and a dark brown, thermoplastic, film-forming resin was formed. The authors formulated this as a spiro derivative of *p*-dithiane (**217**), but presented no evidence for this structure.



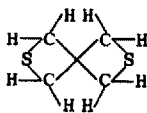
c. Structure and Physical Properties

p-Dithiane is a white, crystalline compound which melts at 111-112° and boils at 200° at atmospheric pressure. The compound is very volatile—it sublimates at room temperature and is readily steam-distilled. It is soluble in the common organic solvents and only slightly soluble in water. The compound forms a colorless solution in concentrated sulfuric acid and can be recovered unchanged.²⁸⁶ Its odor has been described variously as almost odorless,³⁵² strong but not too unpleasant,²⁸⁶ and very unpleasant.³⁵⁸ This may be a reflection of purity.

The structure of *p*-dithiane has been thoroughly investigated. Hassel²⁴⁸ and Hassel and Viervoll²⁴⁹ determined the structure of *p*-dithiane by electron diffraction. They found that two possible models fit their data, the now expected chair form (**218**) and a skew form (**219**). They considered that these might be in equilibrium. Although there is nothing inherently wrong with structure **219**, it has not been confirmed by other methods. The results for a number of sulfur-containing compounds have been tabulated by Allen and Sutton.³



218



219

The most precise determination of the structure of *p*-dithiane has been carried out by X-ray diffraction. The crystal is monoclinic.^{129,162,286} Dothie¹⁶² determined in a preliminary investigation that the molecule possesses a center of symmetry. Marsh³⁴⁷ carried out a detailed investigation and obtained results in striking confirmation of those of Hassel and Viervoll, as shown below, for *p*-dithiane existing in the staggered chair conformation (218).

	Electron diffraction	X-ray
S-C distance	1.81 Å	1.81 Å
C-C distance	1.54 Å	1.49 Å
S-S distance (non-bonded)		3.45 Å
S-C-C angle	111°	112.7°
C-S-C angle	100°	99.0°

Marsh did not consider the difference between his carbon-carbon distance and Hassel's to be significant. The sulfur-carbon distance equals the sum of the covalent radii and is therefore perfectly normal.

Calderbank and LeFèvre⁸⁵ found a zero dipole moment for *p*-dithiane in benzene. Inasmuch as the molecule is not flat, they were forced to the conclusion that there is no mobile equilibrium between boat and chair forms, and that the molecule exists in a rigid chair form. Presumably, the two bulky sulfur atoms *para* to each other introduce sufficient steric hindrance to prevent the boat form from contributing to the structure of the molecule.

There have been several determinations of the ultraviolet absorption spectrum of *p*-dithiane. Gibson, Graham, and Reid²¹³ found only general absorption for the molecule. Houston, Canning, and Graham²⁷¹ found that the absorption of several sulfur heterocycles decreases in the order *p*-dithiane > tetrahydrothiapyran > *p*-oxathiane, the same order found by Clarke¹²³ for their reactivity (see section III A-1g) and by Macbeth³³⁹ for the color found in complexes with tetranitromethane. Mohler³⁶⁶ found that *p*-dithiane in ethanol has an absorption band at 280 mμ, which he attributed to the free electrons on the sulfur atoms, whereas Fehnel and Carmack^{175a} reported an inflection at 225 mμ, which they too attributed to a direct S-S interaction. Mohler and Sorge³⁶⁷ found absorption maxima at 196 mμ and 226 mμ in hexane. The Raman spectrum of *p*-dithiane was determined by Médard,³⁵⁷ who found it to be much like that of diethyl sulfide, by Chernitskaya and Syrkin,¹⁰⁰ and by Hayasaki,^{253a} who also reported the Raman spectrum. Bedov

and Sergienko³⁷ determined the parachor of *p*-dithiane; it agreed closely with the calculated value.

d. Complexes of *p*-Dithiane

p-Dithiane, like many other sulfur-containing compounds, forms stable complexes with salts of heavy metals. Unlike complexes of many other sulfur compounds, however, these metal complexes are not sharp-melting compounds and are of little use, therefore, for identification purposes. The complexes are sometimes crystalline, sometimes microcrystalline, and sometimes amorphous powders. They are generally insoluble in organic solvents with very limited solubility in water. Because of their non-recrystallizability it is frequently difficult to determine if pure addition compounds were formed, and many unusual complexes have been reported.^{43,405,410}

Hendra and Powell^{254a} investigated the infrared spectra of a series of complexes C₄H₈S₂·MCl₂, where M = Cu, Hg, Cd, and Pt, as well as the AuCl₃ complex. They found the spectra to be very much like the spectrum of uncomplexed *p*-dithiane. Since the latter exists in the chair form, the complexes probably exist in the chair form too, and are not transformed into the boat form to satisfy the normal valences of the metals. For the metals to have their normal valences, the complexes must be polymeric, thus accounting for their insolubility and lack of sharp melting points. *p*-Oxathiane, on the other hand, forms monomeric, sharp-melting complexes of the type 2C₄H₈OS·MCl₂.

Table 9 lists those complexes whose stoichiometry appears reasonable.

Husemann²⁸⁶ and Bouknight and Smith⁵⁹ reported the majority of these complexes. The latter authors prepared the complexes by adding an alcoholic solution of *p*-dithiane to the metal salt dissolved generally in alcohol or in an aqueous solution. In several instances the formula of the precipitated complex depended on its method of formation. Thus, treatment of chloroplatinic acid in dioxane with *p*-dithiane yielded C₄H₈S₂·PtCl₄ and its dioxanate, C₄H₈S₂·PtCl₄·C₄H₈O₂, while in alcohol the complex isolated was 2C₄H₈S₂·PtCl₄. Other examples are shown in the table.

Schroyer and Jackman⁴⁴⁸ and West⁵⁰⁷ recommended *p*-dithiane as a precipitant for the gravimetric determination of mercury. Duval and Xuong¹⁶⁶ claimed that this procedure is unsatisfactory because the complex C₄H₈S₂·HgCl₂ loses weight above 97°.

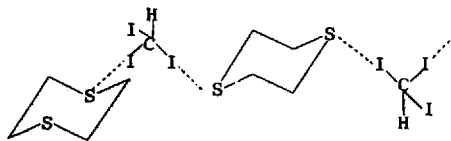
p-Dithiane forms a 1:1 addition compound with iodoform, m.p. 72°, whose structure was determined crystallographically by Bjorvatten and Hassel.^{50a} The *p*-dithiane molecules are situated in centers of symmetry, with the iodoform molecules in symmetry planes. Two iodine atoms of an iodoform molecule are linked to the sulfur atoms of neighboring *p*-dithiane molecules, resulting in an endless chain of alternating *p*-dithiane and iodoform molecules (219a).

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TABLE 9. Complexes of *p*-Dithiane with Metal Salts

Formula	Description	Ref.
$C_4H_8S_2 \cdot HgCl_2$	Microscopic plates, white	59, 166, 254a, 286, 448
$2C_4H_8S_2 \cdot 3HgCl_2$		286
$C_4H_8S_2 \cdot HgBr_2$	White leaflets	59, 286
$C_4H_8S_2 \cdot HgI_2$	Microscopic crystals, white	59, 286
$C_4H_8S_2 \cdot Hg(NO_3)_2$	White	59
$2C_4H_8S_2 \cdot Hg(ClO_4)_2$	White	59
$C_4H_8S_2 \cdot AgClO_4$	White	59
$C_4H_8S_2 \cdot 2AgNO_3$	White	59
$2C_4H_8S_2 \cdot AgNO_3$	White	59
$3C_4H_8S_2 \cdot 4AgNO_3$	Crystals dec. 140°	286
$C_4H_8S_2 \cdot CuCl_2$	Black	59, 254a
$C_4H_8S_2 \cdot CuBr_2$	Black	59
$2C_4H_8S_2 \cdot CuF_2$	Black	59
$C_4H_8S_2 \cdot Cu_2Cl_2$	White	59
$C_4H_8S_2 \cdot Cu_2Br_2$	White	59
$2C_4H_8S_2 \cdot Cu_2I_2$	White	59
$2C_4H_8S_2 \cdot Cu_2(CN)_2$	White	59
$C_4H_8S_2 \cdot PtCl_4$	Orange or yellow powder	59, 286
$C_4H_8S_2 \cdot PtCl_4 \cdot C_4H_8O_2$	Lemon yellow	59
$2C_4H_8S_2 \cdot PtCl_4$	Yellow	59
$C_4H_8S_2 \cdot PtCl_2$	White-pink	59, 254a, 409
$C_4H_8S_2 \cdot AuCl_3$		254a
$C_4H_8S_2 \cdot 2AuCl_3$	Red crystalline powder	286
$C_4H_8S_2 \cdot CdCl_2$	White	59, 254a
$C_5H_8S_2 \cdot CdBr_2$	White	59
$C_4H_8S_2 \cdot CdI_2$	White	59

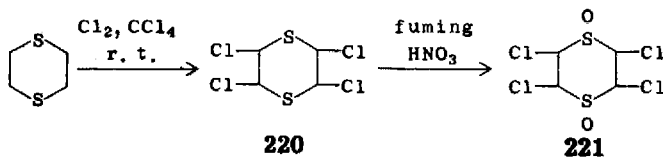
C₄S₂ Ring Systems



219a

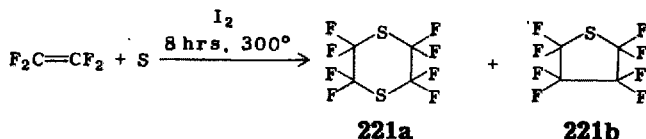
e. Halogen Derivatives

Two different types of halogen derivatives of *p*-dithianes have been reported, those with carbon-halogen bonds and those with sulfur-halogen bonds. Few derivatives of the first class are known. Varvoglis and Tsatsaronis⁴⁹⁹ chlorinated *p*-dithiane with chlorine in carbon tetrachloride and isolated a tetrachloride, m.p. 195-196°, with a weak camphoraceous odor, soluble in most organic solvents except alkanes. They formulated the compound as 2, 3, 5, 6-tetrachloro-*p*-dithiane (**220**), but offered no unequivocal proof for this assignment (see section III E). The compound decomposed in hot water, which would be expected. That the chlorine atoms are not attached to sulfur was shown by oxidizing the compound to 2, 3, 5, 6-tetrachloro-*p*-dithiane 1, 4-dioxide (**221**), m.p. 102°.



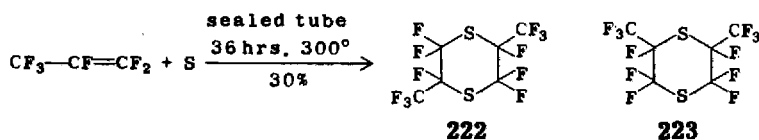
Haubein²⁵¹ chlorinated *p*-dithiane in carbon tetrachloride at -10° with somewhat less than one mole of chlorine to prepare chloro-*p*-dithiane. With more chlorine at $5-10^\circ$, a mixture of crystals and liquid was obtained, the latter boiling at $145-160^\circ$ at 16 mm and analyzing as a dichloro-*p*-dithiane,²⁵⁰ while with four moles of chlorine at $55-80^\circ$, a tetrachloro-*p*-dithiane was formed.²⁵² No attempt was made to isolate pure compounds or to prove the structures.

Krespan³¹⁷ reported that tetrafluoroethylene reacts with sulfur, preferably in the presence of iodine, to give a 44% yield of 2,2,3,3,5,5,6,6-octafluoro-*p*-dithiane (**221a**), b.p. 81°, n_D^{25} 1.3568, plus some octafluorothiolane (**221b**).

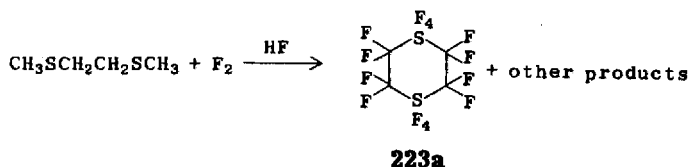


Brown⁷⁶ heated sodium heptafluorobutyrate with sulfur in a sealed tube and isolated a pure compound, b.p. 112-113°, n_D^{25} 1.3390-1.3406, which analyzed as $C_6F_{12}S_2$. Inasmuch as the salt is known to undergo pyrolysis to hexafluoropropene, the reaction was carried out on the latter and the same compound was isolated. The compound was stable to refluxing alkali; it is therefore not a disulfide, since fluorocarbon

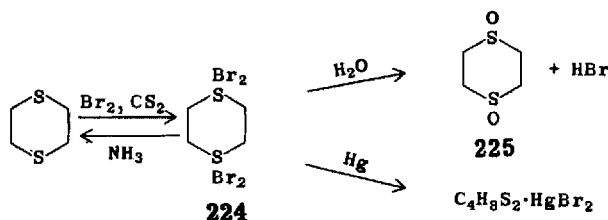
polysulfides hydrolyze readily. Brown therefore formulated it as either 2, 5-bis(trifluoromethyl)-2, 3, 3, 5, 6, 6-hexafluoro-*p*-dithiane (**222**) or 2, 6-bis(trifluoromethyl)-2, 3, 3, 5, 5, 6-*p*-dithiane (**223**).



Dresdner and Young^{165a} fluorinated 1,2-bis(methylthio)ethane by the Simons electrolytic procedure and isolated a crystalline compound, m.p. 76-76.5°, which they formulated on the basis of analysis as perfluoro-*p*-dithiane octafluoride (**223a**).

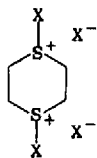


The very earliest reports on *p*-dithiane by Crafts^{129,130} and by Husemann²⁸⁶ described the reaction of *p*-dithiane with halogens. Chlorine gave a product too unstable to be isolated. Bromine in carbon disulfide, however, gave a yellow tetrabromide, $C_4H_8S_2Br_4$ (**224**), which began to lose bromine at 70° and melted at 96° with decomposition. That the bromine is attached to sulfur and not to carbon was shown by the fact that treatment with water or alcohol gave *p*-dithiane 1,4-dioxide (**225**) and hydrogen bromide. Mercury formed the mercuric bromide complex of *p*-dithiane, while treatment with ammonia regenerated *p*-dithiane.



Iodine gave a more stable compound, $C_4H_8S_2I_4$, isolated as needle-like crystals which were red by transmitted light and black by reflected light. It began to lose iodine below 100° and melted at $132-133^\circ$. However, it was stable to water and to alcohol.²⁸⁶ Bachem²² investigated the use of the tetraiodide as an antiseptic on wounds with inconclusive results.

The work of Böhme and Boll⁵⁴ would suggest that these halogenides have the structure 226.

**226**

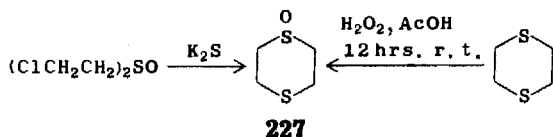
However, a preliminary crystallographic determination by McCullough, Chao, and Zuccaro^{339a} showed that the diiodide is a molecular complex with, according to Hassel, equatorial iodines, the S-S-I angle being 130° (**226a**). Good, Major, and co-workers,²²⁸ also claimed that iodine complexes of ethyl mercaptan, diethyl sulfide, and diethyl disulfide are molecular and not ionic complexes.

**226a**

Nevertheless, in the corresponding *p*-diselenane complex (see Chapter 13, section 3 B-1) the Se-I distance is close to the expected covalent bond distance, and the I-I distance is longer than expected, indicating probably a structure approaching that of **226**. It is interesting that the *p*-diselenane complex has a different conformation, in spite of an apparent isomorphism between it and the *p*-dithiane complex.

f. Oxides

A variety of sulfoxides and sulfones derived from *p*-dithianes have been reported, as illustrated in Table 10. *p*-Dithiane 1-oxide (**227**) was first prepared by Bell and Bennett⁴⁰ by the condensation of bis(2-chloroethyl) sulfoxide with potassium sulfide; the yield was low, the major product being polymer. It was also formed, together with higher oxidation products, by the oxidation of *p*-dithiane with a limited amount of hydrogen peroxide.



The water-soluble, crystalline sulfoxide, m.p. 125°, was converted into its platinum chloride and gold chloride complexes.

The disulfide, *p*-dithiane 1,4-dioxide (**228**), was the first oxidation product isolated. It was prepared by Crafts by hydrolysis of 1,1,4,4-tetrabromo-*p*-dithiane (**224**)^{129,130} and by nitric acid oxidation of *p*-dithiane;^{131,132} both procedures were used by Husemann,²⁸⁶ and the nitric acid oxidation by Dehn.^{151,152}

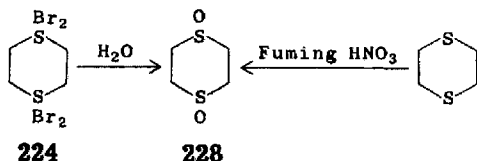
TABLE 10. Oxides of *p*-Dithiane

Substituents	Yield (%)	M.p. (°C)	Remarks	Ref.
1-Oxide	28	125		40
1-Oxide · 1/2 PtCl ₄			Pale yellow powder	40
1-Oxide · AuCl ₃			Deep orange powder	40
1,1-Dioxide	low	206		2, 244
	9.3	203		40
		200		199
	39	205-207		507a
2, 6-(CH ₃) ₂ 4, 4-dioxide	49, 39	146		26, 351
		dec. ~200	Rhombic needles, prisms	129-132, 151, 152, 286
	100			199
	62	dec. 263	α-form, plates, monoclinic	38
	13		β-form, needles, anorthic	38
	93-94	263-265 (dec.)	α-form	507a
	6-7	242-243 (dec.)	β-form	507a
?			White crystals	286
2-Cl ₂ 1, 4-dioxide		102		499
2 3, 5, 6-Cl ₄ 1, 4-dioxide		278-279		40, 199
1, 1, 4-Trioxide				34, 43, 131, 132, 238b,
1, 1, 4, 4-Tetroxide	100			286, 376, 406, 426a

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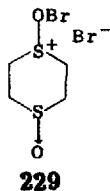
2-CH ₃ -1,1,4,4-tetroxide		304-306 (dec.)	203
2-ClCH ₂ -1,1,4,4-tetroxide	79-83	303-304 (dec.)	204
2-HOCH ₂ -1,1,4,4-tetroxide	85-91	255-256 (dec.)	204
2-CH ₃ CO ₂ CH ₂ -1,1,4,4-tetroxide	70	277-278	204
2-C ₆ H ₅ CO ₂ CH ₂ -1,1,4,4-tetroxide	70	256-257	204
2-(CH ₂ =)1,1,4,4-tetroxide		261-262 (dec.)	204
Δ ^{3,2} -2-CH ₃ -1,1,4,4-tetroxide	77	233-234 (dec.)	204
2,5-(CH ₃) ₂ 1,1,4,4-tetroxide	50	250-251 (dec.)	Compounds were isolated pure, but structures were not assigned
		31 _b	464
		320	284
	35, 90	334, 332	227
	95	332 ± 2	351
		320	26
2,6-(CH ₃) ₂ 1,1,4,4-tetroxide	100	313	351
2,5-(<i>n</i> -C ₃ H ₇) ₂ 1,1,4,4-tetroxide	40, 90	257, 254-256	227, 350
		249-251	349
2,5-(<i>n</i> -C ₆ H ₁₃) ₂ 1,1,4,4-tetroxide	40	265	227
2,5-(<i>n</i> -C ₇ H ₁₅) ₂ 1,1,4,4-tetroxide	14	260-261	227
2,5-(C ₆ H ₅) ₂ 1,1,4,4-tetroxide	25, 80-85	279, 280	227
	42	>325	373b
2,5-[-(CH ₂) ₈ CO ₂ H] ₂ 1,1,4,4-tetroxide		164-18 _b	349
2- <i>n</i> -C ₃ H ₇ -5-[-(CH ₂) ₆ CO ₂ H]1,1,4,4-tetroxide	75	198	349
2,5-(C ₆ H ₅ SO ₂ CH ₂) ₂ 1,1,4,4-tetroxide			494
2,5-(<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ CH ₂) ₂ 1,1,4,4-tetroxide			494

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Fromm and Ungar¹⁹⁹ claimed a quantitative yield of **228** with the calculated amount of hydrogen peroxide in acetic acid, while Whitaker and Sisler^{507a} obtained a quantitative yield with dinitrogen tetroxide in chloroform at 0° . *p*-Dithiane 1,4-dioxide was isolated as rhombic needles or prisms. It is soluble in water and in acetic acid, and can be recrystallized from hot ethanol.^{40, 507a} Husemann²⁸⁶ treated a water solution with chlorine and isolated a dichloro derivative, $\text{C}_4\text{H}_6\text{O}_2\text{S}_2\text{Cl}_2$, as microscopic needles; its structure was not determined, but the analysis showed that chlorination took place by substitution.

That the disulfoxide should exist in two stereoisomeric forms is now well known, but Bell and Bennett³⁸ first proved that sulfoxides are not planar by separating *p*-dithiane 1,4-dioxide into its *cis* and *trans* isomers. *p*-Dithiane was oxidized with the theoretical quantity of hydrogen peroxide in acetic acid at 0° . The two forms were separated by crystallization from aqueous ethanol, the less soluble form being designated the α -isomer and the more soluble the β -isomer. The two isomers differed in their crystal form as well, the α -isomer forming plates and the β -isomer needles. The α -isomer was identical with Crafts' disulfoxide, and the $\alpha:\beta$ ratio was about 9:1. Both isomers were reduced to *p*-dithiane with zinc and hydrochloric acid or with hydrogen iodide, showing that neither compound was a sulfone. They formed crystalline adducts with mercuric chloride, $\text{C}_4\text{H}_8\text{S}_2\text{O}_2 \cdot 2\text{HgCl}_2$, and here too the β -isomer gave the more soluble product.⁴⁰ They both formed unstable monohydrochlorides, hydrobromides and dibromides; for the last of these, structure **229** was proposed.⁴⁰

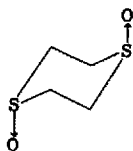


Whitaker and Sisler^{507b} obtained 93-94% α -isomer and 6-7% β -isomer with dinitrogen tetroxide in chloroform.

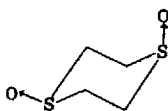
Attempts to interconvert the two isomers by treatment with hot hydrochloric acid were unsuccessful; *p*-dithiane was formed.³⁸ By analogy with other systems Bell and Bennett tentatively assigned the *trans* structure to the less soluble α -form.³⁸ This has been confirmed by Shearer⁴⁵¹ and Montgomery,^{367a} who recently carried out X-ray crystallographic determinations of the structures of the α - and β -isomers. The α -isomer was found to exist in the chair form with the oxygen

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atoms, rather surprisingly, *trans*-diaxial (**230**). The β -isomer exists in the chair form with the oxygens *cis* (**231**).



230



231

Bond distances and angles are normal, with fairly good agreement between the two structures:

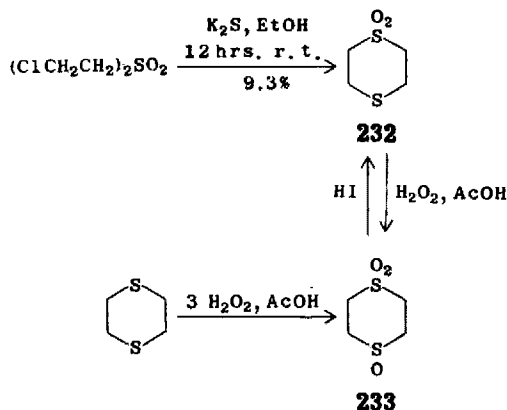
	α -Isomer	β -Isomer
C—C	1.51 Å	1.47 Å
C—S	1.81 Å	1.78 Å
S—O	1.48 Å	1.42 Å
C—C—S angle	112.3°	112.9°
C—S—C angle	97.9°	97.1°
C—S—O angle	107.4°	110.4°

Gibson, Graham, and Reid²¹³ found only general absorption in the ultraviolet region for *p*-dithiane 1,4-dioxide. Chernitskaya and Syrkin¹⁰⁰ reported the Raman spectrum of the disulfoxide.

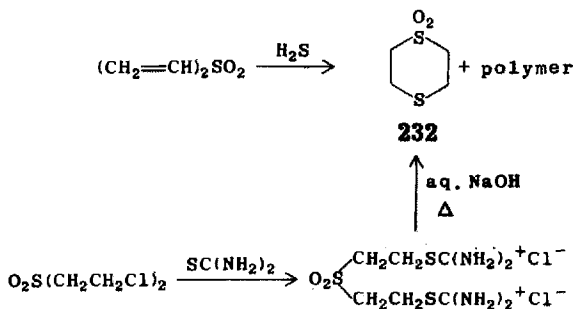
A compound, to which the structure 2,3,5,6-tetrachloro-*p*-dithiane had been assigned,⁴⁹⁹ was oxidized to the corresponding 1,4-dioxide with fuming nitric acid.

Helfrich and Reid²⁵⁴ reacted bis(2-chloroethyl) sulfone with sodium sulfide and isolated an amorphous white solid which they tentatively designated as *p*-dithiane 1,1-dioxide (**232**). Bell and Bennett⁴⁰ repeated the experiment and showed Helfrich and Reid's compound to be a polymer. They succeeded in isolating, however, a crystalline, water-soluble compound, m.p. 203°, which was undoubtedly *p*-dithiane 1,1-dioxide, inasmuch as it was identical with a product prepared by Fromm and Ungar¹⁹⁹ by the reduction of *p*-dithiane 1,1,4-trioxide (**233**), and it could be oxidized to a product identical with their trioxide.

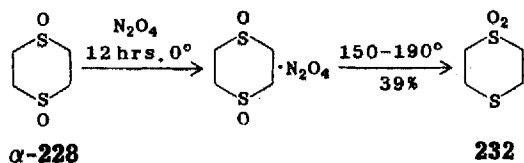
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Alexander and McCombie² isolated a small amount of *p*-dithiane 1,1-dioxide (**232**), along with much polymer, by the reaction of divinyl sulfone with hydrogen sulfide. Harley-Mason²⁴⁴ obtained the same results on alkaline hydrolysis of the bis(thiuronium chloride) from bis(2-chloroethyl) sulfone.



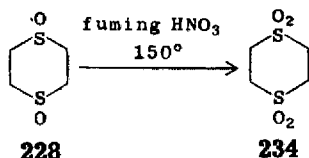
Whitaker and Sisler^{507a} reported an unusual synthesis of *p*-dithiane 1,1-dioxide (**232**). Treatment of *p*-dithiane α -1,4-dioxide (**228**) with dinitrogen tetroxide at 0° gave, probably, a 1:1 adduct. Heating the adduct converted it into the monosulfone. Although the β -1,4-dioxide also formed an adduct, it yielded no sulfone on heating.



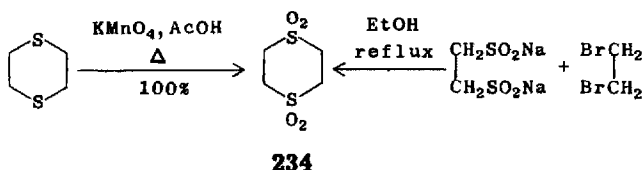
Thus, with the well-known tetroxide, all the possible oxides of *p*-dithiane have been described: one monosulfoxide, two disulfoxides, one sulfoxide-sulfone, and one disulfone.

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The disulfone, *p*-dithiane 1, 1, 4, 4-tetroxide (**234**), was first reported by Crafts,^{131,132} who prepared it by oxidizing *p*-dithiane 1, 4-dioxide (**228**) with fuming nitric acid at 150°; this was confirmed by Husemann.²⁸⁶

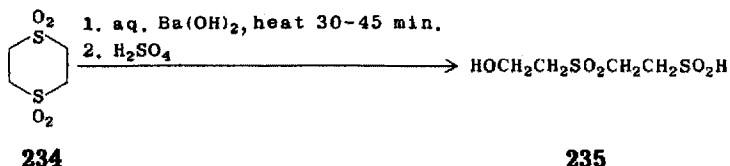


Otto³⁷⁶ claimed that permanganate in acetic acid is much superior to fuming nitric acid, and also prepared the disulfone from sodium 1, 2-ethanedisulfinate and ethylene bromide.



Baumann and Walter³⁴ obtained the same results by oxidizing *p*-dithiane with potassium permanganate and sulfuric acid. Rây⁴⁰⁶ used the same procedure on his so-called triethylene trisulfide, but Bennett and Berry⁴³ proved that the product was *p*-dithiane 1, 1, 4, 4-tetroxide. Fromm and Ungar¹⁹⁹ claimed a quantitative yield of the disulfone by oxidizing *p*-dithiane with hydrogen peroxide in acetic acid. According to Hesse, Reichold, and Majmudar²⁵⁷ Fromm and Ungar's product was a polymer, a surprising conclusion in view of the other *p*-dithiane oxidations carried out by Fromm and Ungar, and others, with this reagent.

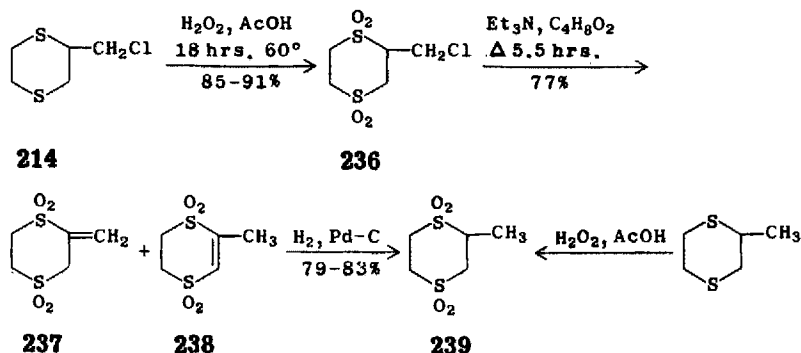
p-Dithiane 1, 1, 4, 4-tetroxide is a white crystalline compound; it does not have a melting point. It is insoluble in water and in organic solvents but dissolves in hot concentrated nitric or sulfuric acids.^{34,131,376} In contrast to its extreme stability under acidic conditions, it is readily decomposed under alkaline conditions,^{34,376} in agreement with Stuffer's rule,⁴⁷³ to give 2-(2-hydroxyethylsulfonyl)ethanesulfinic acid (**235**).



2-Methyl-*p*-dithiane 1, 1, 4, 4-tetroxide (**239**) was first prepared by Fuson and Speziale²⁰³ by hydrogen peroxide oxidation of 2-methyl-*p*-dithiane. It was also prepared, however, by these same authors²⁰⁴ from 2-chloromethyl-*p*-dithiane (**214**). Oxidation of **214** yielded 2-chloromethyl-*p*-dithiane 1, 1, 4, 4-tetroxide (**236**) which, on treatment with triethyl-

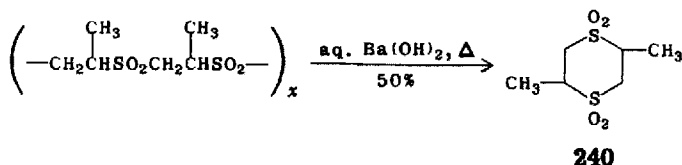
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amine, gave a mixture of 2-methylene-*p*-dithiane 1,1,4,4-tetroxide (237) and 2,3-dihydro-5-methyl-*p*-dithiin 1,1,4,4-tetroxide (238); the mixture was separated into the two pure compounds, but the compounds were not identified. Both were reduced to 2-methyl-*p*-dithiane 1,1,4,4-tetroxide (239), identical with that prepared from 2-methyl-*p*-dithiane.



The same mixture of unsaturated sulfones was obtained by treatment of 2-hydroxymethyl-*p*-dithiane 1,1,4,4-tetroxide with phosphorus oxychloride in pyridine.

Staudinger and Ritzenthaler⁴⁶⁴ found that treatment of poly(propylene sulfone) with aqueous barium hydroxide gave a crystalline solid, m.p. 315°, to which they arbitrarily assigned the structure 2,5-dimethyl-*p*-dithiane 1,1,4,4-tetroxide (240), assuming the polymer to be head-to-tail.

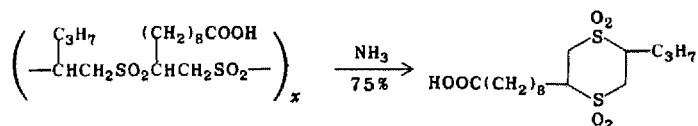


Marvel and co-workers^{227,284,349,350} carried out an intensive investigation of olefin-sulfur dioxide polymers and came to the erroneous conclusion that these polymers were head-to-head, tail-to-tail polymers, and that the disulfone described by Staudinger and Ritzenthaler was actually the 2,6-dimethyl isomer. Subsequently, Marvel and Weil³⁵¹ showed that rearrangement had taken place in their alternative syntheses of these *p*-dithiane derivatives, and that the compounds are actually 2,5-derivatives of *p*-dithiane 1,1,4,4-tetroxide (see section III A-1b) as originally postulated by Staudinger and Ritzenthaler.

Hunt and Marvel²⁸⁴ found that 2,5-dimethyl-*p*-dithiane 1,1,4,4-tetroxide (240) could be obtained in quantitative yield by dissolving the propylene-sulfur dioxide polymer in cold 1*N* sodium hydroxide. Glavis, Ryden, and Marvel²²⁷ carried out the same reaction by dissolving the polymer in liquid ammonia and allowing the ammonia to evaporate. In

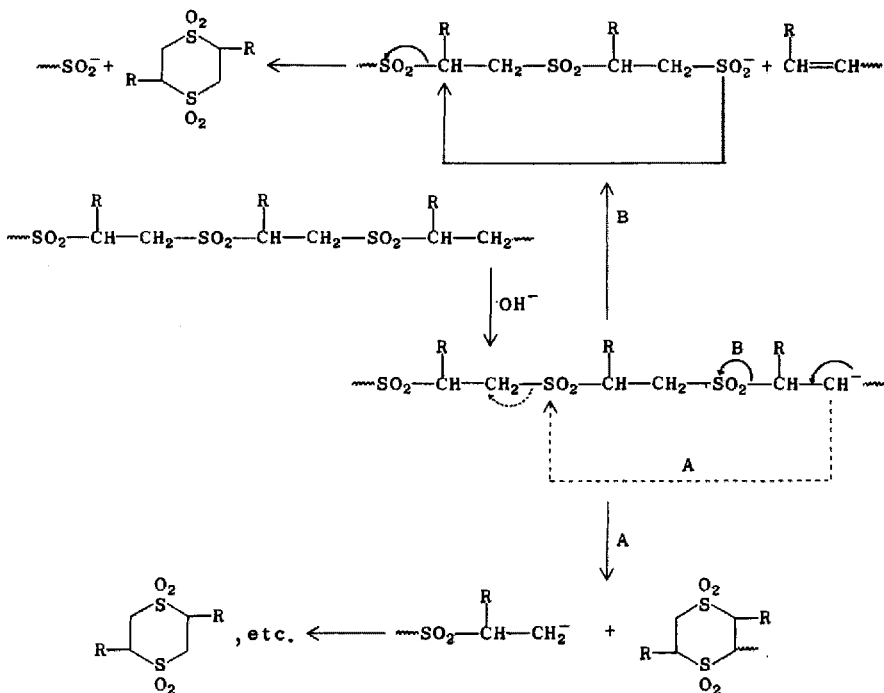
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this way they prepared 2,5-dimethyl-*p*-dithiane 1,1,4,4-tetroxide (**240**) from the propylene-sulfur dioxide polymer, the 2,5-di-*n*-propyl derivative from the 1-pentene polymer, the 2,5-di-*n*-hexyl derivative from the 1-octene polymer, the 2,5-di-*n*-heptyl derivative from the 1-nonene polymer, and the 2,5-diphenyl derivative from the styrene polymer. Marvel, Davis, and Glavis³⁴⁹ prepared a terpolymer from equimolar amounts of 1-pentene and undecylenic acid with sulfur dioxide, and isolated a 75% yield of 2-*n*-propyl-5-(8-carboxyoctyl)-*p*-dithiane 1,1,4,4-tetroxide (**241**) on treatment with ammonia, showing that the copolymer was a strictly alternating one.



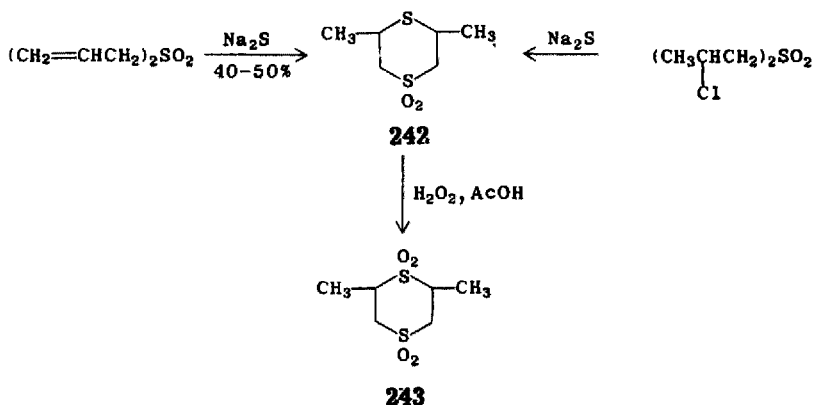
241.

Inasmuch as olefin-sulfur dioxide polymers are readily prepared, this hydrolytic route constitutes one of the simplest methods for the preparation of compounds possessing the *p*-dithiane ring system. Although no mechanisms have been proposed, a reasonable course would involve an unzipping down the chain initiated by carbanion formation by either paths A or B.

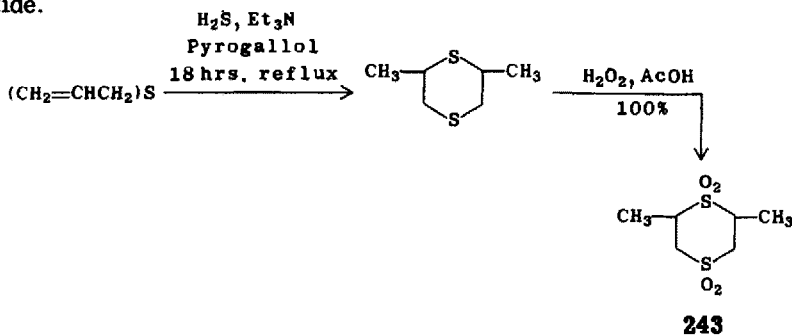


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Backer and van der Ley²⁶ had prepared 2,6-dimethyl-*p*-dithiane 4,4-dioxide (**242**) by the addition of sodium sulfide to diallyl sulfone; oxidation gave the tetroxide (**243**). Marvel and Weil³⁵¹ repeated the preparation, and also prepared the dioxide (**242**) from bis(2-chloropropyl) sulfone.

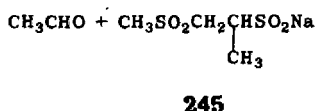
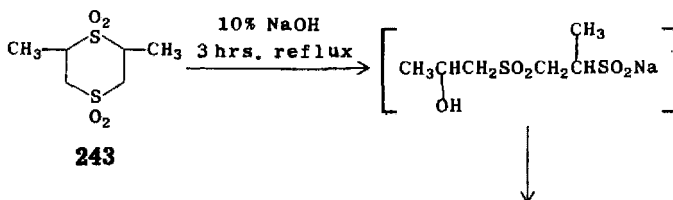
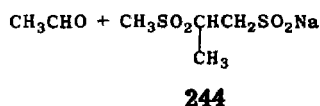
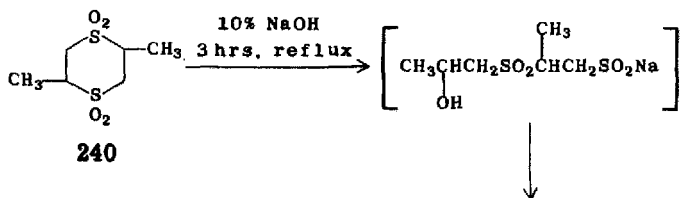


The diallyl sulfone addition probably involved a prior isomerization to dipropenyl sulfone followed by addition. Whereas Backer and van der Ley reported a melting point of 146° for the dioxide, Marvel and Weil found a melting point of 130-140°, presumably a mixture of *cis-trans* isomers, since recrystallization gave a melting point of 146°, and oxidation of the mixture gave the same disulfone as obtained from the pure compound. Backer and van der Ley reported a melting point of 320° for the disulfone, while Marvel and Weil reported it to be 313°. In spite of the similarity of the melting points of 2,5-dimethyl-*p*-dithiane 1,1,4,4-tetroxide (**240**) and the 2,6-isomer (**243**), Marvel and Weil showed their non-identity by infrared spectra. As further proof, Marvel and Weil prepared the 2,6-isomer by the addition of hydrogen sulfide to diallyl sulfide.



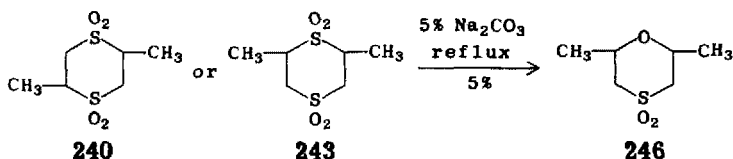
Refluxing the disulfones with 10% sodium hydroxide led to cleavage, the 2,5-isomer (**240**) forming acetaldehyde and sodium 2-methylsulfonyl-1-propanesulfinate (**244**) and the 2,6-isomer (**243**) acetaldehyde and sodium 1-methylsulfonyl-2-propanesulfinate (**245**).³⁵¹

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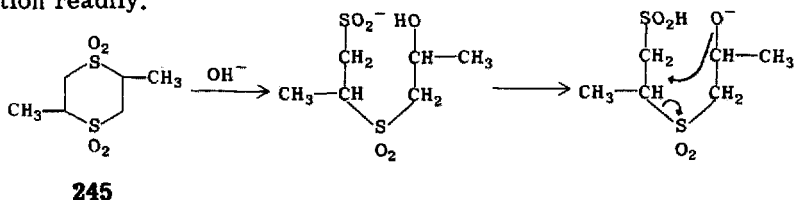


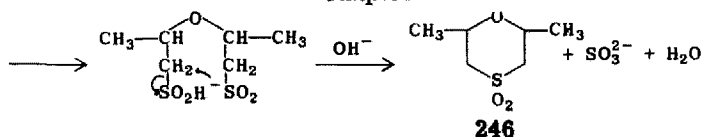
Here, too, the initial work of Hunt and Marvel²⁸⁴ was in error because of a rearrangement which occurred in the presumably unequivocal synthesis of the sulfinate (**245**).

Hunt and Marvel²⁸⁴ had found that refluxing the propylene-SO₂ polymer with aqueous sodium carbonate gave a low yield of 2,6-dimethyl-*p*-oxathiane 4,4-dioxide (**246**). Marvel and Weil³⁵¹ found that the same compound was formed from either **240** or **243**.



A reasonable mechanism for the rearrangement might be as follows, based on the fact that β -hydroxysulfones undergo base-catalyzed etherification readily.

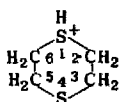




LeFave³²⁴ treated 2, 5-dimethyl-*p*-dithiane 1, 1, 4, 4-tetroxide (**240**) with aqueous potassium cyanide and isolated an acid which he assumed to be methylsuccinic acid.

Pollitzer³⁹⁴ patented the use of *p*-dithiane 1-oxide and 1, 4-dioxide as selective solvents for separating saturated and unsaturated hydrocarbons.

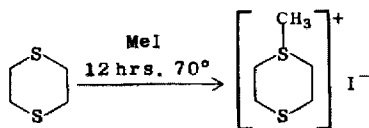
g. 1, 4-Dithianium Compounds (246a)



246a

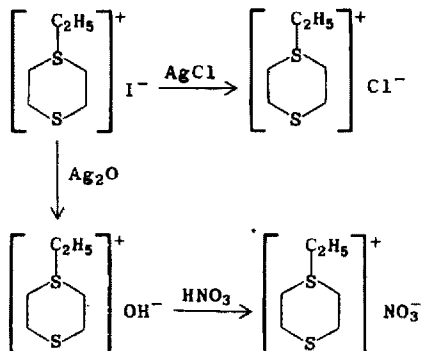
(RRI 268)

The ready alkylation of *p*-dithiane with alkyl halides to form sulfonium compounds was discovered independently by Masson³⁵² and by Mansfeld^{345, 346} in 1886, as illustrated by the preparation of 1-methyl-1, 4-dithianium iodide (**247**).



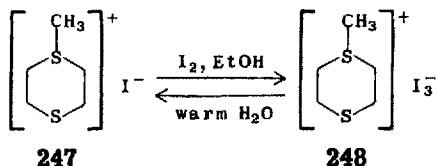
247

Since that time a variety of 1, 4-dithianium compounds have been prepared, as shown in Table 11. With simple alkyl halides only the iodide reacts successfully. 1-Benzyl-1, 4-dithianium bromide could be prepared from benzyl bromide, but the reaction with benzyl chloride failed.³⁴⁶ A number of salts were prepared by metathesis, or by neutralization of the free base with the requisite acid.³⁴⁶

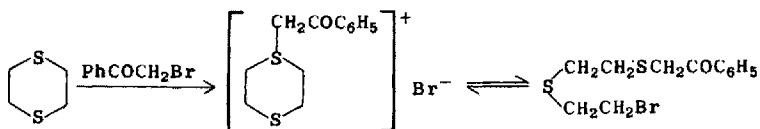


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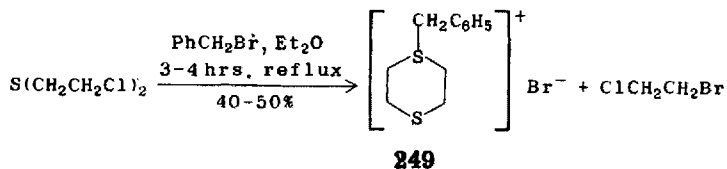
Masson³⁵² obtained a triiodide (**248**) by treatment of the methiodide (**247**) with iodine; warm water regenerated the methiodide.



Clarke¹²³ used sulfonium salt formation with phenacyl bromide to compare the reactivities of *p*-dithiane, tetrahydrothiapyran, and *p*-oxathiane; the adducts were not isolated. Reactivity decreased in the above order, in agreement with several other independent observations. No reasonable explanation has been forthcoming for these differences. In the course of his work Clarke found an unusual effect with *p*-dithiane; the quantity of ionic bromine rose and then fell. Bell, Bennett, and Hock³⁹ attributed this to ring opening *via* reversible sulfonium salt formation.



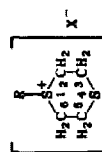
Nenitzescu and Scărlătescu³⁷³ prepared both 1-methyl-1,4-dithianium iodide (**247**) and 1-benzyl-1,4-dithianium bromide (**249**) from bis(2-chloroethyl) sulfide and the corresponding halide; bis(2-bromoethyl) sulfide reacted more rapidly. The reaction can be formulated according to the scheme of Bell, Bennett, and Hock.³⁹



Salts with simple anions are quite soluble in water. However, a variety of sparingly soluble complex compounds with heavy metal salts have been reported; many of these are probably impure mixtures. Masson³⁵² claimed that the methiodide (**247**) sublimed above 100° without melting and regenerated *p*-dithiane; according to Mansfeld,³⁴⁶ however, the methiodide melts at 175°. There can be little doubt, from inspection of the melting points listed in Table 11, that at least some 1,4-dithianium salts possess considerable thermal stability.

1-Methyl-1,4-dithianium hydroxide (**250**), on the other hand, is quite unstable. It exists apparently only in dilute aqueous solution, and decomposes at the boiling point of water; Green and Sutherland²³³ investigated the reaction kinetically. Mansfeld³⁴⁶ isolated a pure compound,

TABLE 11. 1, 4-Dithianium Compounds



R	Other substituents	Anion	Yield (%)	M.p. (°C)	Remarks	Ref.
CH ₃ -		Cl ⁻		225	orange crystals	346, 352
		1/2 PtCl ₆ ²⁻				352
		Cl ⁻ · PtCl ₄			insol. amorphous yellow powder	352
		AuCl ₄ ⁻			yellow crystals	346, 352
		HgCl ₃ ⁻			white needles	352
		Cl ⁻ · 2HgCl ₂		~198		470
		Cl ⁻ · 3HgCl ₂		dec. 230		470
		Cl ⁻ · 6HgCl ₂		175		470
		I ⁻		174	rhombic crystals, white	345, 346, 352
			20-25			4, 373
		I ₃ ⁻		92-93		346
				~89	dark red crystals	352
				172		346, 352
		NO ₃ ⁻			barb-like crystals	352
		NO ₃ ⁻ · AgNO ₃				
		1/2 SO ₄ ²⁻			3.5 H ₂ O, very stable	346, 352
		2, 4, 6-(NO ₂) ₃ C ₆ H ₂ O ⁻		192-193	picrate	346
		2, 4, 6-(NO ₂) ₃ C ₆ H ₂ SO ₃ ⁻		240-242 (dec.)	picrylsulfonate, long yellow needles	342
C ₂ H ₅ -		Cl ⁻				345
		Cl ⁻ · 2HgCl ₂				345
		I ⁻				345

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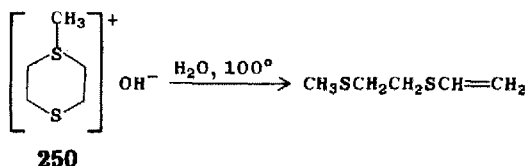
$C_6H_5CH_2-$	Cl^-	143	346
	Br^-	40-50	346, 373
	I^-	dec. 145	346
	NO_3^-		346
	$\frac{1}{2}SO_4^{2-}$		346
	$2, 4, 6-(NO_2)_3C_6H_2O^-$	111-112	346
$HOCH_2CH_2-$	Cl^-	30	147, 463
	$HgCl_3^-$	95-96	147
$ClCH_2CH_2-$	Cl^-	144	463
CH_2CH-	$2, 4, 6-(NO_2)_3C_6H_2SO_3^-$	85	463
$-CH_2CH_2S_2O_3^-$		75-78	463
$+C_5H_5NCH_2CH_2-$	$2Cl^-$	88	463
$-CH_2CO_2H$	F^-	150-152	471
	Cl^-	136 (dec.)	monohydrate
	Cl^-	167 (dec.)	471
	$\frac{1}{2}PtCl_4^{2-}$	dec. 150	crystalline
	$Cl^- \cdot PtCl_4$		amorphous
	Br^-	159 (dec.)	prisms
	NO_3^-	109	monohydrate
	NO_3^-	130 (dec.)	anhydrous
	$C_6H_5SO_3^-$	171	471
	$CH_3CO_2^-$	116-117	471
	$Cl_3CCO_2^-$	91 (dec.)	471
	$2, 4, 6-(NO_2)_3C_6H_2O^-$	149	471
$-CH_2CO_2^-$		108-109	yellow needles
		dec. ~145	dihydrate
			anhydrous

TABLE 11. 1, 4-Dithianium Compounds (contd)

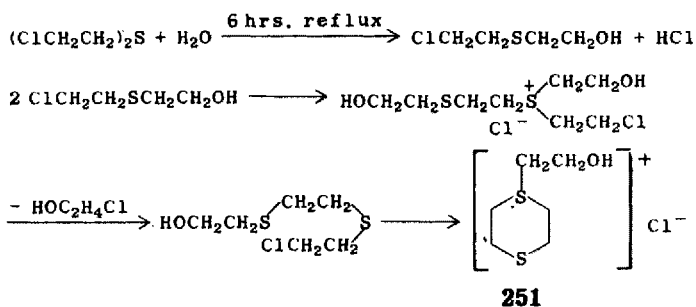
$-\text{CH}_2\text{CO}_2^- \cdot \frac{1}{2}\text{PtCl}_2$					471
$-\text{CH}_2\text{CO}_2^- \cdot \frac{1}{2}\text{HBr}$				179 (dec.)	471
$-\text{CH}_2\text{CO}_2\text{HgCl}$		$\text{Cl}^- \cdot 3\text{HgCl}_2$		180	470
CH_3^-	4-oxide	Br^-		181-184 (dec.)	472
	4-oxide	$\frac{1}{2}\text{PtCl}_6^-$			472
	4-oxide	I^-	87		40
	4-oxide	$2, 4, 6-(\text{NO}_2)_3\text{C}_6\text{H}_2\text{O}^-$	187	mixture of α - and β -forms	40
	4-oxide	$2, 4, 6-(\text{NO}_2)_3\text{C}_6\text{H}_2\text{O}^-$	137	α -form	40
	4-oxide	$\frac{1}{2}\text{PtCl}_6^-$		β -form	40
	4-oxide	$\frac{1}{2}\text{PtCl}_6^-$		α -form, orange plates	40
	4-oxide	$\frac{1}{2}\text{PtCl}_6^-$		β -form, buff	40
$-\text{CH}_2\text{CO}_2\text{H}$	4-oxide	Br^-	158-159	thick plates	471
	4-oxide	$\frac{1}{2}\text{PtCl}_6^-$			
$-\text{CH}_2\text{CO}_2^-$	4-oxide			$4, 5\text{H}_2\text{O}$, red-yellow prisms	471
$-\text{CH}_2\text{CO}_2^- \cdot \frac{1}{2}\text{HBr}$	4-oxide		133 (dec.)	long leaflets	471
$\text{Br}_2\text{CH}-$	4-oxide	Cl^-	168		471
	4-oxide	Br^-	dec. ~ 156		471
	4-oxide		dec. ~ 135	colorless prisms or needles	471

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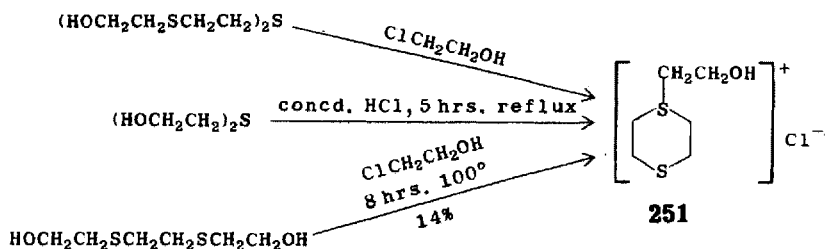
C₅H₁₀S₂, from the decomposition; V. Meyer³⁵⁸ obtained the same compound from the methiodide and sodium hydroxide. They both suggested that the compound might be vinyl 2-methylthioethyl sulfide, and this was confirmed by Demuth and V. Meyer¹⁵³ by an unequivocal synthesis. Its formation is analogous to the Hofmann degradation.



Davies and Oxford¹⁴⁷ investigated the hydrolysis of mustard gas, bis(2-chloroethyl) sulfide. With excess water the expected product, bis(2-hydroxyethyl) sulfide, was obtained. With a limited amount of water, however, a complex mixture of sulfonium compounds was formed, from which was isolated 1-(2-hydroxyethyl)-1,4-dithianium chloride (**251**). One plausible mechanism suggested by these authors involves reversible sulfonium salt formation.

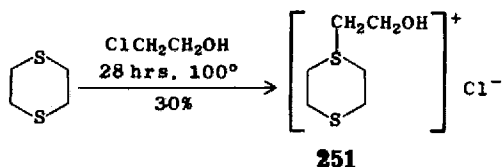


As evidence for this scheme it was shown that **251** is formed from bis(2-hydroxyethyl) sulfide and limited amounts of concentrated hydrochloric acid, from bis(2-hydroxyethylthioethyl) sulfide and ethylene chlorohydrin, and from 1, 2-bis(2-hydroxyethylthio)ethane and ethylene chlorohydrin.

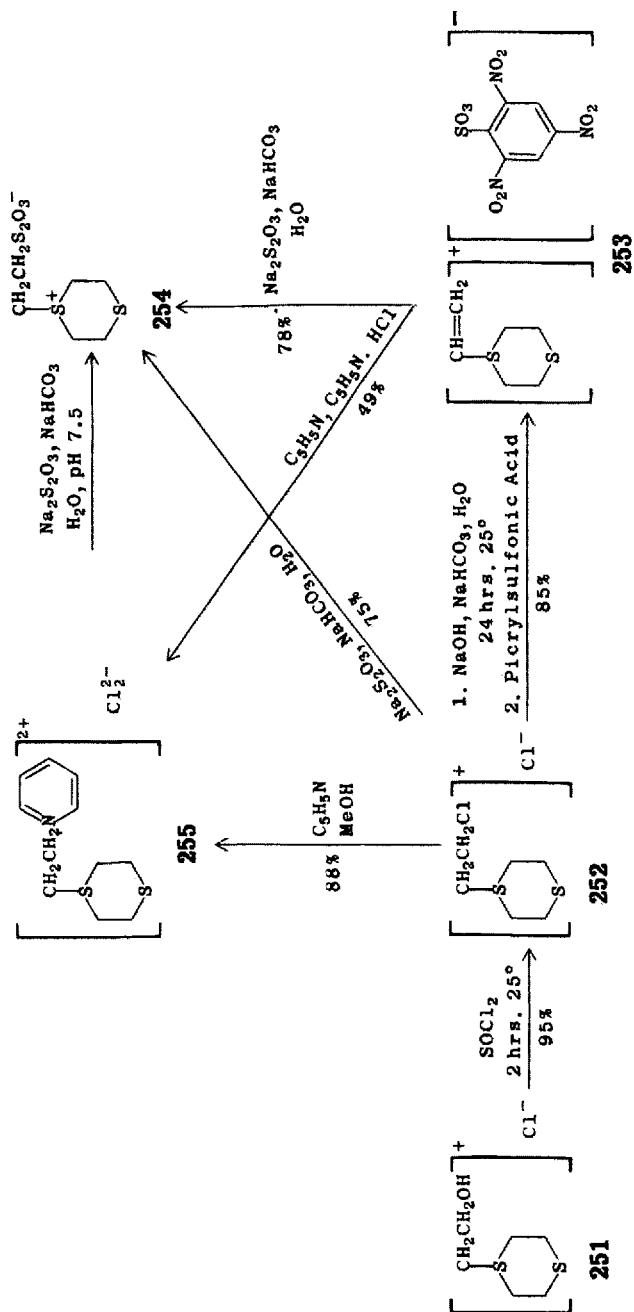


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For preparative purposes, and to prove the structure of **251**, it was prepared from *p*-dithiane and ethylene chlorohydrin.

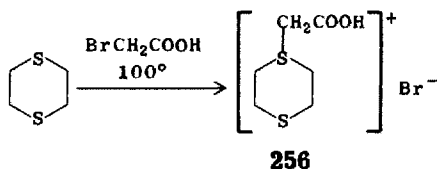


Stahmann, Fruton, and Bergmann⁴⁶³ carried out an interesting series of reactions on **251** and isolated a number of pure crystalline compounds. Treatment with thionyl chloride gave 1-(2-chloroethyl)-1,4-dithianium chloride (**252**) in 95% yield. This, treated with sodium hydroxide and sodium bicarbonate, gave the 1-vinyl-1,4-dithianium compound, isolated at its picrylsulfonate (**253**). Both the chloro compound (**252**) and the vinyl compound (**253**) reacted with sodium thiosulfate to yield 1-(2-thiosulfonatoethyl)-1,4-dithianium (**254**), a zwitterion; evidence was presented that the chloro compound was first converted into the vinyl compound in this reaction. The chloro compound (**252**) reacted with pyridine to give 1-[2-(pyridinio)ethyl]-1,4-dithianium dichloride (**255**), which could also be prepared from the vinyl compound (**253**), pyridine, and pyridine hydrochloride. The pyridinium compound (**255**) also yielded the thiosulfate. That **255** is an alkylating agent was shown by its reaction with alanine, the amino group disappearing in 48 hours. The following chart summarizes these reactions:

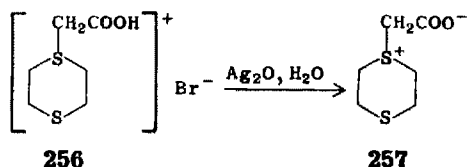


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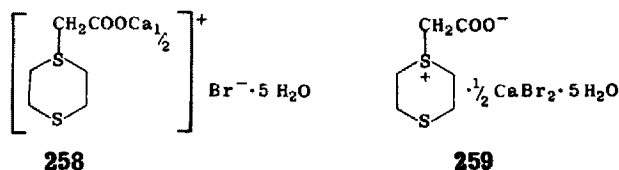
Strömholm⁴⁷¹ prepared an intriguing series of compounds from 1-carboxymethyl-1, 4-dithianium bromide (**256**), which he synthesized from *p*-dithiane and bromoacetic acid.



256 was obtained as prisms melting at 159° (dec.). It gave an acid reaction in water and was converted to the starting materials when heated in water. Strömholm reported a bewildering number of salts, since not only could the anion be varied but metallic salts of the carboxyl group could also be formed. Some of these salts are listed in Table 11, but it is a fairly safe assumption that many of the salts reported by Strömholm are not pure compounds. Starting with the bromide he prepared the calcium, barium, copper, zinc, and aluminum salts, all isolated as hydrates. The most interesting compound prepared was the inner salt or zwitterion (**257**).



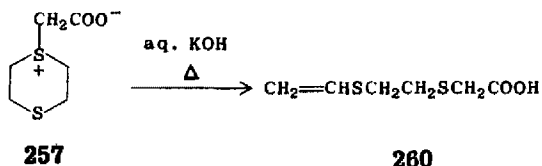
It was isolated as a dihydrate, which lost its water *in vacuo*. Although Strömholm formulated **257** generally as containing a four-membered ring, he recognized its correct structure, since he compared it with the betaines and argued for its ionic character in view of its solubility in water and alcohol and its insolubility in ether. With this zwitterion as a starting material, he prepared a variety of derivatives, in which the anion was varied, by treating the inner salt with the corresponding acid. Many of these were also converted into metal salts. Although there is little reason to doubt the structures of most of the compounds with a free carboxyl group and various anions, the question should be raised as to whether the metal salts are as represented by Strömholm (**258**) or are actually complexes of the zwitterion with the simple salt (**259**).



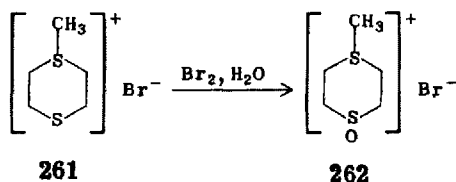
Treatment of the inner salt (**257**) with alkali yielded a compound which Strömholm formulated as 2-vinylthioethylthioacetic acid (**260**) by anal-

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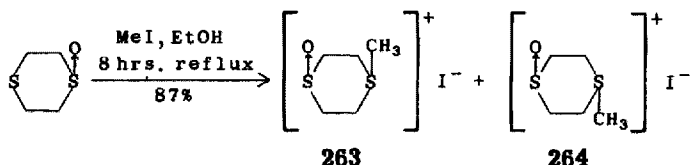
ogy with the basic cleavage of 1-methyl-1, 4-dithianium salts reported by Demuth and V. Meyer.¹⁵³



A number of 1-alkyl-1, 4-dithianium 4-oxide salts have been reported, as shown in Table 11. Strömholm^{470, 472} prepared 1-methyl-1,4-dithianium bromide 4-oxide (**262**) as a white, crystalline compound by treating 1-methyl-1, 4-dithianium bromide (**261**) with bromine in water.



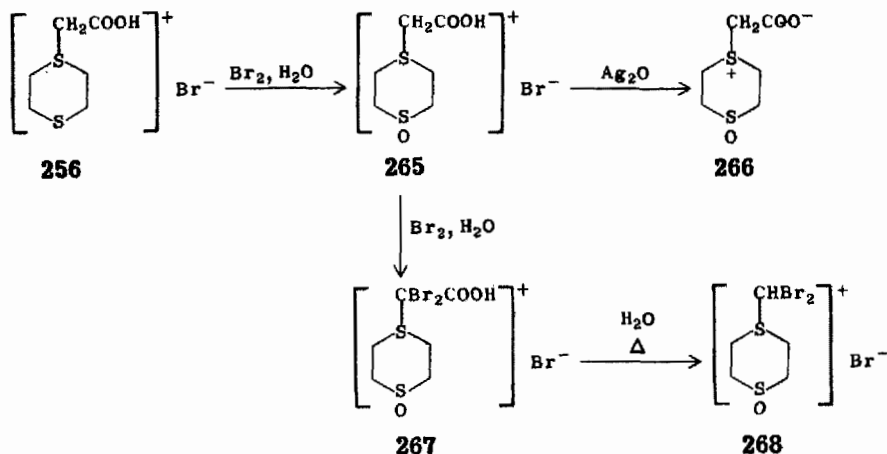
He isolated a chloroplatinate⁴⁷² and several mercuric chloride complexes,⁴⁷⁰ the latter of questionable structure. The use of chlorine instead of bromine led to ring chlorination.⁴⁷⁴ Strömholm was unsuccessful in his attempt to isolate stereoisomers of the sulfonium oxide (**262**). This was first done successfully by Bell and Bennett;⁴⁰ treatment of *p*-dithiane 1-oxide with methyl iodide yielded a mixture of *cis*- and *trans*-1-methyl-1, 4-dithianium iodide 4-oxide (**263** and **264**).



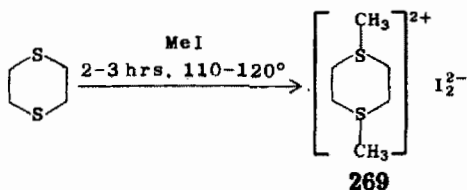
Recrystallization from aqueous ethanol gave the α -isomer, isolated as its picrate and chloroplatinate. Recrystallization of a mixture of isomeric picrates yielded the pure α - and β -forms; the latter was also converted into a chloroplatinate. The α - and β -forms were obtained in the ratio of 4 : 1. The two isomeric picrates had different melting points and the chloroplatinates differed in color, leaving no doubt that two different compounds were present. As in the case of the 1, 4-dioxides the less soluble, higher melting form was designated as the α -isomer, and the more soluble, lower melting form as the β -isomer. If the analogy holds (see section III A-1f), the α -isomer would be *trans* and the β -isomer *cis*. This work was further evidence that a trisubstituted sulfur is not planar.

Strömholm prepared 1-carboxymethyl-1, 4-dithianium bromide 4-oxide (**265**) by oxidation of the sulfonium salts (**256**) with bromine water.

He prepared a hydrated chloroplatinate and several questionable mercuric chloride complexes.⁴⁷⁰ The inner salt form (**266**) was prepared by treatment of the bromide with silver oxide. Treatment of the bromide with excess bromine yielded a compound which Strömholm formulated as 1-dibromomethyl-1, 4-dithianium bromide 4-oxide (**268**), presumably formed by decarboxylation of the intermediate dibromo acid (**267**); other salts derived from **268** were prepared.⁴⁷¹



Mansfeld^{345, 346} reported that, when *p*-dithiane was heated with excess methyl or ethyl iodide in a sealed tube at 110–120°, a disulfonium salt (**269**) was formed in low yield.



Nenitzescu and Scărlătescu³⁷³ isolated the same compound by heating bis(2-ethoxyethyl) sulfide with methyl iodide. Table 12 lists the compounds which have been reported. Strömholm⁴⁷² suggested that, in view of the high temperature of the reaction, the compounds might be trimethylsulfonium derivatives. Differentiating between $\text{C}_3\text{H}_9\text{SI}$ and $\text{C}_6\text{H}_{14}\text{S}_2\text{I}_2$ analytically is quite difficult, the only important difference being in the hydrogen content (4.45% *vs.* 3.49%). Actually, in the only analysis reported³⁷³ the hydrogen content was 4.07%. If the reported melting points were accurate, the existence of the dialkyldithianium salts would not be in doubt, since trimethylsulfonium iodide is reported to decompose without melting slightly above 200° and the picrate is reported to melt at 193°. ⁴⁷² However, Strömholm was unable to prepare other bis(sulfonium) salts of *p*-dithiane.

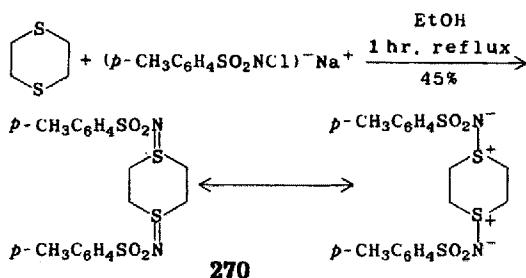
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TABLE 12. Disulfonium Compounds of *p*-Dithiane

R =	Anion	M.p. (°C)	Remarks	Ref.
CH ₃	2 I ⁻	207-208	needles	345, 346
		206-207		373
	PtCl ₆ ²⁻			346
	SO ₄ ²⁻		very hygroscopic	346
	2 NO ₃ ⁻		very hygroscopic	346
	[2, 4, 6-(NO ₂) ₃ C ₆ H ₂ O ⁻] ₂	182-183		346
C ₂ H ₅	2 I ⁻			345

h. Sulfilimines

In 1922 Mann and Pope³⁴⁴ reported the synthesis of a new sulfide derivative, apparently first discovered by H. S. Raper. Treatment of *p*-dithiane with chloramine-T yielded a white solid (**270**). Its structure is analogous to that of a sulfoxide. The authors suggested the name sulfilimine for the structure >S=NH , and this is commonly used. Chemical Abstracts, however, calls **270** 1, 1, 4, 4-tetrahydro-1, 4-bis(*p*-tolylsulfonylimino)-*p*-dithiane.



Although **270** is insoluble in ordinary solvents and does not possess a sharp melting point, other sulfilimines are sharp-melting compounds and are used for characterization; those reported in the *p*-dithiane series are listed in Table 13.

Inasmuch as the sulfilimines are similar to sulfoxides in structure, *p*-dithiane bis(*p*-tolylsulfonyl sulfilimine) (**270**) should exist in two forms, and Bell and Bennett⁴⁰ succeeded in separating Mann and Pope's

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material into two isomers, differing in crystal form and in decomposition temperature, by extraction with hot cyclohexanol. Similarly, they reacted *p*-dithiane 1-oxide with chloramine-T and isolated equal quantities of *cis*- and *trans*-*p*-dithiane 1-(*p*-tolysulfonyl sulfilimine) 4-oxide (**271** and **272**).

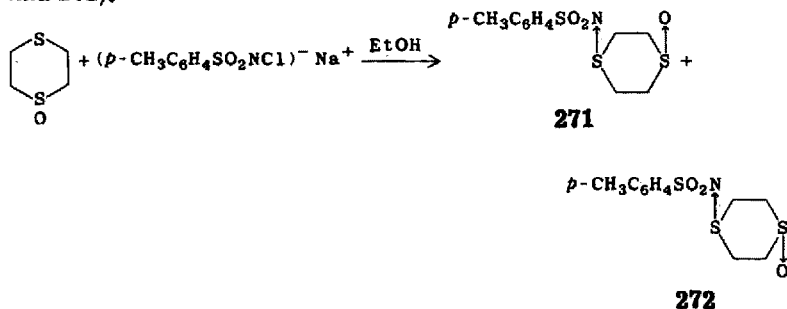
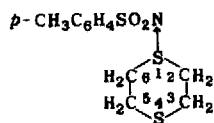


TABLE 13. Sulfilimines of *p*-Dithianes



Substituents	Yield (%)	M.p.(°C)	Ref.
4- <i>p</i> -CH ₃ C ₆ H ₄ SO ₂ N-	45		344
α-4- <i>p</i> -CH ₃ C ₆ H ₄ SO ₂ N-		dec.250-255	40
β-4- <i>p</i> -CH ₃ C ₆ H ₄ SO ₂ N-		dec.200-210	40
2-ClCH ₂ -4-(<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ N-)		153.5-154.5	204
α-4-oxide		230-234 (dec.)	40
β-4-oxide		176-177 (dec.)	40

i. Carboxyl Derivatives

Very few derivatives of *p*-dithiane with a carboxyl group attached to the ring have been reported (see Table 14). Barat³¹ attempted to prepare *cis*- *trans* isomers of *p*-dithiane-2, 3-dicarboxylic acid (**273**) by reaction of dibromofumaric and dibromomaleic acids with 1, 2-dimercaptoethane, but he was unable to isolate any pure compounds.

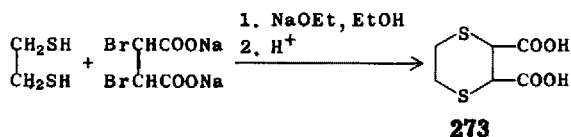
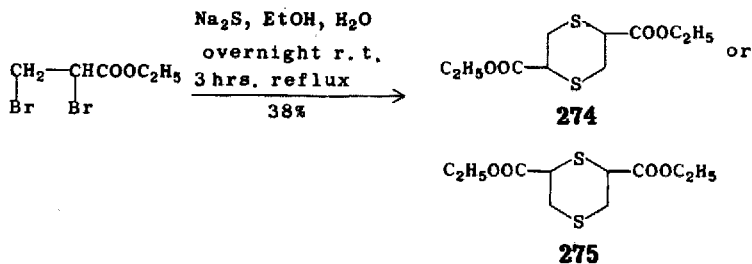


TABLE 14. Carboxyl Derivatives of *p*-Dithiane

Substituents	Yield (%)	M.p.(°C)	B.p.		Ref.
			(°C)	(mm)	
<i>cis</i> -2, 5-(HO ₂ C-) ₂	26-30	160			238a, 238b
<i>trans</i> -2, 5-(HO ₂ C-) ₂	50	247 (dec.)			238a, 238b
<i>trans</i> -2, 5-(CH ₃ O ₂ C-) ₂	17-26	120-121	128-130	0.3	238a, 238b
<i>trans</i> -2, 5-(H ₂ NNHCO-) ₂	65-70	228 (dec.)			238b
2, 6-(HO ₂ C-) ₂		180			238a, 238b
2, 6-(CH ₃ O ₂ C-) ₂	30-39		128-130	0.3	238a, 238b
2, 6-(H ₂ NNHCO-) ₂	27	218 (dec.)			238b
2, 5-(CH ₃ CO-) ₂ , 5-(C ₂ H ₅ O ₂ C-)(?)			100-110	14	72

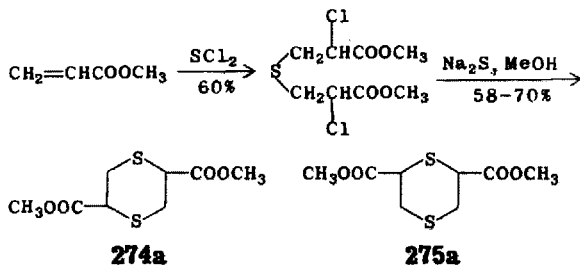
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Varvoglis and Tsatsaronis⁴⁹⁹ reacted ethyl 2, 3-dibromopropionate with sodium sulfide and isolated a compound, b.p. 62-66° at 20 mm., which they formulated as either diethyl *p*-dithiane-2, 5-dicarboxylate (**274**) or the 2, 6-isomer (**275**).



Alkaline hydrolysis yielded the free dicarboxylic acid, while hydrazine gave the dihydrazide. No stereoisomers were reported. The structure was assigned by analogy with known *p*-dithiane syntheses coupled with the fact that the free acid, prepared by alkaline hydrolysis, possessed the correct sulfur analysis and equivalent weight. A dihydrazide was also prepared but not analyzed; the yield was suspiciously low.

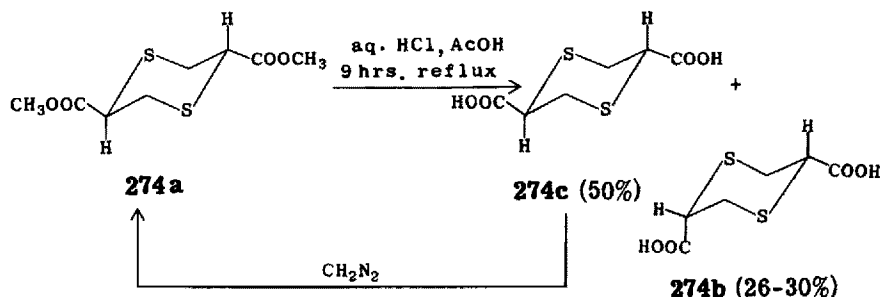
More recently, Gundermann and Burba^{238a, 238b} prepared dimethyl *p*-dithiane-2, 5- and 2, 6-dicarboxylates (**274a** and **275a**), as well as the corresponding acids, and concluded that the structures assigned by Varvoglis and Tsatsaronis are incorrect. Treatment of methyl acrylate with sulfur dichloride yielded dimethyl 2, 6-dichloro-4-thiapimelate. Reaction of this with sodium sulfide yielded a mixture of **274a** and **275a** in a ratio of 2 : 3.



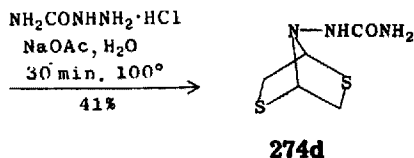
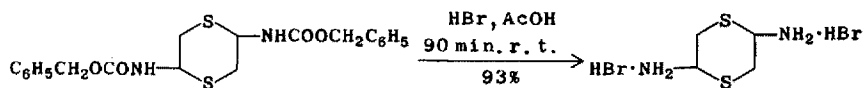
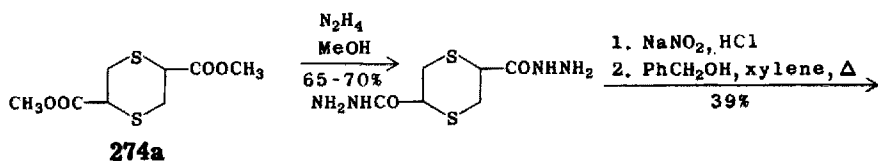
Acid hydrolysis of the 2, 5-isomer (**274a**) yielded a mixture of *cis*- and *trans*-*p*-dithiane-2, 5-dicarboxylic acids (**274b** and **274c**); the higher melting, less soluble isomer was assigned the *trans* configuration. Since esterification of the *trans* isomer (**274c**) gave a methyl ester which has almost the same melting point as the original ester, it appears that the *cis* isomer (**274b**) was formed during hydrolysis, the original

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product (**274a**) being almost completely *trans*. Isomerization under acidic conditions is quite unusual.

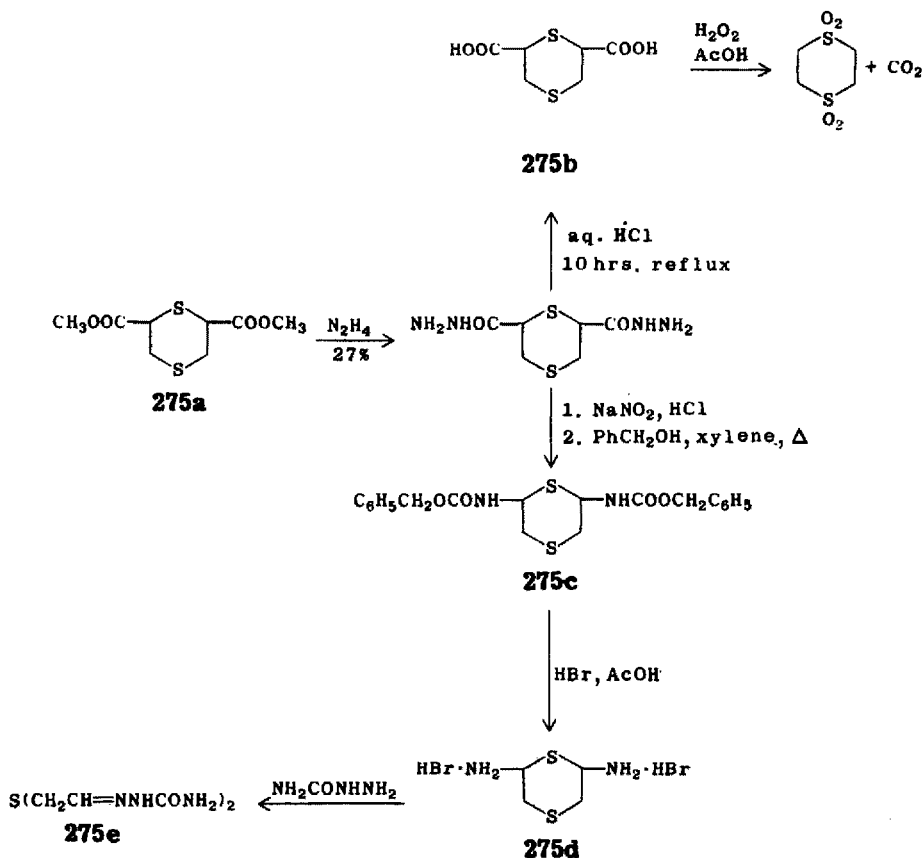


The structure of dimethyl *p*-dithiane-2,5-dicarboxylate (**274a**) was proved by conversion to the known 7-ureido-2,5-dithia-7-azabicyclo[2.2.1]heptane (**274d**), presumably *via* the intermediate formation of mercaptoacetaldehyde and *p*-dithiane-2,5-diol (see section III A-1j).

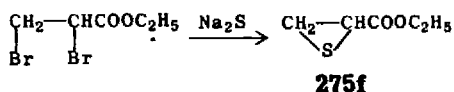


The 2,6-ester (**275a**) yielded only one acid, of unknown geometry (**275b**); oxidation yielded the known *p*-dithiane 1,1,4,4-tetroxide. Treatment of the carbobenzoxy derivative (**275c**) with acid and semicarbazide gave thiobis(acetaldehyde semicarbazone) (**275e**); instability of the intermediate 2,6-diamino-*p*-dithiane hydrobromide (**275d**) is not surprising.

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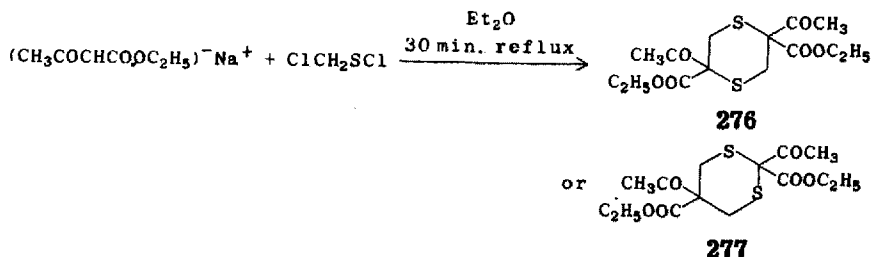


The compound reported by Varvoglis and Tsatsaronis⁴⁹⁹ might be the other geometrical isomer of the *p*-dithiane-2, 6-dicarboxylate, but its boiling point is much too low for this. In fact, from its boiling point it might be expected to be the monomeric product, 2-carbethoxythiirane (**275f**), but it is unlikely that the thiirane ring would be so unreactive as to be unaffected by base and by hydrazine.



Brintzinger and Schmahl⁷² reacted chloromethylsulfenyl chloride with the sodium salt of acetoacetic ester and isolated a compound which they formulated as diethyl 2, 5-diacetyl-*p*-dithiane-2, 5-dicarboxylate (**276**) or as the corresponding *m*-dithiane compound (**277**).

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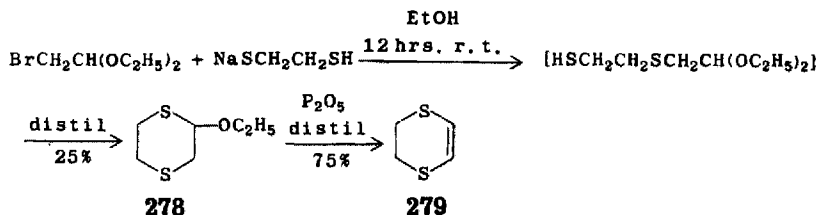


No proof of structure was offered and the boiling point reported by Britzinger and Schmahl is undoubtedly too low for the compound to be a dithiane derivative.

j. Hydroxy, Amino, and Sulfur Derivatives

Hydroxy derivatives of *p*-dithiane and certain nitrogen and sulfur derivatives are listed in Table 15.

Parham, Heberling, and Wynberg³⁸⁴ prepared 2-ethoxy-*p*-dithiane (**278**) from 2-bromoacetaldehyde diethyl acetal and the monosodium salt of 1, 2-dimercaptoethane. Distillation of **278** from phosphorus pentoxide gave 2, 3-dihydro-*p*-dithiin (**279**) (see section III A-2a).



In an attempt to prepare 2-*n*-butylmercaptomethyl-1, 3-dithiolane (**279b**), Schneider and Bagnell^{426a} reacted *n*-butylmercaptoacetaldehyde dimethylacetal with 1, 2-dimercaptoethane. 2-*n*-Butylmercapto-*p*-dithiane (**279a**) was obtained instead, its structure being proved by conversion to the known 2, 3-dihydro-*p*-dithiin (**279**).

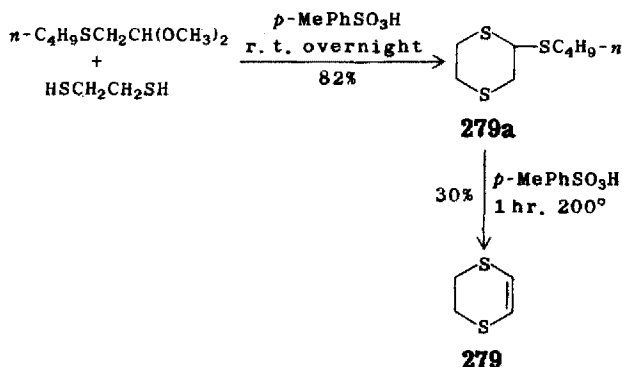
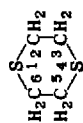


TABLE 15. Hydroxy, Amino and Sulfur Derivatives of *p*-Dithiane

Substituents	Yield (%)	M.p. (°C)	B.p. (°C) (mm)	Remarks	Ref.
2-C ₂ H ₅ O-	25		88 5	n_D^{25} 1.5410	384
2-(α -C ₄ H ₉ S-)	82		110 0.5	n_D^{25} 1.5673, d_4^{25} 1.1292	426a
2, 5-(HO-) ₂	61	142-147		two forms	257
	63	151			281
	47	150-152			486
2, 5-(HO-) ₂ · 2C ₂ H ₅ HgBr		111		α -form	257
2 5-(CH ₃ CO ₂ -) ₂	68	109 173		two forms	257, 258
2, 5-(C ₆ H ₅ CO ₂ -) ₂	85	130 205		two forms	257
2, 5-(CH ₃ O-) ₂	55	83 84-85 91			234 379 257

C₄S₂ Ring Systems

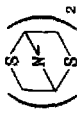
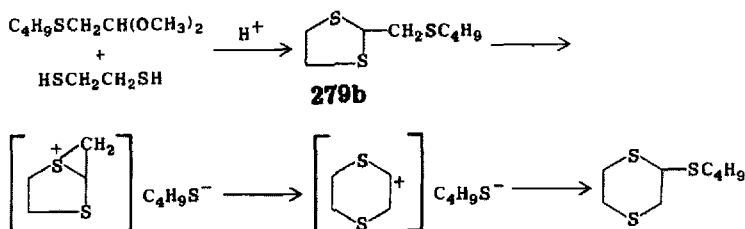
2, 5-(C ₆ H ₅ NH-) ₂	0.7	92-93	281
	46	90-92	379
	40	188	281
2, 5-() ₂		143.5-144	242
2, 5-(NH ₂) ₂ · 2HBr	93		238b
2 5-(C ₂ H ₅ O ₂ CNH-) ₂	68	225 (dec.)	238b
2, 5-(C ₆ H ₅ CH ₂ O ₂ CNH-) ₂	39	231	238b
2 6-(NH ₂) ₂ · 2HBr	90		238b
2, 6-(C ₆ H ₅ CH ₂ O ₂ CNH-) ₂	32	190	238b
2, 5-(CH ₃ -) ₂ -2, 5-(HO-) ₂	68	109-111	277
	59	105-110	375
		80-82	236
		136-138	240
		117-118	240, 48b
		119-120	α-isomer
	74	119-120	391
2, 5-(CH ₃ -) ₂ -3, 6-(C ₂ H ₅ O-) ₂	17	190-191	391
2, 5-(CH ₃ -) ₂ -3, 6-(C ₂ H ₅ O-) ₂ 1, 1, 4, 4-tetroxide	72	65-72	21
2, 5-(C ₂ H ₅ -) ₂ -2, 5-(HO-) ₂	13	112-113	13a
2, 5-(C ₂ H ₅ -) ₂ -2, 5-(HO-) ₂	73	121-128	13a
2, 5-(HO-) ₂ -3, 6-(HOCH ₂ -) ₂	92	130-132	473a

TABLE 15. Hydroxy, Amino and Sulfur Derivatives of *p*-Dithiane (contd)

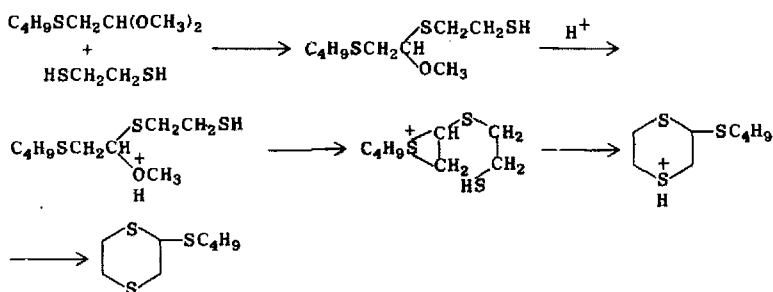
Substituents	Yield (%)	M. p. (°C)	B. p. (°C) (mm)	Remarks	Ref.
2, 5-(CH ₃ CO ₂ -)-3, 6-(CH ₃ CO ₂ CH ₂ -) ₂	53	161-162			473a
2, 5-(CH ₃ -) ₂ -2, 5-(C ₆ H ₅ NH-) ₂	38	124			19
2, 5-(CH ₃ -) ₂ -2, 5-(<i>p</i> -CH ₃ C ₆ H ₄ NH-) ₂		129			19
2, 5-(C ₂ H ₅ -) ₂ -2, 5-(<i>p</i> -CH ₃ C ₆ H ₄ NH-) ₂		135-136			21
2, 5-(CH ₃ -) ₂ -2, 5-(CH ₃ COCH ₂ S-) ₂		116			19
2, 5-(HSCCH ₂ -) ₂ -2, 5-(HO-) ₂	64	85-86			440
	90	85-86			442
	19.5	176-178			442
2, 5-(CH ₃ SCH ₂ -) ₂ -2, 5-(HO-) ₂		144			442
2, 5-(CH ₃ SCH ₂ -) ₂ -2, 5-(CH ₃ CO ₂ -) ₂	37	161			235
2, 5-(C ₆ H ₅ -) ₂ -2, 5-(or 3, 6)-(C ₂ H ₅ S-) ₂		216-217			235
2, 5-(C ₆ H ₅ -) ₂ -2, 5-(or 3, 6)-(C ₆ H ₅ CH ₂ S-) ₂		92			487
2, 5-(C ₆ H ₅ CH ₂ -) ₂ -2, 5-(HO-) ₂	85				
2, 5-(CO ₂ C ₂ H ₅ -) ₂ -2, 5-(HO-) ₂	76	119-128			13
2, 5-(CH ₃ -) ₂ -2, 5-(HO-) ₂ -3, 6-(C ₆ H ₅ -) ₂	82	100-109			487
2, 3, 5, 6-(CH ₃ -) ₄ -2, 5-(C ₂ H ₅ NH-) ₂	43	98-100			14
2, 3-Dihydro derivatives, see Table 18					

C₄S₂ Ring Systems

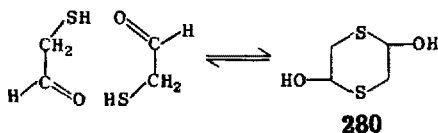
Schneider and Bagnell suggested the following mechanism:



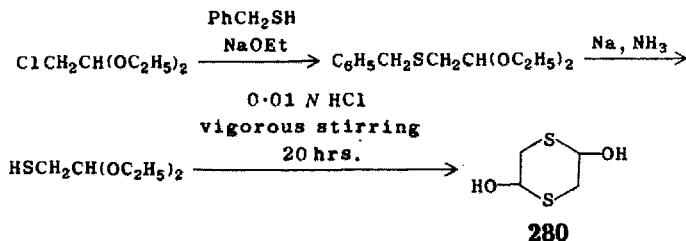
Parham^{426a} preferred a mechanism which avoided the formation of the 1, 3-dithiolane.



p-Dithiane-2, 5-diol (**280**) is a dimer of mercaptoacetaldehyde.



It was first prepared by Hesse and Jörder²⁵⁷ from mercaptoacetaldehyde diethylacetal, prepared in turn from benzylmercaptoacetaldehyde diethylacetal.

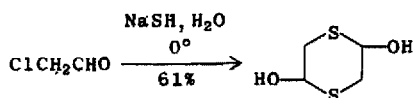


Two forms were isolated, mostly the less soluble α -form plus a trace of the more soluble β -form, which isomerized to the α -form on recrystallization. The best melting point obtained for both forms was 142-147°. Distillation yielded a mercaptan, presumably mercaptoacetaldehyde,

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which reverted to the dimer very rapidly. Hesse and Gampp²⁵⁸ isolated *p*-dithiane-2, 5-diol from the hydrolysis of uscharin, a heart poison.

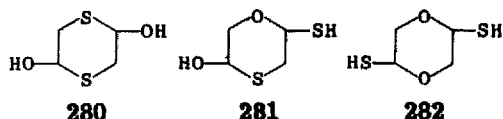
Hromatka and Haberl²⁸¹ prepared *p*-dithiane-2, 5-diol in practically identical yield by the simpler process of condensing chloroacetaldehyde with sodium hydrogen sulfide.



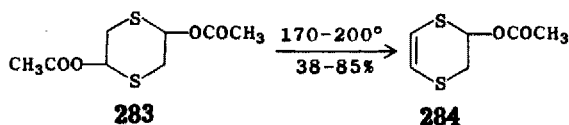
Their product melted at 151° and they reported no evidence for two isomers. Thiel, Asinger, and Schmiedel⁴⁸⁶ obtained the same results, although in somewhat lower yield.

Hesse and Jörder²⁵⁷ proved the structure of *p*-dithiane-2, 5-diol in the following manner. Analysis showed the compound to be $\text{C}_4\text{H}_8\text{O}_2\text{S}_2$, a cryoscopic molecular weight determination in phenol showing the dimeric character. Further evidence against mercaptoacetaldehyde, $\text{C}_2\text{H}_4\text{OS}$, was the high melting point and the insolubility in water and in ether; the compound could be recrystallized from ethanol. Reaction of the α -form with ethylmercuric bromide gave a crystalline adduct, $\text{C}_4\text{H}_8\text{O}_2\text{S}_2 \cdot 2\text{C}_2\text{H}_5\text{HgBr}$. The α -form reacted with acetic anhydride and pyridine to give two diacetates (**283**), m.p. 109° and 173°, in a ratio of 2 : 1; although the results were uncertain, the β -form seemed to give more of the higher melting diacetate. Benzoyl chloride in pyridine gave two dibenzoates.

Hesse and Jörder considered three possible structures, *p*-dithiane-2, 5-diol (**280**), 2-mercapto-*p*-oxathian-5-ol (**281**), and 2, 5-dimercapto-*p*-dioxane (**282**).



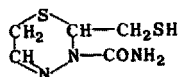
Heating the diacetates (**283**) eliminated one acetic acid molecule at 170–200° and two acetic acid molecules above 200° with no sign of thioacetic acid, thus indicating the correctness of the dithiane structure. The loss of one acetic acid molecule from **283** yielded a compound formulated as 2-acetoxy-2, 3-dihydro-*p*-dithiin (**284**).



Inasmuch as both diacetates gave the same compound, they are probably isomers. Neither the two diacetates nor the two dibenzoates could be interconverted and the authors considered them to be *cis-trans* isomers.

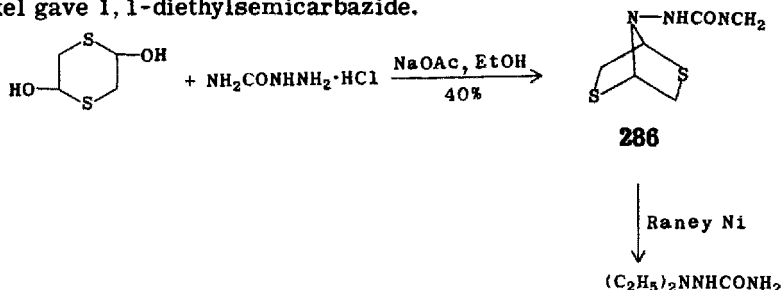
C₄S₂ Ring Systems

Hesse and Jörder²⁵⁷ reacted *p*-dithiane-2, 5-diol with semicarbazide and isolated a compound, C₅H₉ON₃S₂, in 40% yield, to which they assigned the improbable formula of a partially hydrogenated 1, 3, 4-thiadiazine (285).

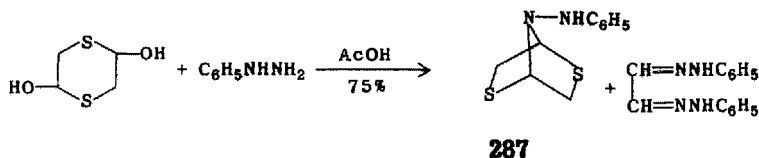


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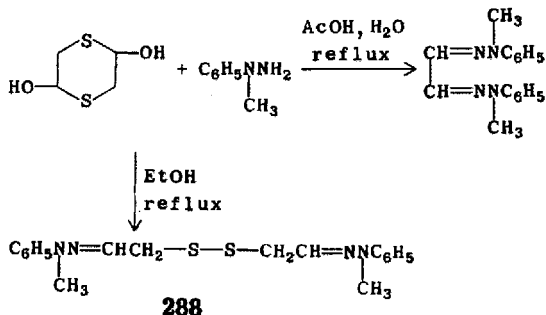
Hromatka and Haberl²⁸¹ prepared the same compound and showed it to be 7-ureido-2, 5-dithia-7-azabicyclo[2. 2. 1]heptane (286) by the following evidence. The compound was insoluble in dilute sodium hydroxide, showing the absence of a free mercapto group, and there was no —SH band in the infrared spectrum at 3. 9 μ. Desulfurization with Raney nickel gave 1, 1-diethylsemicarbazide.



The latter authors found that phenylhydrazine reacted similarly to give a 75% yield of 7-anilino-2, 5-dithia-7-azabicyclo[2. 2. 1]heptane (287) and some glyoxal phenylosazone.



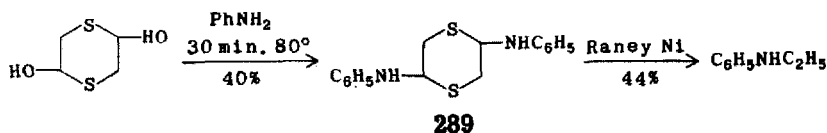
α-Methylphenylhydrazine reacted differently; in acetic acid it gave glyoxal α-methylphenylosazone, while in ethanol it gave the disulfide derived from mercaptoacetaldehyde α-methylphenylhydrazone (288).



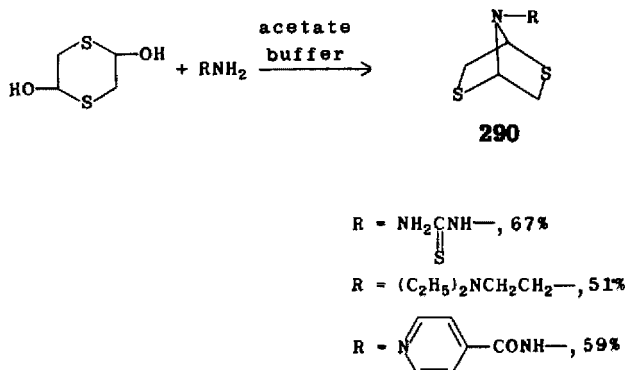
[For references, see pp. 1252-1271.]

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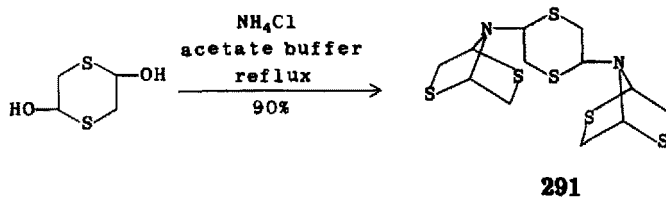
Aniline reacted in still another way, yielding 2, 5-dianilino-*p*-dithiane (**289**), as shown by Raney nickel desulfurization to *N*-ethylaniline; the bicyclic compound would have given *N,N*-diethylaniline.



In further work Haberl and Hromatka²⁴² found that thiosemicarbazide, 2-diethylaminoethylamine, and isonicotinoylhydrazide all reacted to give bicyclic compounds (**290**).



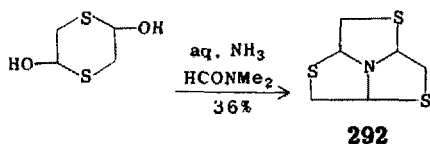
Ammonium chloride, however, reacted differently in an acetate buffer. According to the authors the bicyclic compound was formed initially, but it reacted further to give a compound which they formulated as 2, 5-bis(2, 5-dithia-7-azabicyclo[2. 2. 1]hept-7-yl)-*p*-dithiane (**291**).



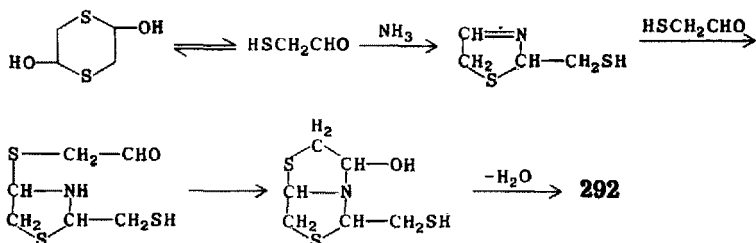
The structure was indicated by its analysis; molecular weight; infrared spectrum, which showed the absence of OH, NH, SH, and carbonyl; and Raney nickel desulfurization to triethylamine.

Thiel, Asinger, and Schmiedel⁴⁸⁶ reacted aqueous ammonia with *p*-dithiane-2, 5-diol in dimethylformamide and isolated a compound, $\text{C}_6\text{H}_9\text{NS}_3$, m.p. 144° , which they formulated as 1, 4, 7-trithia-2, 5, 8-endazacyclononane (**292**) on the basis of its Raney nickel desulfurization to triethylamine.

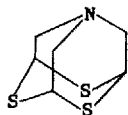
C₄S₂ Ring Systems



They rationalized its formation as follows:



Subsequently, Asinger and Thiel¹² suggested that Haberl and Hromatka's compound (**291**) is actually **292**, ignoring the doubled molecular weight reported by Haberl and Hromatka. They also claimed that the compound prepared by Craig and co-workers,¹³⁴ m.p. 147-148°, which the latter authors formulated as 4, 6, 10-trithia-1-azaadamantane (**293**) (see Chapter 10, section II C), has structure **292**.



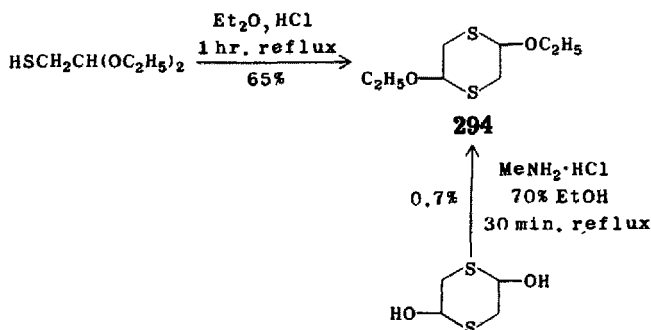
293

More recently these workers cooperated with Haberl and Hromatka^{487a} to show that all three compounds are identical and that the correct structure is **292** as originally suggested by Thiel, Asinger, and Schmiedel.⁴⁸⁶ Identity was shown by melting points and mixed melting points of the three preparations of the free base, its hydrochloride, and its methiodide, as well as by identical infrared spectra. The Haberl and Hromatka structure (**291**) was ruled out by cryoscopic molecular weight determinations in phenol and in carbon tetrachloride, both of which showed the formula to be C₆H₉NS₃. The Rast molecular weight and the ebullioscopic determination in pyridine used originally by Haberl and Hromatka gave high and irreproducible results. The Craig structure (**293**) was ruled out by an unequivocal synthesis of **293** (see Chapter 10, section II C). According to Thiel, Asinger, and co-workers,^{487a} a crystallographic determination by Hofer and Preisinger confirmed **292** as the correct structure.

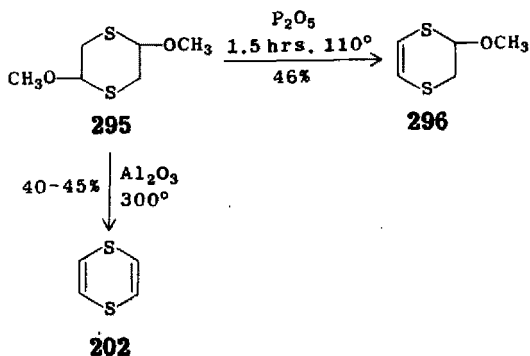
The importance of using an acetate buffer in the reaction of *p*-dithiane-2, 5-diol with amines was shown by Hromatka and Haberl,²⁸¹ who isolated only a trace of 2, 5-diethoxy-*p*-dithiane (**294**) from the reaction of the diol with methylamine hydrochloride in aqueous ethanol. **294** had been prepared by Hesse and Jörder²⁵⁷ by allowing mercaptoacetalde-

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hyde diethyl acetal to stand for a long time, and by Parham, Wynberg, and Ramp³⁷⁹ using an acid catalyst.

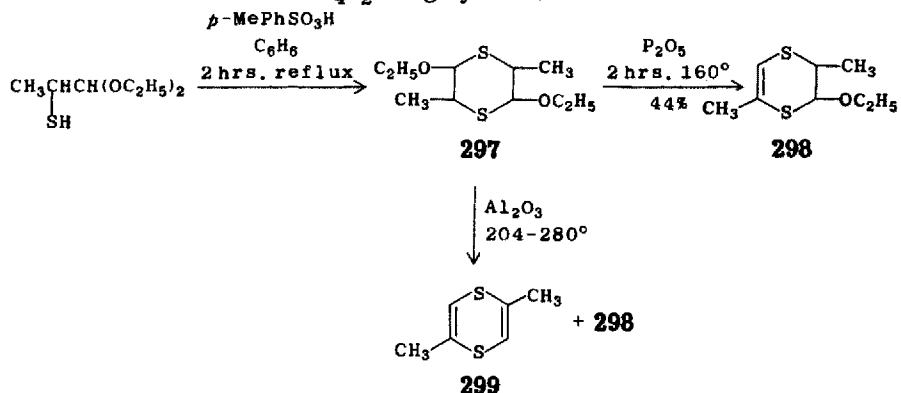


Parham and co-workers obtained two isomers of **294**, presumably *cis* and *trans*, but only the one reported by Hesse and Jörder could be isolated pure. 2, 5-Dimethoxy-*p*-dithiane (**295**) was prepared from the corresponding dimethyl acetal by Grob and von Sprecher²³⁴ and by Parham, Wynberg, and Ramp.³⁷⁹ These latter authors found that it could be converted into 2, 3-dihydro-2-methoxy-*p*-dithiin (**296**) and into *p*-dithiin (**202**). The corresponding diethoxy derivative underwent the same reactions (see section III A-2).



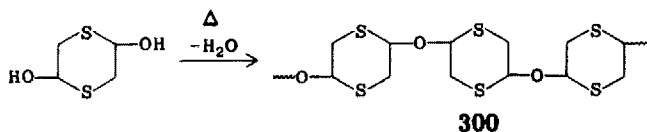
In a somewhat similar fashion Parham, Mayo, and Gadsby³⁹¹ prepared 2, 5-dimethyl-3, 6-diethoxy-*p*-dithiane (**297**) from α -mercaptopropionaldehyde diethylacetal, and converted it into 2, 5-dimethyl-3-ethoxy-2, 3-dihydro-*p*-dithiin (**298**) and 2, 5-dimethyl-*p*-dithiin (**299**).

C_4S_2 Ring Systems



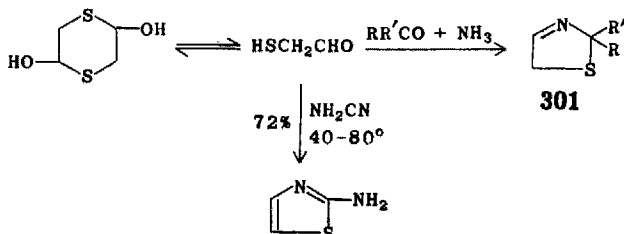
Both **297** and **298** were obtained as isomeric mixtures. A single pure isomer of **297** was isolated and designated as the α -isomer, m.p. 119-120°. Permanganate oxidation of the isomeric mixture of **297** gave a mixture of disulfones from which one isomer, m.p. 190-191°, could be isolated in 17% yield.

Hromatka and Haberl²⁸¹ found that *p*-dithiane-2,5-diol loses water on heating and gives a resin, which they formulated as a polyether (**300**).



In this respect, it differs from 2,5-dialkyl-*p*-dithiane-2,5-diols (*vide infra*).

In many reactions *p*-dithiane-2,5-diol reacts as if it were mercaptoacetaldehyde. Thus, Asinger and co-workers^{12,15,486} found that reaction with aldehydes or ketones and ammonia yields 2-substituted- Δ^3 -thiazolines (**301**), a reaction typical of α -mercaptocarbonyl compounds, while Currie and Beutel^{141a} prepared 2-aminothiazole from *p*-dithiane-2,5-diol and cyanamide.

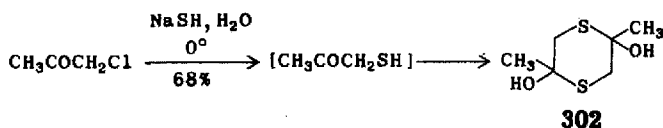


Gundermann and Burba^{238a} prepared *p*-dithiane-2,5-diamine and the 2,6-isomer by a modified Curtius rearrangement starting with the corresponding carboxylate esters. The 2,5-diamine reacted with semicarbazide to give 7-ureido-2,5-dithia-7-azabicyclo[2.2.1]-heptane,

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presumably *via* the intermediate formation of mercaptoacetaldehyde and *p*-dithiane-2, 5-diol, while the 2, 6-diamine gave thiobis(acetaldehyde semicarbazone) (see section III A-1i).

The first dimeric α -mercaptocarbonyl compound was reported in 1926 by Groth,²³⁶ who described the preparation of mercaptoacetone, m.p. 80-82°, by the acid hydrolysis of "thiocarbacetonylmercaptoglycolic acid". Inasmuch as Groth's publication was not generally available, it was not until 1948 that this compound was described in the literature, Hromatka and Engel²⁷⁷ having prepared it from chloroacetone and sodium hydrosulfide.

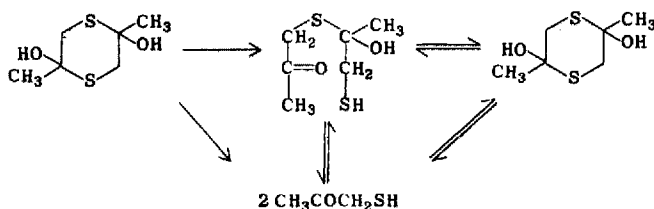


These latter authors reported a melting point of 109-111°. Ohta³⁷⁵ obtained a melting point of 105-110° on repeating the preparation. The fact that the compound is only slightly soluble in cold water, ethanol, ether, and chloroform led Hromatka and Engel to suspect that the compound was not monomeric. However, it formed an oxime, indicative of the mercaptoacetone structure. It also formed a crystalline mercuric chloride adduct, m.p. 118°; a benzoate, m.p. 8°; and a *p*-nitrobenzoate, m.p. 104-104.5°. Unfortunately, no molecular weight determinations were reported, and it is not clear, therefore, whether these are derivatives of mercaptoacetone or of its dimer, 2, 5-dimethyl-*p*-dithiane-2, 5-diol (**302**). By analogy with *p*-dithiane-2, 5-diol it would be suspected that they are derivatives of **302**.

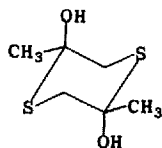
Schotte⁴⁴¹ investigated both Groth's and Hromatka and Engel's compounds. Molecular weight determinations showed both to be dimeric, confirming Hromatka and Engel's suspicion. Schotte was able to convert Groth's compound to the higher melting form by grinding, and the higher melting to the lower melting by steam distillation *in vacuo*. Inasmuch as they give identical X-ray powder diagrams, Schotte concluded that they are polymorphic forms rather than stereoisomers. Haberl, Grass, and co-workers,²⁴⁰ carried out a more thorough investigation and reached a different conclusion. Very careful purification of the two materials raised the 80-82° melting point to 136-138° and the 109-111° melting point to 117-118°. The increased melting points were attributed to the fact that they were taken on a microscope slide rather than in a sealed capillary; with the latter method decomposition to the monomeric form lowered the melting points. X-ray powder diagrams showed significant differences between the two forms. Small differences were found in the infrared, but both compounds showed strong absorption in the 3 μ hydroxyl region, indicating the correctness of the assigned structure, 2, 5-dimethyl-*p*-dithiane-2, 5-diol (**302**). In accord with this structure the compounds showed no carbonyl absorption and no carbon-carbon double bonds. In contrast to Schotte's results, Haberl, Grass, and co-workers found that grinding the 117-118° melting material con-

C₄S₂ Ring Systems

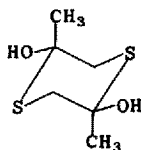
verted it into the high-melting form, but the reverse could not be achieved; steam-distillation accomplished the same change. Both forms could be recrystallized unchanged from benzene, but the lower melting form was converted into the higher melting by recrystallization from pyridine. Inasmuch as the infrared spectrum in pyridine showed a strong carbonyl bond, the isomerization takes place by ring opening.



Both compounds could be distilled, the boiling point of 64° at 12 mm being presumably that of mercaptoacetone, and the distillate solidified to the high-melting form. Thus, there is little doubt that the high-melting form is the stable one. These same authors carried out an X-ray crystallographic study of the two forms. The 117-118° melting form is monoclinic and crystallizes as leaflets, while the 136-138° form is triclinic and crystallizes as short rods. Both forms have a center of symmetry, indicating that they must both be *trans* isomers. The intensities of the X-ray lines were in agreement with the low-melting form having both hydroxyl groups axial (**303**), while in the high-melting form they are equatorial (**304**).

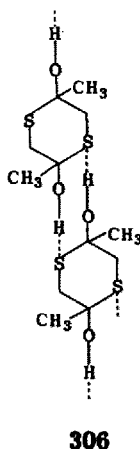
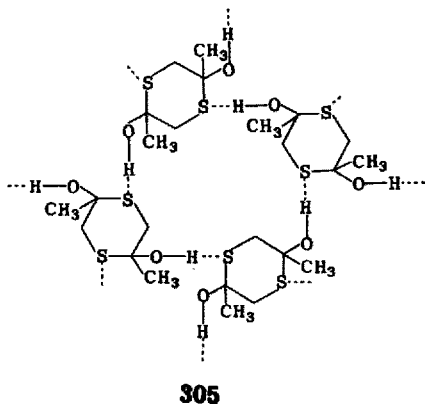


303



304

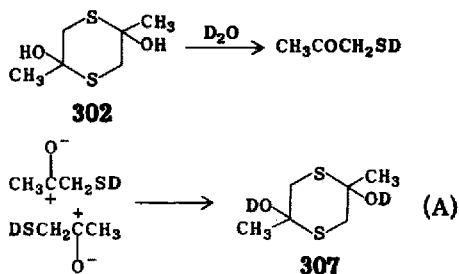
Since the two isomers do not interconvert spontaneously, it follows that the rings are rigid. This unusual conclusion is in agreement with the findings of Calderbank and LeFèvre⁸⁵ that *p*-dithiane does not exist in a mobile equilibrium between chair and boat forms (see section III A-1c). A further unusual conclusion from the X-ray investigation was that the low-melting isomer has a ring of four molecules in the crystal held together by oxygen-hydrogen-sulfur links (**305**), while the high-melting isomer has the molecules in a chain (**306**).



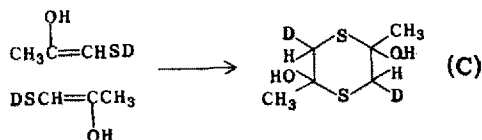
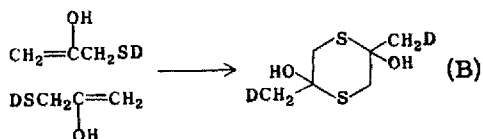
Evidence cited for the hydrogen bridge between oxygen and sulfur was the infrared spectrum and the short oxygen-sulfur bond distance found by X-ray. Although Haberl, Grass, and co-workers,²⁴⁰ cited several references for this type of bridging in inorganic compound, this is apparently the first example reported of a hydrogen bridge between oxygen and sulfur in organic compounds.

In view of the unusual nature of these conclusions, a more detailed investigation would be desirable. An especially puzzling feature of this work is the assignment of the axial hydroxyls to the unstable form, for which there is confirmatory evidence (*vide infra*). According to Dauben and Pitzer¹⁴⁵ the free energy difference between an axial and an equatorial methyl group in cyclohexane is 1.8 kcal, while for a hydroxyl group the difference is only 0.8 kcal. Thus, the more stable structure should have equatorial methyl groups and axial hydroxyl groups. Perhaps in the *p*-dithiane ring the bulky sulfur interferes with an equatorial methyl group in the 2-position and inverts the expected stability.

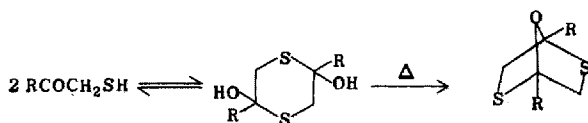
Haberl and Grass²⁴¹ investigated the mechanism of formation of 2, 5-dimethyl-*p*-dithiane-2, 5-diol (**302**). Steam-distillation of **302** from D₂O gave deuterated mercaptoacetone which, on dimerization, gave a diol containing only O-D bonds (**307**) as demonstrated by infrared analysis. Thus, of the three possible mechanisms considered, only mechanism A can be correct.



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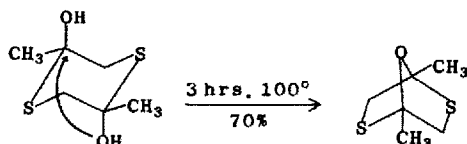


One of the most typical reactions of α -mercaptoketones, either monomeric or dimeric, is their ready dehydration to 7-oxa-2,5-dithiabicyclo[2.2.1]heptanes (**308**) (see Chapter 4, section II B-1).



308

Thus, Hromatka and Engel²⁷⁷ obtained a 70% yield of 1,4-dimethyl-7-oxa-2,5-dithiabicyclo[2.2.1]heptane (**309**) by heating the low-melting isomer of 2,5-dimethyl-*p*-dithiane-2,5-diol (**303**) for three hours at 100°. The high-melting isomer (**304**), on the other hand, underwent only slight decomposition at 150°. This is in agreement with their structural assignment, the axial hydroxyls in **303** being so disposed as to favor an S_N2 displacement.



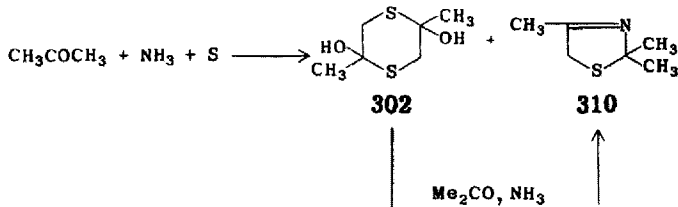
303

309

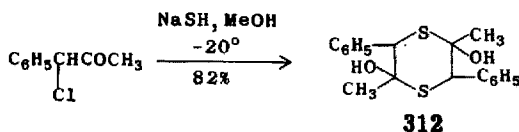
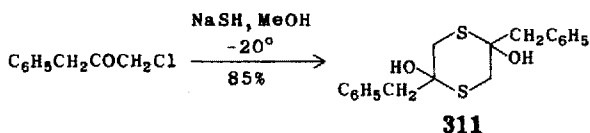
The same reasoning can be used to explain the fact that *p*-dithiane-2,5-diol dehydrates to form a polymer; in the unalkylated compound the hydroxyl groups should be equatorial and are so arranged as to favor intermolecular dehydration over transannular. 2,5-Diaryl-*p*-dithiane-2,5-diols apparently dehydrate in still another way, forming *p*-dithiin derivatives (see section III A-2a); the reason for this is obscure.

Thiel and Asinger⁴⁸⁵ isolated a small amount of 2,5-dimethyl-*p*-dithiane-2,5-diol (**302**) by heating acetone with ammonia and sulfur; the major product was 2,2,4-trimethyl- Δ^3 -thiazoline (**310**). Heating the *p*-dithiane with acetone and ammonia converted it into the thiazoline, presumably *via* monomeric mercaptoacetone.¹⁵

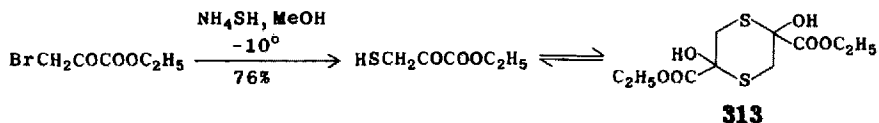
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Although there appears to be no clear-cut distinction as to which α -mercaptoketones are monomeric and which dimeric, there seems to be some indication that those with the mercapto group on a terminal carbon atom have a greater tendency to dimerize. Thus, Thiel, Asinger, and Fedtke⁴⁸⁷ reported that 3-chloro-1-phenyl-2-propanone gives 2, 5-dibenzyl-*p*-dithiane-2, 5-diol (**311**) as a sharp-melting compound, whereas 2, 5-dimethyl-3, 6-diphenyl-*p*-dithiane-2, 5-diol (**312**), prepared from 1-chloro-1-phenyl-2-propanone, has a broad melting point. It is debatable, of course, whether the broad melting point is a reflection of ready reversion to monomer or of a mixture of isomers.



Asinger, Thiel, and co-workers,¹³ attributed the broad melting point of diethyl 2, 5-dihydroxy-*p*-dithiane-2, 5-dicarboxylate (**313**), prepared from ethyl bromopyruvate, to an equilibrium between monomer and dimer.

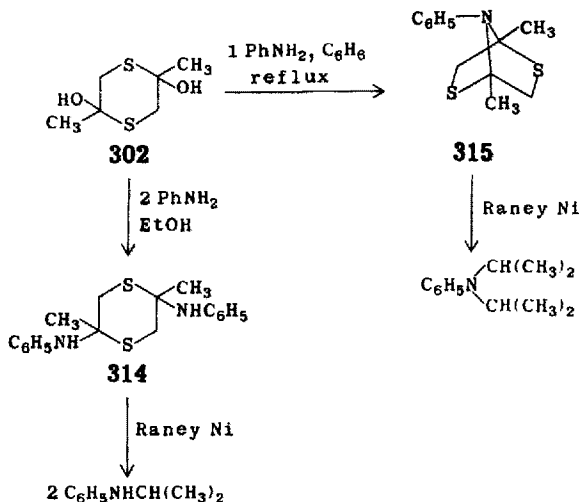


Bacchetti and Pinaroli²¹ isolated a mixture of 1-mercapto-2-butanone and 2, 5-diethyl-*p*-dithiane-2, 5-diol from 1-chloro-2-butanone, sodium hydroxide, and hydrogen sulfide. Compounds such as 2-mercapto-3-butanone are generally described as monomeric,¹² although their dimerization to the corresponding 7-oxa-2, 5-dithiabicyclo[2. 2. 1]heptanes has been reported.^{279,280} On the other hand, Geiseler and Stache^{208a} quoted the following degrees of polymerization for α -mercaptoketones based on molecular weight determinations in non-polar solvents by Asinger (unpublished): 2-mercapto-3-butanone 1. 54, 2-mercapto-2-methyl-3-butanone 2. 00, 2-mercapto-3-pentanone 1. 09, 3-mercapto-4-heptanone 1. 00. However, Geiseler and Stache concluded,

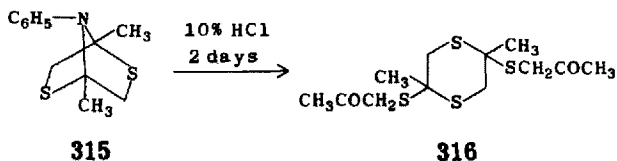
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from an investigation of infrared spectra, that the association is a result of hydrogen bonding and not of equilibria between monomer and dimer in these compounds.

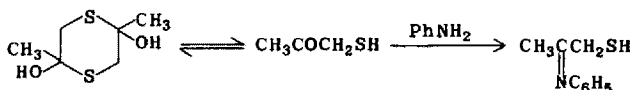
2, 5-Dimethyl-*p*-dithiane-2, 5-diol (**302**) reacts with amines in much the same fashion as *p*-dithiane-2, 5-diols. Thus, Bacchetti and Ferrati¹⁹ found that reaction of the low-melting isomer of **302** with aniline gives either 2, 5-dimethyl-2, 5-dianilino-*p*-dithiane (**314**) or 1, 4-dimethyl-7-phenyl-2, 5-dithia-7-azabicyclo[2. 2. 1]heptane (**315**), depending on the ratios used. Structures were assigned by Raney nickel desulfurization.



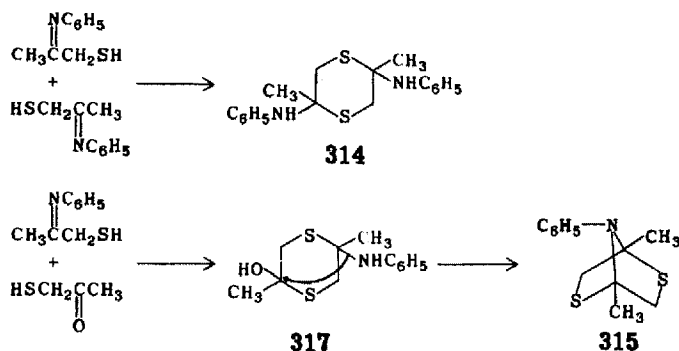
p-Toluidine reacted similarly, although with 2, 5-diethyl-*p*-dithiane-2, 5-diol only 2, 5-diethyl-2, 5-di(*p*-tolylamino)-*p*-dithiane was reported. In no case were isomers of the *p*-dithiane derivatives found. Hydrolysis of **315** yielded a compound to which the structure 2, 5-dimethyl-2, 5-bis(acetylthio)-*p*-dithiane (**316**) was assigned.



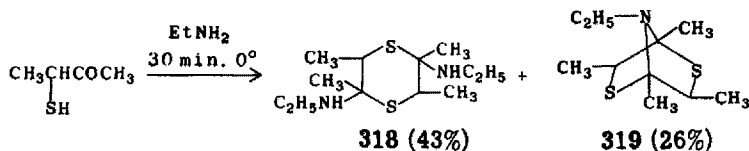
These reactions probably all take place *via* mercaptoacetone, as illustrated here with aniline.



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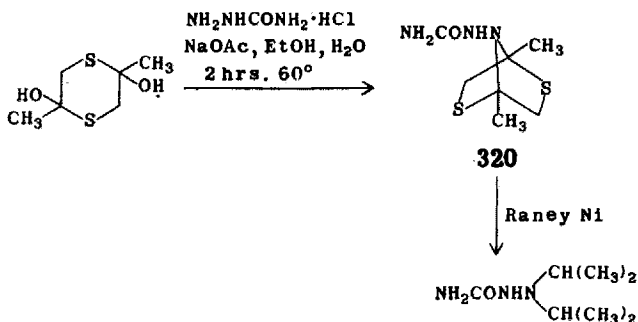


A slightly different view has been taken by Asinger, Thiel, and Hauthal.¹⁴ They found that 2-mercapto-3-butanone reacts with ethylamine to give a mixture of 2,5-bis(ethylamino)-2,3,5,6-tetramethyl-*p*-dithiane (**318**) and 7-ethyl-1,3,4,6-tetramethyl-2,5-dithia-7-azabicyclo[2.2.1]heptane (**319**), and concluded from this that the diamino compound (**318**) is the intermediate for the bicyclic compound (**319**) rather than the hydroxyamino compound (**317**) pictured above.



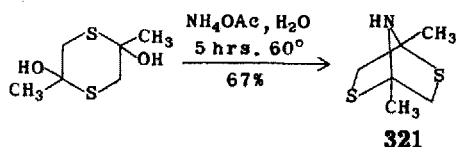
Only the bicyclic compound (**319**) was isolated when ethylamine hydrochloride was used. Rather surprisingly, methylamine gave only the 7-methyl analog of **319** under either set of conditions.

Bacchetti and Ferrati²⁰ found that 2,5-dimethyl-*p*-dithiane-2,5-diol reacts with semicarbazide in the same way as it does with aniline to form 1,4-dimethyl-7-ureido-2,5-dithia-7-azabicyclo[2.2.1]heptane (**320**). Raney nickel desulfurization gave *N,N*-diisopropylsemicarbazide.

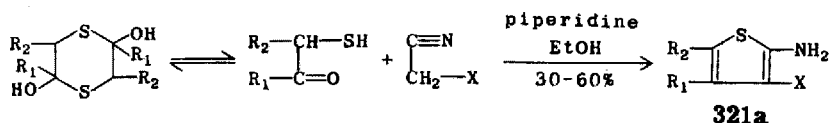


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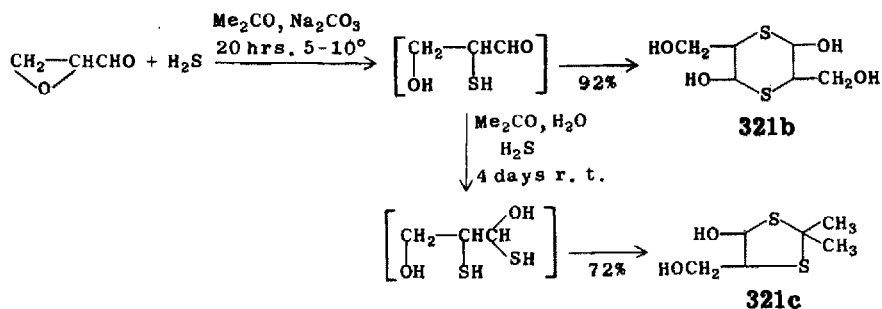
Both Haberl and Hromatka²⁴² and Thiel and Asinger⁴⁸⁵ found that ammonium acetate reacts normally to give 1,4-dimethyl-2,5-dithia-7-azabicyclo[2.2.1]heptane (**321**).



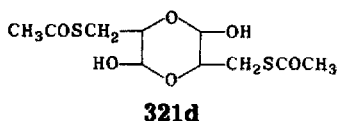
According to Gewald^{212a} both monomeric and dimeric α -mercapto-aldehydes and ketones react with active hydrogen compounds containing a nitrile group, such as malononitrile, ethyl cyanoacetate, etc., to give 2-aminothiophenes (**321a**).



Sullivan and Williams^{473a} found that hydrogen sulfide adds abnormally to glycidaldehyde in dry acetone to yield 2-mercapto-3-hydroxypropionaldehyde, isolated as its dimer, 3,6-bis(hydroxymethyl)-*p*-dithiane-2,5-diol (**321b**). A small amount of 2,2-dimethyl-4-hydroxymethyl-1,3-dithiolan-5-ol (**321c**) was formed as well, presumably by addition of hydrogen sulfide to the carbonyl group followed by reaction with the acetone solvent (see Chapter 5, section IIA-1a).

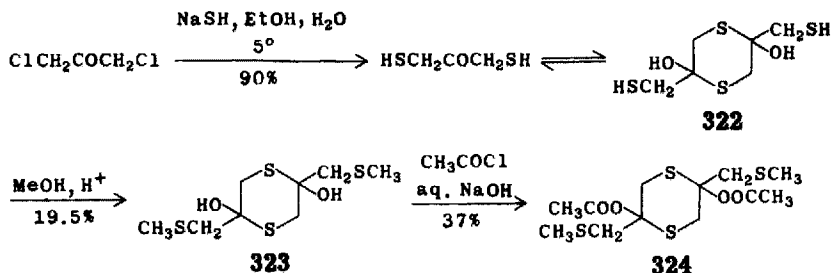


In aqueous acetone the 1,3-dithiolane (**321c**) became the major product. The structure of **321b** was indicated by its infrared spectrum, which showed the presence of hydroxyl and thioether groups and the absence of mercapto groups. The tetraacetate of **321b** similarly had infrared bands attributable to carboxylate and none attributable to thiocarboxylate. Thioacetic acid added normally to glycidaldehyde to yield a dioxane derivative (**321d**), whose tetraacetate differed from that of **321b**.

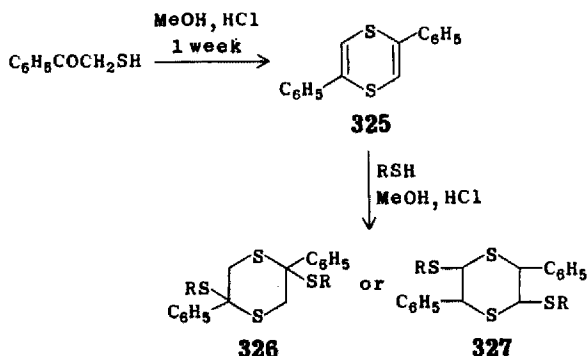


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Schotte^{440, 442} prepared 2, 5-bis(mercaptomethyl)-*p*-dithiane-2, 5-diol (**322**), the dimer of 1, 3-dimercaptoacetone, from 1, 3-dichloroacetone and sodium hydrosulfide. Its dimeric character was indicated by its molecular weight which, although low for the dimer, was much too high for the monomer; presumably the two forms are in equilibrium in solution. Further evidence for the assigned structure was the formation of a crystalline sulfide (**323**) and the corresponding diacetate (**324**). However, Schotte cited numerous experiments in which the compound reacted as monomeric 1, 3-dimercaptoacetone.

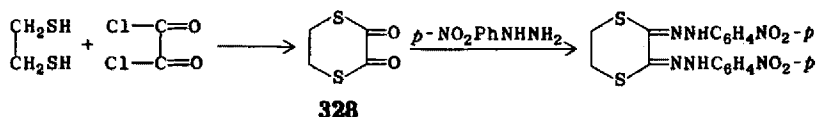


Groth²³⁵ reacted monomeric mercaptoacetophenone with ethyl and benzyl mercaptans. In light of the previous discussion, the compounds would be expected to be the corresponding 2, 5-diphenyl-2, 5-bis(ethylthio- or benzylthio)-*p*-dithianes (**326**). However, under the same conditions, but in the absence of mercaptan, mercaptoacetophenone formed 2, 5-diphenyl-*p*-dithiin (**325**) (see section III A-2a), which also reacts with the mercaptans. Thus, it is not clear whether the compounds should be formulated as **326** or **327**.



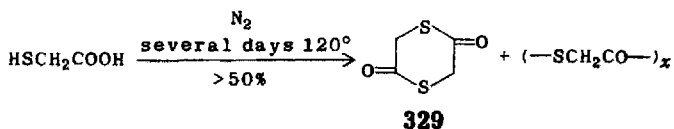
k. Oxo Derivatives and Related Compounds

Tsatsaronis⁴⁹⁵ condensed 1, 2-dimercaptoethane with oxalyl chloride and isolated a compound which he formulated as *p*-dithiane-2, 3-dione (**328**), primarily because it gave a *p*-nitrophenylosazone.

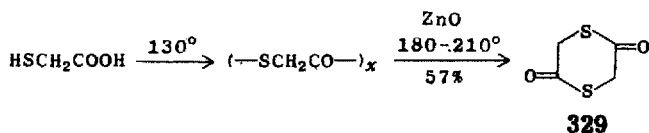


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p-Dithiane-2, 5-dione (**329**), or dithioglycolide, was first prepared by Schöberl and Krume⁴²⁷ in 1944 by dehydration of thioglycolic acid in a current of dry nitrogen. Inasmuch as 90% of the calculated quantity of water was eliminated but only about 60% of **329** was isolated, a linear polymer must have formed concurrently.



Unlike glycolic and lactic acids, thioglycolic acid did not lose water on simple distillation, and treatment with acid gave a different reaction. Schöberl and Wiehler^{430, 431} investigated the reaction more thoroughly and found that the initial product of the dehydration is the linear polymer which, on heating, yields the dione (**329**); zinc oxide and cobalt salts catalyze the depolymerization.⁴³⁵

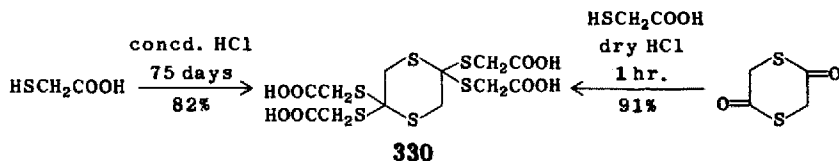


The 2, 5-dione crystallizes in colorless leaflets, m.p. 96.5-97.5°; the initially reported⁴²⁷ melting point of 119.5° is in error. Total analysis and molecular weight showed the compound to be C₄H₄O₂S₂, and the infrared absorption at 5.96 μ indicated a thiolactone structure. The pure compound is odorless and can be preserved indefinitely in a closed container. As a thiolactone it can of course be hydrolyzed readily to thioglycolic acid, and it is readily cleaved by amines to amides of thioglycolic acid^{435a} and by alcohols to esters. However, a catalytic quantity of primary or secondary amine at room temperature converted the dione quantitatively back to polythioglycolide.^{432a, 435} The same result was obtained at 130° in the presence of traces of water or thioglycolic acid. In spite of its instability to a variety of reagents, a mono-2, 4-dinitrophenylhydrazone could be isolated. Reduction with lithium aluminum hydride yielded mercaptoethanol.

In 1952 Schöberl⁴²⁸ reported that crystals form in aged samples of thioglycolic acid. They melt at 204° with decomposition and are insoluble in cold water and in organic solvents. Titration showed the compound to be acidic with a neutral equivalent of 119.4. Esterification with methanol in the usual manner gave the methyl ester, whose molecular weight showed the original compound to be a tetracarboxylic acid. Schöberl therefore formulated it as 2, 2, 5, 5-tetrakis(carboxymethylthio)-*p*-dithiane (**330**), the bis[bis(carboxymethyl)mercaptol] of *p*-dithiane-2, 5-dione. There is little doubt from the more detailed study by Schöberl and Wiehler⁴²⁹⁻⁴³¹ that this structure is correct. Thus, the compound is formed only in the presence of a trace of acid, and the same material can be isolated from *p*-dithiane-2, 5-dione and thioglycolic acid.

[For references, see pp. 1252-1271.]

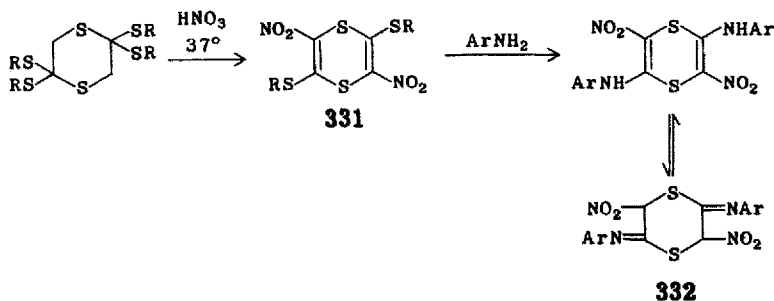
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Boron trifluoride is a better reagent than hydrochloric acid for converting thioglycolic acid into the mercaptole. Similarly, the methyl ester of **330** can be prepared by esterification of the mercaptole, by treatment of methyl thioglycolate with boron trifluoride, and by reaction of methyl thioglycolate with *p*-dithiane-2, 5-dione; the first method gives the best yields. Treatment of the methyl ester of **330** with hydrazine gave the tetrahydrazide, and benzylamine gave the tetra(benzylamide). Other mercaptols were prepared by the acid-catalyzed reaction of *p*-dithiane-2, 5-dione with 3-mercaptopropionic acid, with benzyl mercaptan, and with thiophenol; the reaction failed, however, with ethyl mercaptan, 2-mercaptopropionic acid, 2-mercaptophenylacetic acid, and 2-mercaptodiphenylacetic acid.

The mercaptols are quite stable to both acid and base, but are readily decomposed by mercuric chloride. A very typical reaction shown by all these compounds is halochromism in concentrated sulfuric acid or in 70% perchloric acid; i.e. solutions in these acids are colored, and the colors disappear on dilution. Schöberl attributed this to sulfonium salt formation. These compounds and the colors they give in sulfuric acid are listed in Table 16.

A number of these mercaptols can be nitrated in excellent yields to dinitro derivatives with the loss of two mercaptan groups. Although the structures have not been proved, Schöberl and Wiehler formulated them as substituted *p*-dithiin derivatives (**331**). These reacted with aromatic amines to give the same compound (**332**) (see section III A-2).



Graul²³² found that thioglycolic acid is physiologically harmless when used in hair-waving lotions, but felt that *p*-dithiane-2, 5-dione might be a toxic impurity. In view of Schöberl's results the dione is probably absent, but the toxicity of the mercaptole (**330**) should be of concern.

1. Phosphorus Derivatives

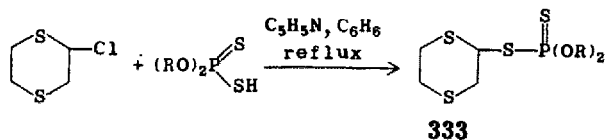
Haubein²⁵¹ reacted 2-chloro-*p*-dithiane with dialkyl dithiophosphates

TABLE 16. *p*-Dithianediones and Related Compounds

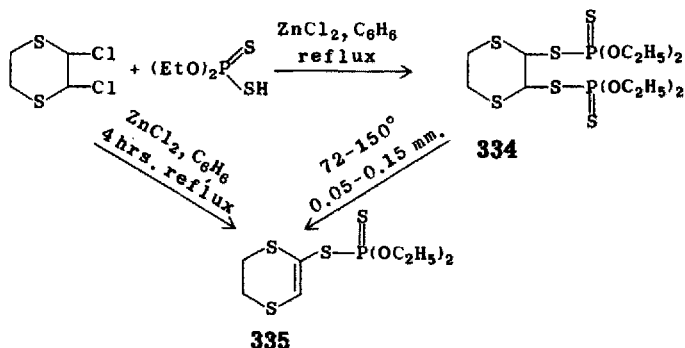
Substituents	Yield (%)	M.p. (°C)	Color in concd. H ₂ SO ₄	Ref.
2, 3-(O=) ₂		176-177		495
2, 3-(<i>p</i> -O ₂ NC ₆ H ₄ NHN=) ₂		241		495
2 5-(O=) ₂	57	96.5-97.5		427, 430, 431
2-(O=)-5-[2, 4-(O ₂ N) ₂ C ₆ H ₃ NHN=]	27	230-231.5 (dec.)		431
2, 2 5, 5-(SCH ₂ CO ₂ H) ₄	91	204 (dec.)	orange-red to cherry-red	428, 430, 431
2, 2 5, 5-(-SCH ₂ CO ₂ H) ₄ tetra(S-benzylthiouronium salt)	92.5	164.5-166 (dec.)		429, 431
2, 2, 5 5-(-SCH ₂ CO ₂ CH ₃) ₄	96.3	118-119	cherry-red	428, 431
2, 2, 5, 5-(-SCH ₂ CO ₂ C ₂ H ₅) ₄	85	93.6		429-431
2, 2, 5, 5-(-SCH ₂ CONHNH ₂) ₄	93	210-212 (dec.)	orange-red	431
2, 2, 5, 5-(-SCH ₂ CONHC ₆ H ₅) ₄	96	180-181 (dec.)	orange-red to red	431
2, 2, 5, 5-(-SCH ₂ CH ₂ CO ₂ H) ₄	75	181-182.5 (dec.)	dichromate color	430, 431
2, 2, 5, 5-(-SCH ₂ CH ₂ CO ₂ H) ₄ tetra(S-benzylthiouronium salt)	77	158-160 (dec.)		431
2, 2, 5, 5-(-SCH ₂ C ₆ H ₅) ₄	81	154.5-155		430, 431
2, 2, 5, 5-(-SC ₆ H ₅) ₄	82	190 (dec.)		430, 431

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and formed *p*-dithian-2-yl alkyl phosphorodithioates (**333**), in which the alkyl group contained 1-4 carbons.

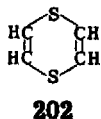


Dichloro-*p*-dithiane reacted with two dithiophosphates,²⁵⁰ and tetrachloro-*p*-dithiane with two or three, depending on the amount used.²⁵² According to Diveley¹⁵⁸ 2, 3-dichloro-*p*-dithiane reacted with diethyl dithiophosphate in the presence of a zinc chloride catalyst to yield *p*-dithian-2, 3-diyl ethyl phosphorodithioate (**334**). If the heating time was increased, or if **334** was pyrolyzed *in vacuo*, 2, 3-dihydro-*p*-dithiin-5-yl ethyl phosphorodithioate (**335**) formed.



These compounds, none of which has been described as a pure entity, have been patented as potent insecticides and miticides.

2. *p*-Dithiin (202)

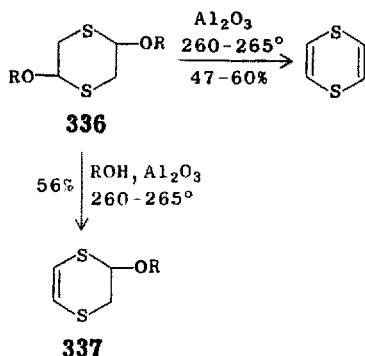


Levi³²⁷ in 1890 reported the synthesis of *p*-dithiin, which he called biophene, by the reaction of thiodiacetic acid with phosphorus trisulfide. A number of workers^{278, 379, 499} have been unable to repeat the synthesis. In 1919 Tscherniac⁴⁸⁴ reported that heating thiocyanacetone yielded a compound which he called "isomethylrhodim"; this on acid hydrolysis yielded a compound $\text{C}_6\text{H}_8\text{S}_2$, which he formulated as 2, 5-dimethyl-*p*-dithiin. However, Hromatka and Engel²⁷⁷ have shown that this compound has the formula $\text{C}_6\text{H}_{10}\text{OS}_2$ and is actually 1, 4-dimethyl-7-oxa-2, 5-dithiabicyclo[2. 2. 1]heptane (see Chapter 4, section II B-1).

C₄S₂ Ring Systems

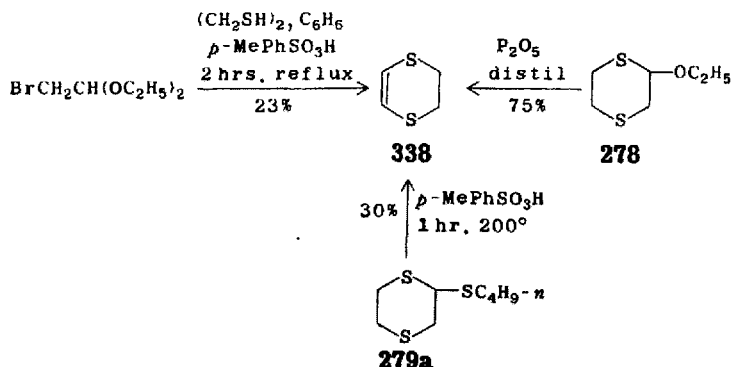
a. Preparation

The parent compound, *p*-dithiin, was first prepared by Parham, Wynberg, and Ramp³⁷⁹ in 1953. Treatment of 2,5-dimethoxy-*p*-dithiane (**336**, R = CH₃) (see section III A-1j) with phosphorus pentoxide at 110° gave a 46% yield of 2,3-dihydro-2-methoxy-*p*-dithiin (**337**, R = CH₃) and a trace of *p*-dithiin. Initially these authors reported that passage of an alcoholic solution of the dimethoxy or diethoxy compound over alumina at 300° gave 40-45% yields of *p*-dithiin, plus some **337** (R = CH₃ or C₂H₅). More recently, however, Parham, Gadsby, and Mikulec³⁸⁰ reported that this synthesis could not be repeated, but that good yields of *p*-dithiin could be obtained if molten **336** (R = C₂H₅) was passed over alumina at 260-265°. Use of an alcoholic solution at this lower temperature gave only the dihydro compound (**337**, R = C₂H₅).



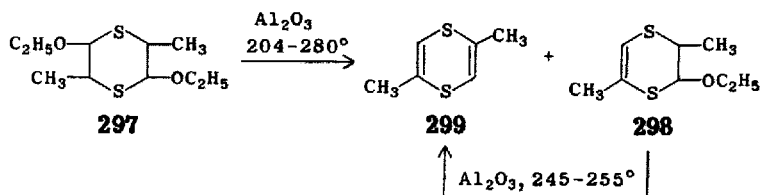
Hesse and Jörder²⁵⁷ prepared 2-acetoxy-2,3-dihydro-*p*-dithiin (**337**, R = CH₃CO) by pyrolysis of 2,5-diacetoxy-*p*-dithiane (**336**, R = CH₃CO).

2,3-Dihydro-*p*-dithiin (**338**) was prepared by Parham, Heberling, and Wynberg³⁸⁴ by two different routes, condensation of bromoacetaldehyde diethylacetal with 1,2-dimercaptoethane, and elimination of ethanol from 2-ethoxy-*p*-dithiane (**278**). Schneider and Bagnell^{426a} prepared it from 2-*n*-butylmercapto-*p*-dithiane (**279a**) by treatment with acid (see section III A-1j).



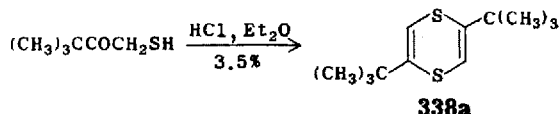
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2, 5-Dimethyl-*p*-dithiin (**299**) and 2, 5-dimethyl-3-ethoxy-2, 3-dihydro-*p*-dithiin (**298**) were prepared by Parham, Mayo, and Gadsby³⁹¹ by pyrolysis of the isomeric mixture of 2, 5-dimethyl-3, 6-diethoxy-*p*-dithiane (**297**). Pyrolysis of the dihydro compound (**298**) also yielded 2, 5-dimethyl-*p*-dithiin (**299**).

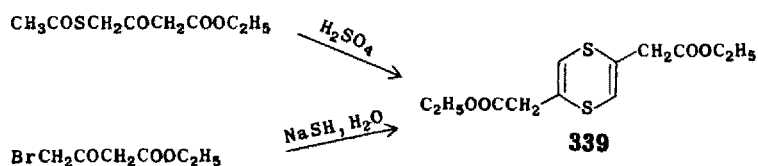


Yields were not reproducible, 14-38% of **299** and 15-64% of **298** being obtained. As already mentioned (see section III A-1j) the dihydro compound (**298**) was an isomeric mixture whose refractive index differed from that of **298** prepared from **297** with an acid catalyst.

Asinger, Thiel, and co-workers,^{13a} prepared 2, 5-di-*t*-butyl-*p*-dithiin (**338a**) in low yield from 3, 3-dimethyl-1-mercapto-2-butanone and acid. It is interesting that the 7-oxa-2, 5-dithiabicyclo[2. 2. 1]heptane derivative was not formed in this case (See Chapter 4, section II B-1).



The first *p*-dithiin derivative was apparently prepared by Steude⁴⁶⁷ in 1891. He treated ethyl γ -acetylthioacetoacetate with sulfuric acid and isolated a low yield of a compound, m.p. 168° , which he formulated as 2, 5-bis(carboethoxymethyl)-*p*-dithiin (**339**); reaction of ethyl γ -bromoacetoacetate with sodium hydrosulfide gave the same compound.

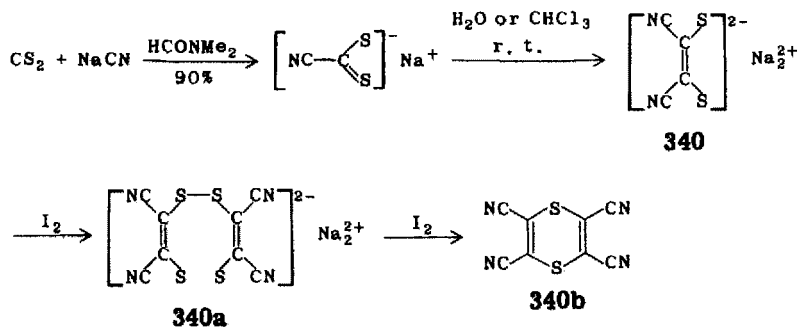


Parham, Wynberg, and Ramp³⁷⁹ reported that the ultraviolet absorption spectrum of Steude's compound indicated that it possessed a *p*-dithiin ring, but the compound was not investigated further.

Bähr and Schleitzer²⁸ reported in 1955 that sodium cyanide adds to carbon disulfide in dimethylformamide to give an excellent yield of sodium cyanodithioformate. These same authors^{28a-28c} found that the salt spontaneously loses sulfur to yield the disodium salt of dimercapto-maleonitrile (**340**). In view of the numerous ring closures that **340** undergoes (see Chapter 3, section I A, and Chapter 5, section II A-6),

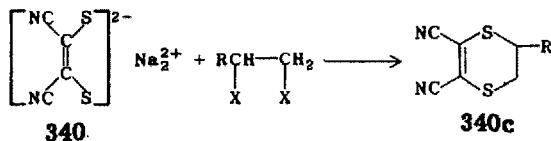
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there can be little doubt that **340** exists as the *cis* isomer, in spite of the close proximity of the two negatively charged sulfur atoms in this form. According to Bähr,^{28c} **340** reacts with iodine to yield an olive-green disulfide (**340a**), which, on further treatment with iodine, is converted into 2, 3, 5, 6-tetracyano-*p*-dithiin (**340b**).

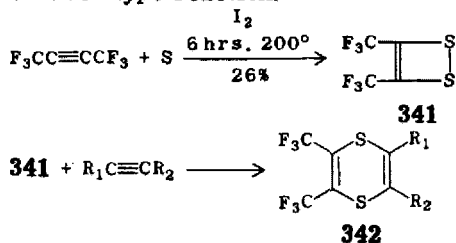


Blomstrom and Smith^{51b} prepared the tetracyano compound quantitatively from **340** and thionyl chloride; sulfur monochloride, sulfur dichloride, or sulfur plus chlorine gave somewhat lower yields. The chemistry involved in this transformation has been beautifully elucidated by Simmons and co-workers.^{456a}

Wolf, Degener, and Peterson^{150a, 510a} prepared a number of 2-substituted-2, 3-dihydro-5, 6-dicyano-*p*-dithiins (**340c**, R = H, CH₃, C₆H₅, CN, CH₃OCH₂) from **340** and various 1, 2-dihalides. Yields were good and no polymers were formed, in marked contrast to the reaction of 1, 2-dimercaptoethane with dihalides.

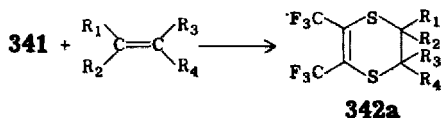


Krespan, McKusick, and Cairns^{316, 317a, 317b} prepared a number of trifluoromethyl-*p*-dithiins (**342**) and 2, 3-dihydro-*p*-dithiins (**342a**) by an interesting synthesis. Passage of hexafluoro-2-butyne into hot sulfur in the presence of iodine yielded bis(trifluoromethyl)-1, 2-dithietene (**341**) plus other products (see section III D-2). Reaction of **341** with acetylenic compounds yielded **342**, while olefins yielded **342a** in a Diels-Alder type reaction.

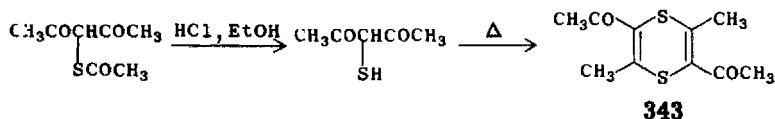


[For references, see pp. 1252-1271.]

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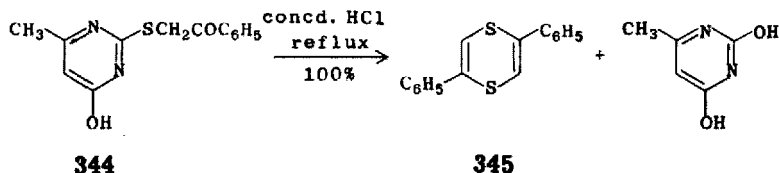


Böhme, Freimuth, and Mundlos⁵³ hydrolyzed 3-acetylthio-2,4-pentanedione to 3-mercapto-2,4-pentanedione. The latter gave a high-boiling oil on distillation and the structure 2,5-dimethyl-3,6-diacetyl-*p*-dithiin (**343**) was suggested for the compound.



The structural assignment was made on the basis of a postulated similarity between the ultraviolet absorption spectrum of **343** and of other *p*-dithiin derivatives. Actually the spectra are not too similar; **343** has absorption maxima in methanol at 220 mμ (ε = 4000) and 295 mμ (ε = 4750), *p*-dithiin in ethanol at 262 mμ (ε = 5400) and 266-270 mμ (ε = 5280), and 2,5-diphenyl-*p*-dithiin in ethanol at 259 mμ (ε = 22,100) and 309 mμ (ε = 8900).³⁹⁰ However, the two acetyl groups would be expected to cause a considerable shift in the absorption maxima, and the assigned structure may be correct.

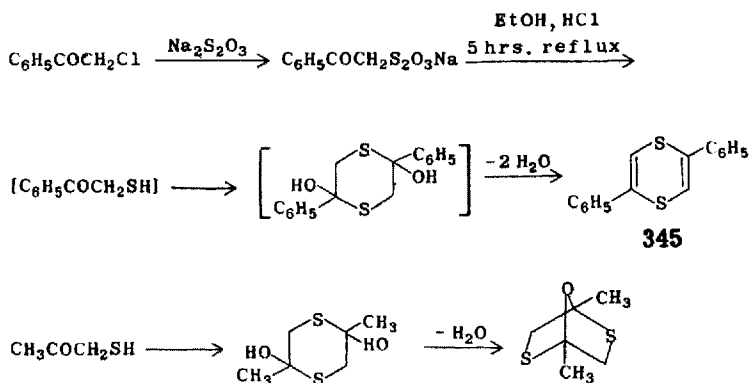
Most of the investigations of *p*-dithiins have been carried out on the 2,5-diaryl derivatives. In 1913 Johnson, Moran, and Kohmann²⁹⁸ hydrolyzed 2-benzoylmethylthio-4-hydroxy-6-methylpyrimidine (**344**) and isolated a quantitative yield of a yellow solid, m.p. 118-119°, which they formulated correctly as 2,5-diphenyl-*p*-dithiin (**345**) on the basis of its analysis, its molecular weight, and its non-reactivity with lead acetate, mercuric chloride, and silver nitrate. 6-Methyluracil was the other product of the hydrolysis.



The corresponding *p*-tolyl derivative reacted similarly. In 1924 Groth²³⁵ prepared phenacyl mercaptan, undoubtedly the intermediate in the above reaction, and showed that it dimerized in the presence of acid to the same product reported by Johnson, Moran and Kohmann. Baker and Barkenbus³⁰ investigated this reaction more thoroughly in 1936 and developed the first general synthesis for 2,5-diaryl-*p*-dithiins. Their procedure consisted of the preparation of the Bunte salt from phenacyl chloride; this, on acid hydrolysis, yielded the 2,5-diaryl-*p*-dithiin directly. The nature of the aryl group had little effect on the reaction, yields of 59-74% being obtained with phenyl, *m*-nitrophenyl and β-

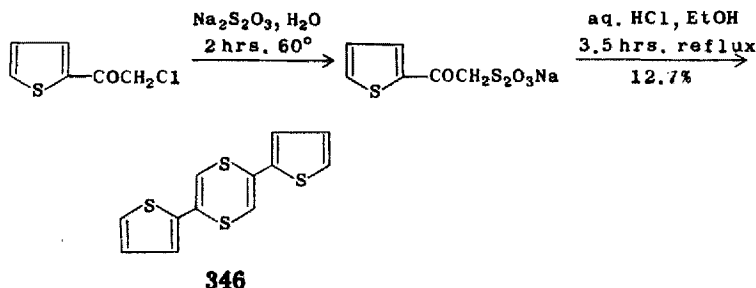
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naphthyl. Substitution on the carbon holding the sulfur atom lowered the yield considerably, however; 2-chloro-1-phenyl-1-propanone gave an 11% yield of 2,5-dimethyl-3,6-diphenyl-*p*-dithiin. The reaction fails with all alkyl substituted α -mercaptoketones except the *t*-butyl derivative, dehydration yielding the 1,4-dialkyl-7-oxa-2,5-dithiabicyclo[2.2.1]heptanes (see section III A-1j). Since it is reasonable to assume that both reactions take place *via* the intermediate dimer, which has not been isolated in the case of the aryl derivatives, it is not clear why the reaction follows different paths in the two cases.



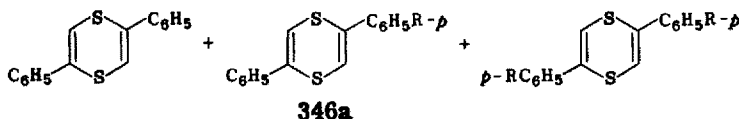
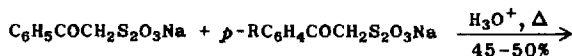
Apparently, the increased stabilization resulting from the conjugation of the double bond with the benzene ring is sufficient to favor the formation of the dithiin over the bicyclic compound. A similar explanation, involving conjugation with a carbonyl group, would explain the formation of 2,5-dimethyl-3,6-diacetyl-*p*-dithiin (**343**) from 3-mercapto-2,4-pentanedione.

Wynberg, Logothetis, and VerPloeg⁵¹³ applied this synthesis to the preparation of 2,5-bis(2-thienyl)-*p*-dithiin (**346**).

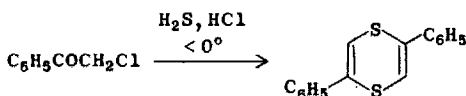


Parham, Harper, and Berger^{391a} used a mixture of Bunte salts to prepare mixed 2,5-diaryl-*p*-dithiins, 2-*p*-methoxyphenyl-5-phenyl-*p*-dithiin (**346a**, R = CH₃O) and 2-*p*-nitrophenyl-5-phenyl-*p*-dithiin (**346a**, R = NO₂). The three possible *p*-dithiins were formed in both cases in essentially statistical yields.

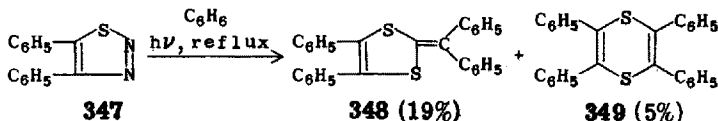
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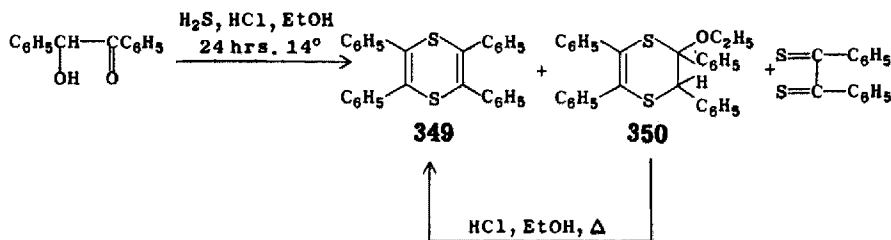
Böhme, Pfeiffer, and Schneider⁵² found that 2, 5-diphenyl-*p*-dithiin could also be prepared by the reaction of phenacyl chloride with hydrogen sulfide in the presence of acid.



According to Kirmse and Horner^{308,309} 4-phenyl-1, 2, 3-thiadiazole yields 2-benzylidene-4-phenyl-1, 3-dithiole upon irradiation (see Chapter 5, section II A-6). 4, 5-Diphenyl-1, 2, 3-thiadiazole (**347**) reacted somewhat differently, however, giving a mixture of 2-diphenylmethylene-4, 5-diphenyl-1, 3-dithiole (**348**) and 2, 3, 5, 6-tetraphenyl-*p*-dithiin (**349**); the latter undoubtedly arises by dimerization of the diradical formed by photochemical elimination of nitrogen from the 1, 2, 3-thiadiazole. Its structure was proved by Raney nickel desulfurization to 1, 2-diphenyl-ethane.



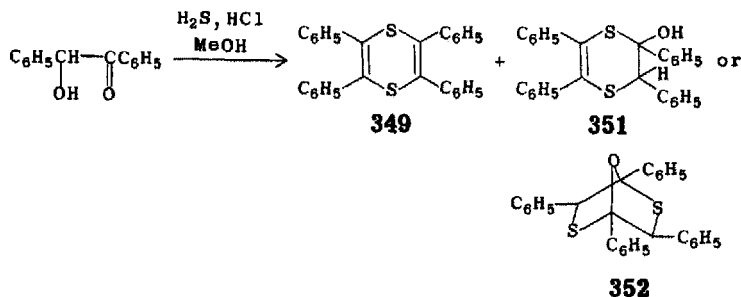
349 had previously been prepared by Mitra³⁶² from benzoin, hydrogen sulfide, and hydrogen chloride in ethanol, although he did not recognize its correct structure. Mitra isolated three compounds: **349**, a compound which analyzed as **349** plus one molecule of ethanol, and a compound which analyzed as $\text{C}_{14}\text{H}_{10}\text{S}_2$, which Mitra formulated as dithiobenzil. It is tempting to formulate the ethanol adduct as 2-ethoxy-2, 3, 5, 6-tetraphenyl-2, 3-dihydro-*p*-dithiin (**350**), inasmuch as heating it with alcoholic hydrogen chloride converted it into **349**. The ethanol adduct was also formed from the ethyl ether of benzoin under the same conditions.



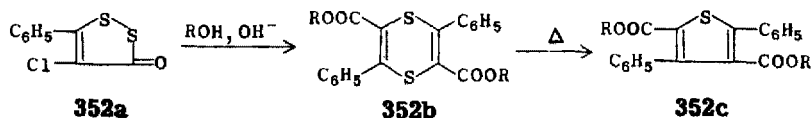
When methanol was substituted for ethanol in this reaction, a mixture of

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349 and a compound which analyzed as **349** plus a molecule of water was isolated. There is no evidence, however, on which to decide whether this is 2, 3, 5, 6-tetraphenyl-2, 3-dihydro-*p*-dithiin-2-ol (**351**) or 1, 3, 4, 6-tetraphenyl 7-oxa-2, 5-dithia-bicyclo[2. 2. 1]heptane (**352**).



Boberg^{51c} reported the formation of 2, 5-diphenyl-3, 6-dicarbalkoxy-*p*-dithiin (**352b**, R = CH₃, C₂H₅) by the base-catalyzed alcoholysis of 4-chloro-5-phenyl-1, 2-dithiol-3-one (**352a**) (Chapter 5, section I A-2a-(3)). Their structures were proved by conversion to the known 2, 4-diphenyl-3, 5-dicarbalkoxythiophene (**352c**).



Schöberl and Wiehler^{429, 431} reported the preparation of a different type of *p*-dithiin derivative. Certain bis(mercaptols) of *p*-dithiane-2, 5-dione (see section III A-1k) could be nitrated to yield a dinitro derivative with the elimination of two RSH groups. These compounds were formulated as 2, 5-bis(sulfides) of 3, 6-dinitro-*p*-dithiin (**331**), but no evidence has been advanced to substantiate this assignment. The compounds are listed in Table 17, together with other *p*-dithiin derivatives. 2, 3-Dihydro-*p*-dithiin compounds which have been reported are listed in Table 18.

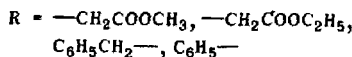
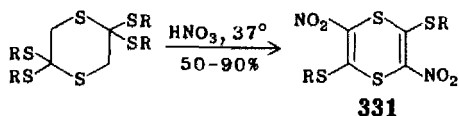


TABLE 17. *p*-Dithiun Derivatives

Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
None	47-60		71.5	17	n_D^{25} 1.6343	379, 390
			181	735		
1,1 (or 1,4)-Dioxide	60	99-100				379
1,1,4,4-Tetroxide	72	241.5-242.5 (dec.)				379
		241 (dec.)				381
1-(<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ N-)	84	155-156				381
2,5-(CH ₃ -) ₂	14-38		61-62	2	n_D^{25} 1.5754	391
2,5-(CH ₃ -) ₂ 1,1,4,4-tetroxide	99	218-221				391
2,5-(<i>t</i> -C ₄ H ₉ -) ₂	3.5	80				13a
2,5-(CH ₂ CO ₂ C ₂ H ₅) ₂	low	168				467
2,3-(F ₃ C-) ₂	3		48	10		317b
2,5-(C ₆ H ₅ -) ₂		118				235
	74	115-117				30
	100	118-119			Yellow prisms	52, 298
		117-118				382
2,5-(C ₆ H ₅ -) ₂ 1-oxide		114-115				481
	82	109 (dec.)				482
2,5-(C ₆ H ₅ -) ₂ 1,1-dioxide		151.5-153				481
	67	152-154				481
	72	152-154				482

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2, 5-(C_6H_5) ₂ 1, 1, 4, 4-tetroxide	50. 5	232		480
		234		373b
2, 5-(C_6H_5) ₂ · 2, 4-diphenylthiophene	33	128-129	Yellow crystals	382, 480
	70	126-128		481
2, 5-(C_6H_5) ₂ · 2, 4-diphenylfuran		111-112		481
2-(p - $CH_3OC_6H_4$)-5- C_6H_5 -	12	119-120		391a
2-(p - $CH_3OC_6H_4$)-5- C_6H_5 - 1, 1 (or 4, 4)- dioxide		129-130		391a
2-(p - $CH_3OC_6H_4$)-5- C_6H_5 - 1, 1, 4, 4-tetroxide	67	215-219		391a
2-(p - $O_2NC_6H_4$)-5- C_6H_5 -		138. 5-139		391a
2, 5-(p - $CH_3C_6H_4$) ₂	88	137-138	Yellow needles	298
2, 5-(p - $CH_3OC_6H_4$) ₂	54	167-169		391a
2, 5-(p - $CH_3OC_6H_4$) ₂ 1-oxide	95	141-145 (dec.)		391a
2, 5-(p - $CH_3OC_6H_4$) ₂ 1, 1-dioxide	76	204. 5-205. 5		391a
2, 5-(p - $CH_3OC_6H_4$) ₂ 1, 1, 4, 4-tetroxide	95	252-255		391a
2, 5-(m - $O_2NC_6H_4$) ₂	69	220-222		30
2, 5-(β - $C_{10}H_7$) ₂	59	198-200		30
2, 5-(2-Thienyl) ₂	12. 7	135-136	Yellow crystals	513
2, 5-(C_6H_5) ₂ -3-Br	75	85-86		386
	52	85. 5-86. 5		481
2, 5-(C_6H_5) ₂ -3-Br 1-oxide	61	115-116 (dec.)		482
2, 5-(C_6H_5) ₂ -3-Br 1, 1-dioxide	48	176. 5-178. 5		386
		176-178		482
2, 5-(C_6H_5) ₂ -3-NO ₂	74	132-133 (dec.)	Deep red needles	383

TABLE 17. *p*-Dithiin Derivatives (contd)

Substituents	Yield (%)	M.p. (°C)	B.P. (°C) (mm)	Other properties	Ref.
2, 5-(C ₆ H ₅) ₂ -3-NO ₂ 4-oxide	57	108 (dec.)		Yellow crystals	482
2, 3-(C ₂ H ₅) ₂ -5, 6-(F ₃ C)- ₂	15		77-79 4		371b
2, 3, 5, 6-(F ₃ C)- ₄	33	24-25	54-55 25		317a
2, 5-(CH ₃) ₂ -3, 6-(C ₆ H ₅) ₂	11	135-138	oil		30
2, 5-(CH ₃) ₂ -3, 6-(CH ₃ CO)- ₂				λ _{max} 220, 295 mμ (CH ₃ OH)	53
2, 3, 5, 6-(CN) ₄	100	208-209		Yellow needles	28, 51b
2, 3, 5, 6-(C ₆ H ₅) ₄	5	184 (dec.)			308
		195			362
2, 3, 5, 6-(C ₆ H ₅) ₄ tetrabromide		139			362
2, 5-(C ₆ H ₅) ₂ -3, 6-Br ₂	50	165-166			386
	56	164-165			481
2, 5-(C ₆ H ₅) ₂ -3-Br-6-NO ₂	65-67	143-144			386
2, 5-(C ₆ H ₅) ₂ -3-Br-6-NO ₂ 1-oxide	43	124-125 (dec.)		Yellow-orange crystals	482
2, 5-(C ₆ H ₅) ₂ -3, 6-(NO ₂) ₂	75	136.5 (dec.)			386
2, 5-(NO ₂) ₂ -3, 6-(CH ₃ O ₂ CCH ₂ S-) ₂	74	141-141.5 (dec.)		Yellow needles	429, 431
2, 5-(NO ₂) ₂ -3, 6-(C ₂ H ₅ O ₂ CCH ₂ S-) ₂	60	129.5-130 (dec.)		Yellow needles	429, 431
2, 5-(NO ₂) ₂ -3, 6-(C ₆ H ₅ CH ₂ S-) ₂	50	142.5-143.5 (dec.)		Yellow needles	431
2, 5-(NO ₂) ₂ -3, 6-(C ₆ H ₅ S-) ₂	90	176.5-177 (dec.)		Orange-red prisms	431
2, 5-(NO ₂) ₂ -3, 6-(C ₆ H ₅ NH-) ₂	78	179-180 (dec.)		Orange-red needles	431
2, 5-(NO ₂) ₂ -3, 6-(<i>p</i> -CH ₃ C ₆ H ₄ NH-) ₂	72	163.5-164 (dec.)		Brownish-yellow needles	431
2, 5-(NO ₂) ₂ -3, 6-(<i>o</i> -C ₁₀ H ₇ NH-) ₂	35	199-200 (dec.)		Brownish-yellow needles	431
2, 5-(C ₆ H ₅) ₂ -3, 6-(CH ₃ O ₂ C-) ₂		dec. 151-153			51c
2, 5-(C ₆ H ₅) ₂ -3, 6-(C ₂ H ₅ O ₂ C-) ₂		dec. 99-105			51c

TABLE 18. 2, 3-Dihydro- β -dithiin Derivatives

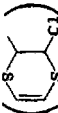
Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	B.p. (mm)	Other properties	Ref.
None	75		101	29	n_D^{25} 1.6295	384
	23		88	20	1.6273	
	30		75	15	1.6296	426a
1, 1, 4, 4-Tetroxide		dec. 200-300				384
	90	>280				426a
1-(<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ N-)		128.5-129				384
2-CH ₃ O-	46		63.1-63.2	4	n_D^{25} 1.5942	379
2-C ₂ H ₅ O-	27.2		68-72	2	n_D^{25} 1.5731	379
	56					380
2-CH ₃ CO ₂ -	38-80		133-135	11		257
			85-87	0.3		390
2, 3-Cl ₂	22	104.5-105.5				390
2-Cl-3-()	29	157-158 (dec.)				390
5, 6-(CN) ₂	89	139				150a, 510a

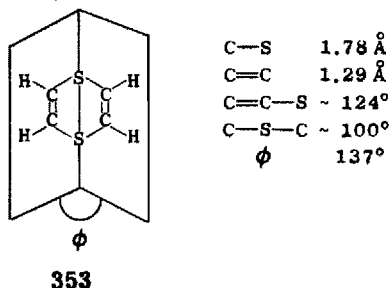
TABLE 18. 2, 3-Dihydro-*p*-dithiin Derivatives (contd)

Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
5, 6-(CN) ₂ 1, 1-dioxide	176					510a
5, 6-(CO ₂ H) ₂ anhydride	116					510a
5, 6-(F ₃ C-) ₂	24	29	106	25		317b
2-C ₂ H ₅ O-5, 6-(F ₃ C-) ₂	50		79	2		317b
2-(<i>n</i> -C ₄ H ₉ S-)-5, 6-(ClCF ₂ CF ₂ -) ₂	31		125-127	1		317b
2-CH ₃ -5, 6-(CN) ₂	60	88				150a, 510a
2-C ₆ H ₅ -5, 6-(CN) ₂	29	130				150a, 510a
2, 5, 6-(CN) ₃	164 (dec.)					510a
2-(CH ₃ OCH ₂ -)-5, 6-(CN) ₂	44		104-105	5.3	Yellow crystals	150a, 510a
2, 5-(CH ₃ -) ₂ -3-C ₂ H ₅ O-	44		60-62	0.25	n_D^{27} 1.5437	391
	15-64		90-92.5	2.4	Isomeric mixtures n_D^{27} 1.5383	
2, 3-(C ₆ H ₅ -) ₂ -5, 6-(F ₃ C-) ₂	36	160-162				317b
2, 2, 3, 3-(CH ₃ -) ₄ -5, 6-(F ₃ C-) ₂	47	21-22	84	4		316, 317, 317b
2-C ₂ H ₅ O-2, 3, 5, 6-(C ₆ H ₅ -) ₄	126					362
2-C ₂ H ₅ O-2, 3, 5, 6-(C ₆ H ₅ -) ₄ Br ₅	178					362

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b. Structure

The structure of *p*-dithiin is of considerable theoretical interest. As pointed out by Parham and co-workers,^{381,385} the molecule might exist in a chair form, a boat form, or as a planar ring, the last because of the possibility of resonance forms with multiple bonds to sulfur. Of these, the boat form would be preferred because of the expected planarity of the —S—C=C—S— group. This hypothesis was confirmed by Howell, Curtis, and Lipscomb,²⁷⁶ who carried out a single crystal X-ray determination and found *p*-dithiin to exist in the boat form (**353**).



Thus the compound is aliphatic and forms such as **354** should contribute little to the structure.



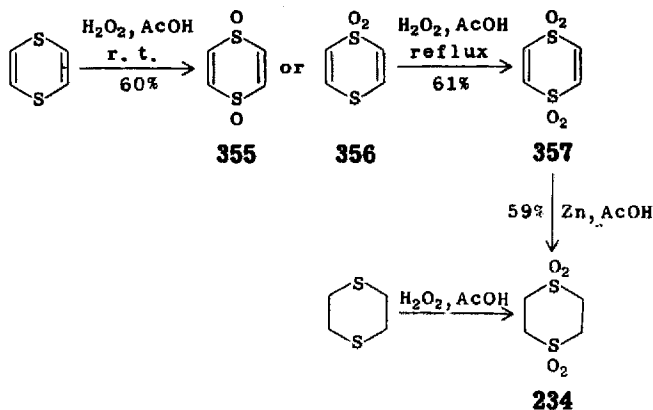
354

Kreevoy³¹⁵ carried out a theoretical study of *p*-dithiin by the LCAO-MO method, neglecting overlap, σ - π interactions, and participation by the d-orbitals of the sulfur atoms. The calculations were in accord with the boat-like geometry, and predicted a 6.4 kcal barrier to turning the boat inside-out. The molecule should have semi-aromatic character with a resonance energy of 28 kcal, intermediate between that of thiophene and furan. *p*-Dithiin should be highly basic compared to benzene, quite susceptible to oxidation, to attack by electrophilic reagents, and to attack by free radicals. These predictions are fairly well borne out by the reactions of *p*-dithiin (see section III A-2c).

c. Properties and Reactions

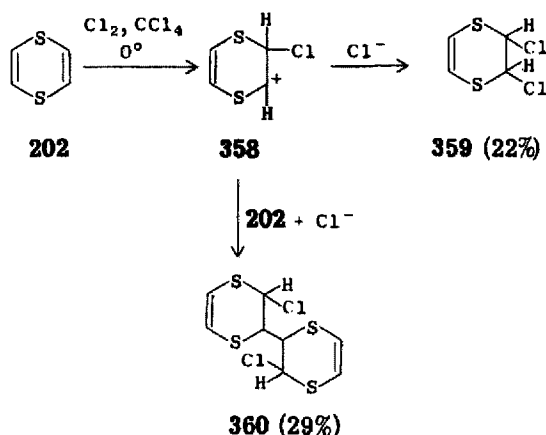
p-Dithiin is a distillable liquid with a pleasant olefinic odor according to Parham and co-workers,^{379,390} who studied its chemistry. In many of its reactions it is similar to *p*-dithiane. Thus, oxidation with hydrogen peroxide in acetic acid at room temperature gave a dioxide, either *p*-dithiin 1,4-dioxide (**355**) or 1,1-dioxide (**356**), which was oxidized further to the tetroxide (**357**); a monoxide could not be isolated.³⁹⁰ The disulfone, on reduction, yielded *p*-dithiane 1,1,4,4-tetroxide (**234**); this

was identical, by X-ray diffraction, with a sample prepared by the oxidation of *p*-dithiane, thus proving the structure of *p*-dithiin.



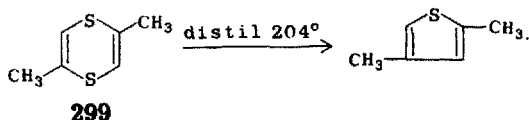
Parham and co-workers^{381,390} carried out a number of additional reactions on *p*-dithiin to prove its non-aromatic nature. Chloramine-T gave a monosulfilimine, a Friedel-Crafts reaction failed to yield a ketone, it could not be nitrated, and Lewis acids polymerized it readily. Furthermore, *p*-dithiin 1,1,4,4-tetroxide (**357**) underwent Diels-Alder reactions with a number of dienes. Thus, *p*-dithiin shows reactions typical of a vinyl sulfide, in complete agreement with its structure as determined by X-ray diffraction. 2,3-Dihydro-*p*-dithiin reacts similarly.³⁸⁴

The chlorination of *p*-dithiin was investigated by Parham, Gadsby, and Mikulec.³⁹⁰ Two compounds were isolated, a crystalline, air-sensitive derivative, $\text{C}_4\text{H}_4\text{Cl}_2\text{S}_2$, and an insoluble solid which appeared to be $\text{C}_8\text{H}_8\text{Cl}_2\text{S}_4$. These were assigned structures **359** and **360** on the basis of their infrared and ultraviolet spectra, which indicated that both molecules possessed the grouping $\text{RSCH}=\text{CHSR}$. Their formation was visualized as the proceeding *via* the intermediate formation of **358**; only one isomer of each was isolated.



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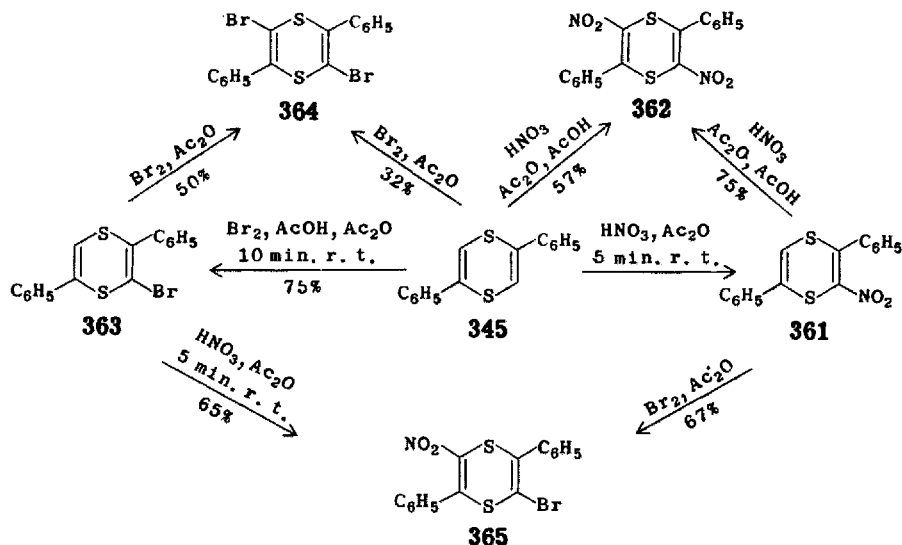
Parham, Mayo, and Gadsby³⁹¹ found 2, 5-dimethyl-*p*-dithiin (**299**) to be very much like *p*-dithiin in its reactions. Thus, excess hydrogen peroxide oxidized it to a disulfone, while aluminum chloride yielded a polymer. No isolable compounds were obtained on treatment with bromine, chlorine, nitric acid, acetic anhydride plus phosphoric acid, mercuric ion or dimethylformamide plus phosphorus oxychloride, i.e. it did not undergo electrophilic substitution. Unlike *p*-dithiin, however, it decomposed on heating to form 2, 4-dimethylthiophene; in this respect it reacted like 2, 4-diphenyl-*p*-dithiin (*vide infra*).



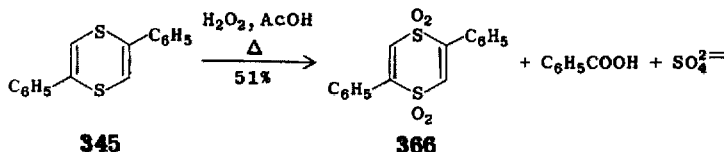
2, 5-Diaryl-*p*-dithiins are yellow, crystalline solids. One of their most typical reactions is their halochromism in concentrated sulfuric acid, attributed to salt formation by Johnson, Moran, and Kohmann,²⁹⁸ who first noted their intense red or purple colors in concentrated sulfuric acid, which faded on dilution with water.

Most of our knowledge of the chemistry of 2, 5-diaryl-*p*-dithiins stems from the work of Parham and Szmant and their co-workers. Johnson, Moran, and Kohmann²⁹⁸ treated 2, 5-di-*p*-tolyl-*p*-dithiin with nitric acid and isolated a yellow nitro derivative. Bromine gave a blue compound, but these authors made no attempt to determine the structures of these adducts. Parham and Traynelis³⁸³ nitrated 2, 5-diphenyl-*p*-dithiin (**345**) and obtained a deep red, crystalline, mononitro derivative. Inasmuch as permanganate oxidation yielded only benzoic acid and no nitrobenzoic acid, the compound must be 2, 5-diphenyl-3-nitro-*p*-dithiin (**361**). This, on further nitration by Parham, Nicholson, and Traynelis,³⁸⁶ yielded 2, 5-diphenyl-3, 6-dinitro-*p*-dithiin (**362**), whose structure was proved in the same way. Similarly, bromine gave either 2, 5-diphenyl-3-bromo-*p*-dithiin (**363**) or 2, 5-diphenyl-3, 6-dibromo-*p*-dithiin (**364**), depending on the conditions of the reaction; Szmant and Alfonso⁴⁸¹ obtained the same results with *N*-bromosuccinimide. Nitration of the monobromo derivative (**363**) and bromination of the mononitro derivative (**361**) yielded the identical compound, undoubtedly 2, 5-diphenyl-3-bromo-6-nitro-*p*-dithiin (**365**). Thus, 2, 5-diphenyl-*p*-dithiin, unlike *p*-dithiin itself, readily undergoes electrophilic substitution.

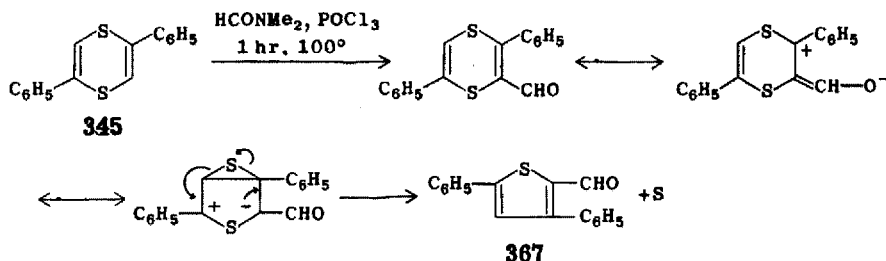
Chapter 12



Szmant and Dixon⁴⁸⁰ succeeded in oxidizing 2,5-diphenyl-*p*-dithiin to the disulfone, 2,5-diphenyl-*p*-dithiin 1,1,4,4-tetroxide (**366**), with excess hydrogen peroxide, some ring cleavage taking place.

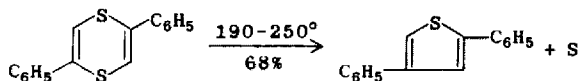


When, however, the reaction was carried out with one mole of hydrogen peroxide, they isolated a yellow solid, $\text{C}_{32}\text{H}_{24}\text{S}_3$, m.p. 128° . The structure of this material was elucidated by Parham and Traynelis.³⁸² These authors attempted to prepare 2,5-diphenyl-3-formyl-*p*-dithiin by the Vilsmeier reaction, treating **345** with dimethylformamide and phosphorus oxychloride. Much to their surprise they isolated instead, in 48% yield, 3,5-diphenyl-2-thenaldehyde (**367**), whose structure was proved by an unequivocal synthesis. They postulated the following mechanism, essentially an intramolecular Diels-Alder reaction, to explain its formation.



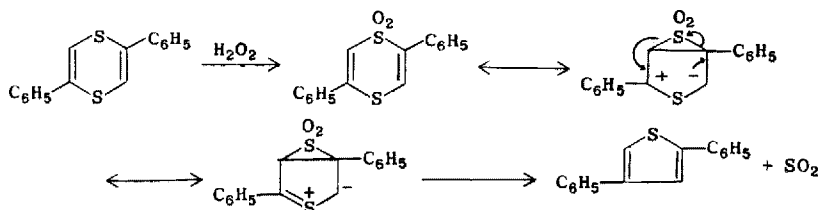
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With this clue, they then heated 2, 5-diphenyl-*p*-dithiin and isolated a 60% yield of 2, 4-diphenylthiophene and a 67% yield of sulfur.

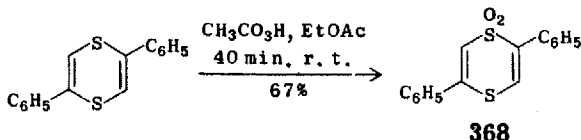


Thus, a purely thermal reaction, not involving oxidation, also leads to the formation of a thiophene derivative, although higher temperatures are required. In this respect 2, 5-diphenyl-*p*-dithiin and 2, 5-dimethyl-*p*-dithiin differ from *p*-dithiin, which does not form a thiophene derivative on pyrolysis.³⁹⁰ From these results it was relatively easy to show that Szmant and Dixon's unknown compound was a 1 : 1 complex of 2, 5-diphenyl-*p*-dithiin and 2, 4-diphenylthiophene by recrystallizing a 1 : 1 mixture of the two compounds. Szmant and Alfonso⁴⁸¹ confirmed this structure by a molecular weight determination and by the ultraviolet absorption spectrum. The complex exists only in the solid state, and Szmant and Alfonso cited its separation into its component parts by chromatography as evidence against the complex being a readily reversible Diels-Alder adduct. These authors suggested that the molecules in the complex are stacked like a deck of cards, overlapping of the π -orbitals of the benzene rings holding them together. As evidence for this, they showed that 2, 4-diphenylfuran also forms a 1 : 1 complex with 2, 5-diphenyl-*p*-dithiin, but that 2, 5-diphenylthiophene does not; in the latter compound the benzene rings would not be oriented correctly to form the complex.

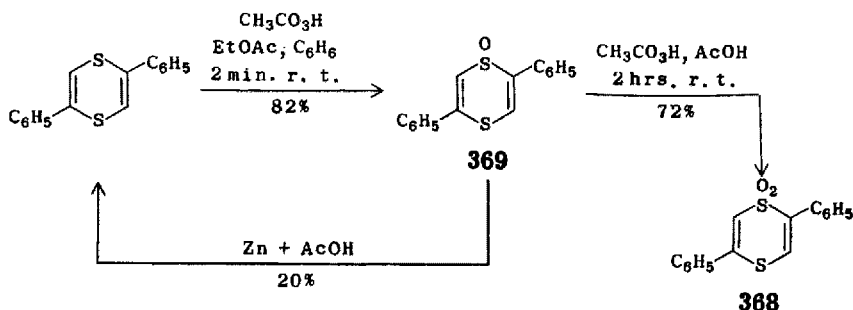
The mechanism of this oxidative ring contraction is interesting. Parham and Traynelis³⁸² pictured it as taking place much like the cleavage of the formyl derivative.



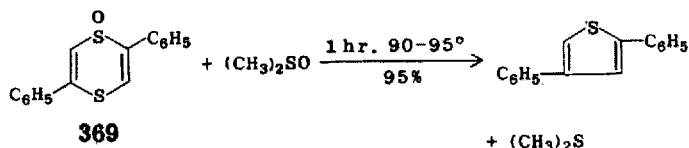
Sulfur dioxide would be eliminated instead of sulfur because of the greater stability of the compounds formed. Szmant and Alfonso,⁴⁸¹ however, prepared 2, 5-diphenyl-*p*-dithiin 1, 1-dioxide (**368**) by treatment of 2, 5-diphenyl-*p*-dithiin or its 1 : 1 complex with 2, 4-diphenylthiophene with peracetic acid; its infrared spectrum showed it to be a sulfone and not a disulfoxide.



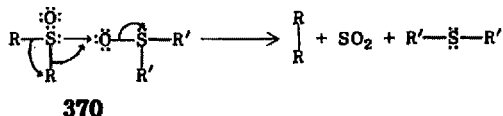
It, however, was stable to 200°, and it did not yield the thiophene derivative under the reaction conditions used with hydrogen peroxide. The sulfone is not, therefore, an intermediate in the ring contraction; this conclusion was also reached by Parham, Nicholson, and Traynelis.³⁸⁶ Szmant and Alfonso⁴⁸² also prepared the monosulfoxide, 2,5-diphenyl-*p*-dithiin 1-oxide (**369**), by limiting the reaction time. Its structure was proved by infrared analysis, by reduction to 2,5-diphenyl-*p*-dithiin, and by oxidation to the sulfone (**368**). It should be noted that Parham, Gadsby, and Mikulec³⁹⁰ were unable to prepare the monosulfoxide of *p*-dithiin, another difference between *p*-dithiin and the 2,5-diphenyl derivative.



The monosulfoxide (**369**) is apparently the intermediate in the oxidative ring contraction.⁴⁸² Heating it in toluene for 25 minutes at 90–95° gave a 56% yield of the 1:1 complex, while in one minute at 135° it gave a 58% yield of 2,4-diphenylthiophene. The best condition found was heating a solution in dimethyl sulfoxide.



The ring contraction takes place, therefore, during the disproportionation of the sulfoxide to sulfone and sulfide perhaps *via* a bimolecular complex (**370**) as formulated by Szmant and Alfonso.

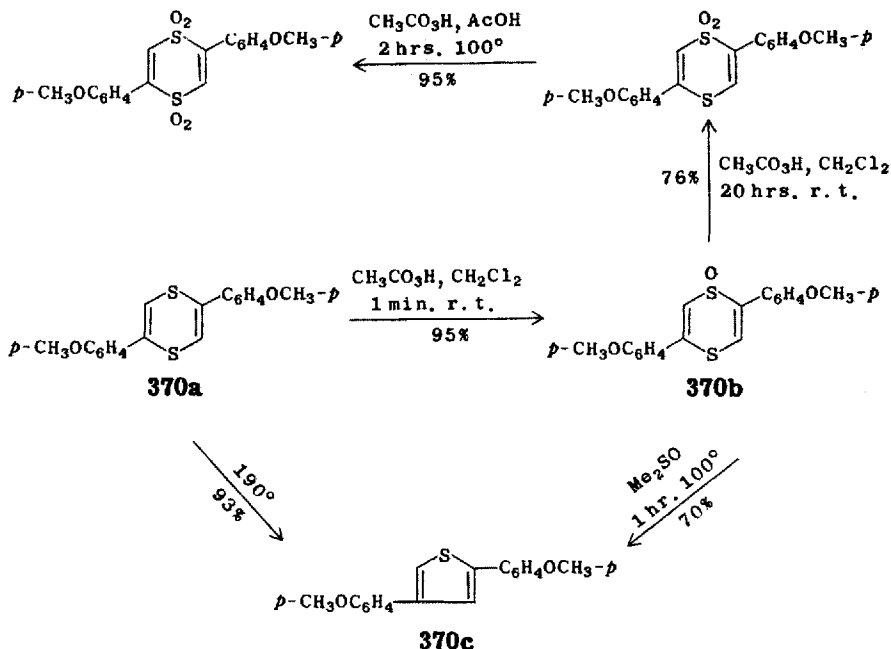


To explain the greater than 50% yield of 2,4-diphenylthiophene formed at 135°, they postulated that at the higher temperature one molecule of sulfoxide decomposed to 2,4-diphenylthiophene and sulfur monoxide, the latter attacking another molecule of sulfoxide to give the thiophene derivative and sulfur dioxide.

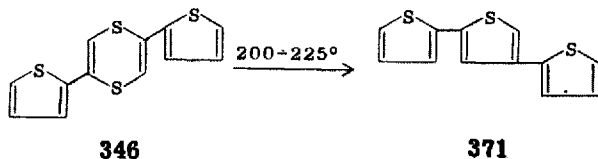
Parham, Harper, and Berger^{391a} prepared three of the four possible oxides of 2,4-di-*p*-methoxyphenyl-*p*-dithiin (**370a**). 2,4-Di-*p*-methoxy-

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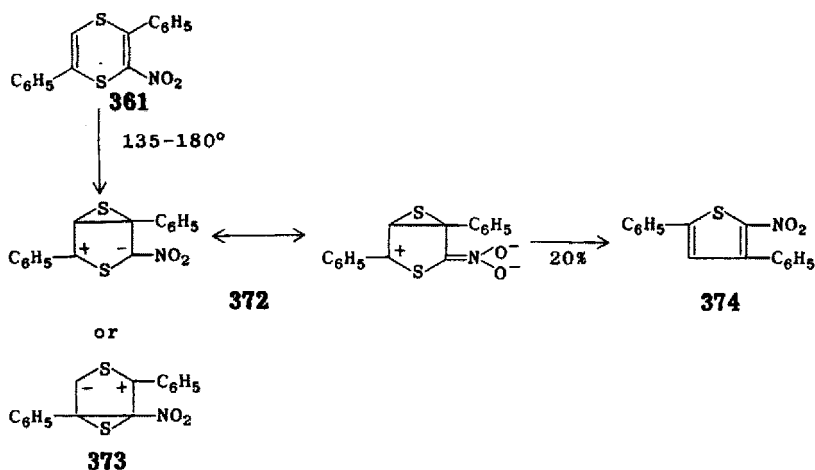
phenylthiophene (**370c**) was obtained from both the *p*-dithiin (**370a**) and the monoxide (**370b**).



This reaction has been generalized by Loudon, Sloan, and Sommers,³³¹ who stated that a sulfur atom is readily "extruded" from a heterocycle if ring contraction leads to an aromatic structure. The elimination reaction has been used to prepare a number of otherwise difficultly accessible substituted thiophenes. Thus, Wynberg, Logothetis, and Ver-Ploeg⁵¹³ prepared 2,2',4',2''-terthienyl (**371**) from 2,5-bis(2-thienyl)-*p*-dithiin (**346**).

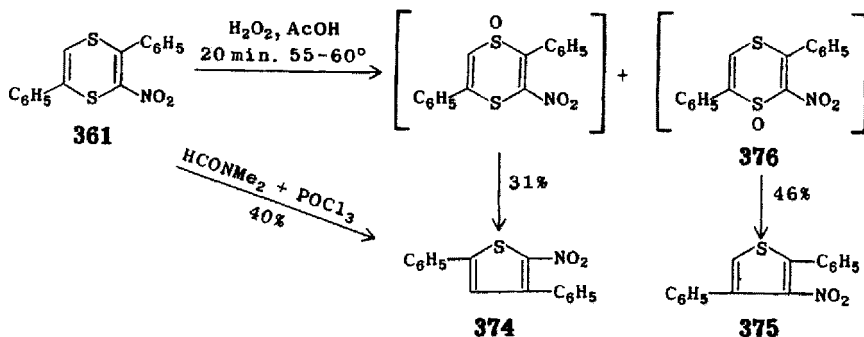


Kirmse and Horner³⁰⁸ prepared tetraphenylthiophene from 2,3,5,6-tetraphenyl-*p*-dithiin both thermally and by peracetic acid oxidation. Likewise, Parham and Traynelis³⁸³ used both methods on 2,5-diphenyl-3-nitro-*p*-dithiin (**361**). Here, however, two thiophenes are possible. Thermally, the product was 2-nitro-3,5-diphenylthiophene (**374**) explained as follows:



The reaction follows the indicated path because the negative charge in **372** but not in **373** can be stabilized by resonance with the nitro group. In addition, an unknown compound, $C_{16}H_{11}O_2NS_2$, m.p. $231-232^\circ$, was formed in 11% yield.

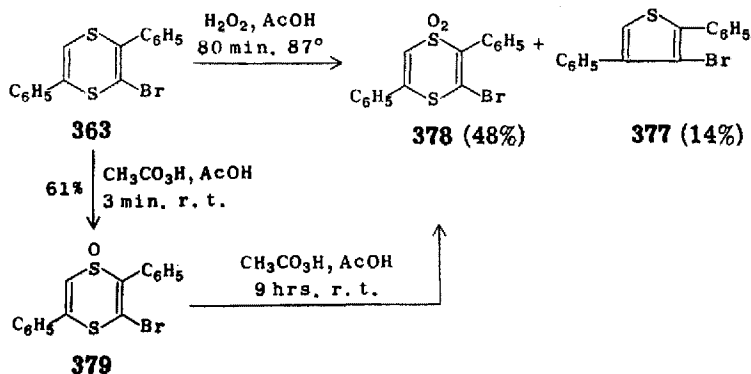
Parham and Traynelis³⁸³ found that with peroxide both isomers were formed, 2-nitro-3, 5-diphenylthiophene (**374**) and 3-nitro-2, 4-diphenylthiophene (**375**), the latter in somewhat greater quantity, presumably because oxidation takes place at the more electron-rich sulfur atom. The Vilsmeier reaction gave the 2-nitrothiophene (**374**) as expected.



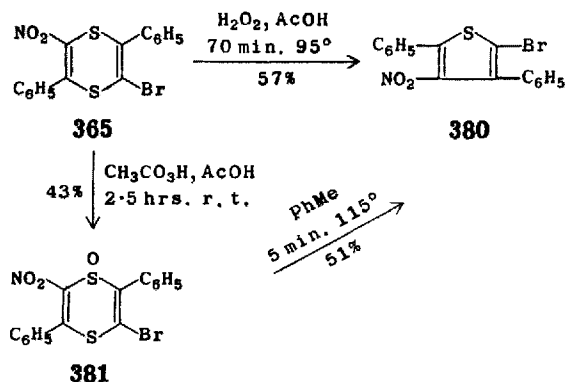
With peracetic acid Szmant and Alfonso⁴⁸² isolated only 2, 5-diphenyl-3-nitro-*p*-dithiin 4-oxide (**376**), its structure being indicated by its conversion into **375**.

Parham, Nicholson, and Traynelis³⁸⁶ oxidized 2, 5-diphenyl-3-bromo-*p*-dithiin (**363**) and isolated a mixture of 3-bromo-2, 4-diphenylthiophene (**377**) and a *p*-dithiin dioxide, to which they tentatively assigned the structure 2, 5-diphenyl-3-bromo-*p*-dithiin 1, 1-dioxide (**378**). This was confirmed by Szmant and Alfonso,⁴⁸² who isolated the monoxide (**379**) and converted it into the same dioxide by further oxidation.

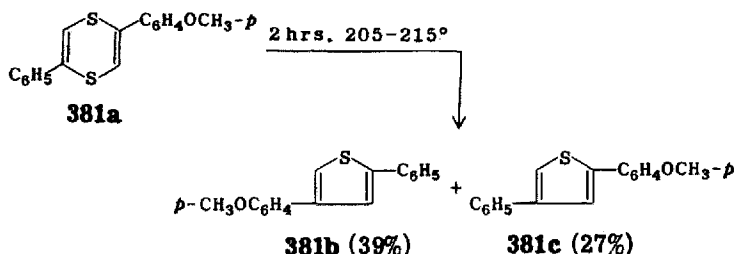
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2, 5-Diphenyl-3, 6-dibromo-*p*-dithiin (**364**) gave a 76% yield of 2, 4-dibromo-3, 5-diphenylthiophene with hydrogen peroxide, while the dinitro compound (**362**) gave a 25% yield of 2, 4-diphenyl-3, 5-dinitrothiophene plus 12% of the same unknown isolated from the mononitro-*p*-dithiin (**361**). The unsymmetrical derivative, 2, 5-diphenyl-3-bromo-6-nitro-*p*-dithiin (**365**) gave only 2-bromo-4-nitro-3, 5-diphenylthiophene (**380**), none of the 2-nitro compound being isolated. Here, too, Szmant and Alfonso⁴⁸² were able to isolate 2, 5-diphenyl-3-bromo-6-nitro-*p*-dithiin 1-oxide (**381**), the position of the oxygen being shown by its decomposition to **380**.

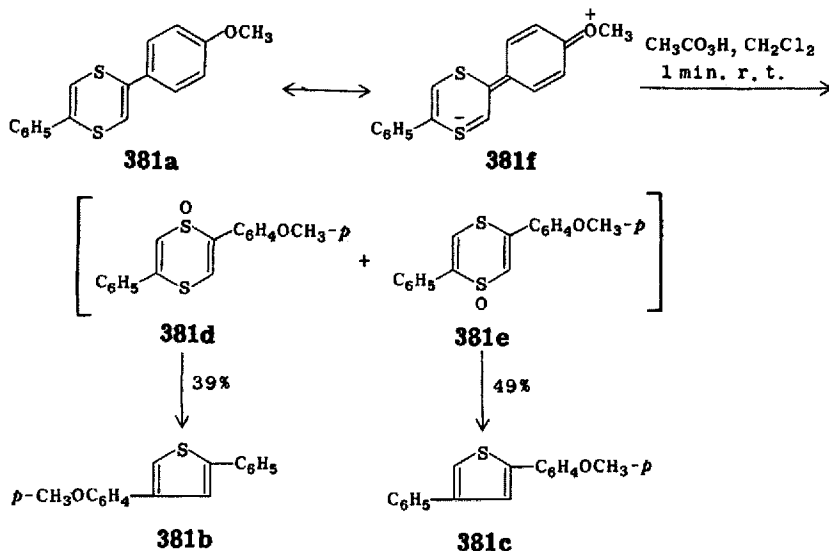


Parham, Harper, and Berger^{391a} investigated the pyrolysis of unsymmetrically substituted 2, 5-diaryl-*p*-dithiins. 2-*p*-Methoxyphenyl-5-phenyl-*p*-dithiin (**381a**) yielded 39% 2-phenyl-4-*p*-methoxyphenylthiophene (**381b**) and 27% 2-*p*-methoxyphenyl-4-phenylthiophene (**381c**).



Inasmuch as the *p*-methoxy group in **381a** would be expected to exert a more profound effect on the direction of cleavage, the authors felt that these results cast some doubt on the ionic mechanism previously postulated to explain the sulfur-elimination reaction.

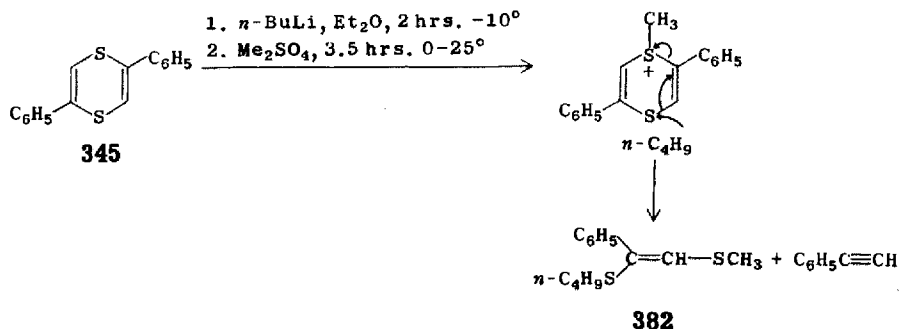
These same authors investigated the oxidation of mixed 2,5-diaryl-*p*-dithiins. Oxidation of **381a** yielded a mixture of sulfoxides, which was converted into a mixture of 39% **381b** and 49% **381c**. Inasmuch as the former would arise from the 1-oxide (**381d**) and the latter from the 4-oxide (**381e**), there appears to be preferential attack in the 4-position as a result of *d*-orbital resonance, such as in **381f**; peracetic acid would be expected to attack the position of higher electron density.



Parham and Kneller³⁸⁸ investigated the metalation of 2,5-diphenyl-*p*-dithiin (**345**). No reaction occurred between **345** and *n*-butyllithium in

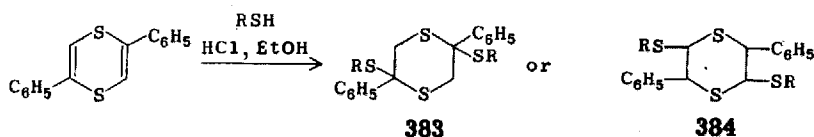
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ether at room temperature. A rapid reaction took place, however, upon the addition of dimethyl sulfate, and an isomeric mixture of 1-*n*-butylthio-1-phenyl-2-methylthioethylene (**382**) and phenylacetylene was isolated. The reaction was formulated as follows:



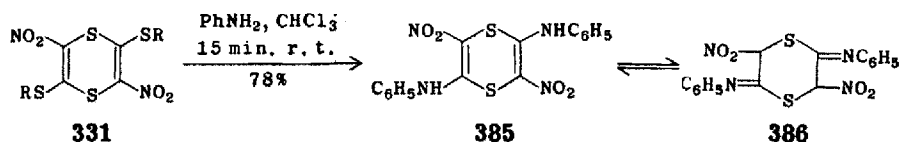
No evidence for the formation of the other expected cleavage product, 1-*n*-butylthio-2-phenyl-2-methylthioethylene, was obtained. The reaction is analogous to the cleavage of 1,4-benzodithiin (see section III E-2).

In quite a different type of reaction Groth²³⁵ treated 2, 5-diphenyl-*p*-dithiin with ethyl and benzyl mercaptans in the presence of hydrogen chloride. Two molecules of mercaptan added, but no attempt was made to prove whether the compounds were 2, 5-diphenyl-2, 5-bis(alkylmercapto)-*p*-dithianes (**383**) or 2, 5-diphenyl-3, 6-bis(alkylmercapto)-*p*-dithianes (**384**).

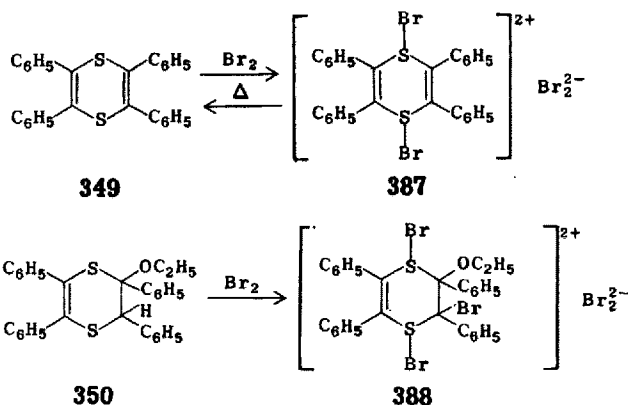


The same product (**383** or **384**, $R = C_6H_5CH_2$) was obtained from phenacyl mercaptan.

In still another type of reaction Schöberl and Wiehler^{429,431} reacted their 2,5-bis(alkylthio)-2,6-dinitro-*p*-dithiins (**331**) with aromatic amines, resulting in displacement of the sulfur moiety by the amine. Thus, all the derivatives gave only one compound with aniline, either 2,5-dianilino-3,6-dinitro-*p*-dithiin (**385**) or 2,5-bis(phenylimino-3,6-dinitro-*p*-dithiane (**386**). *p*-Toluidine and α -naphthylamine reacted similarly.

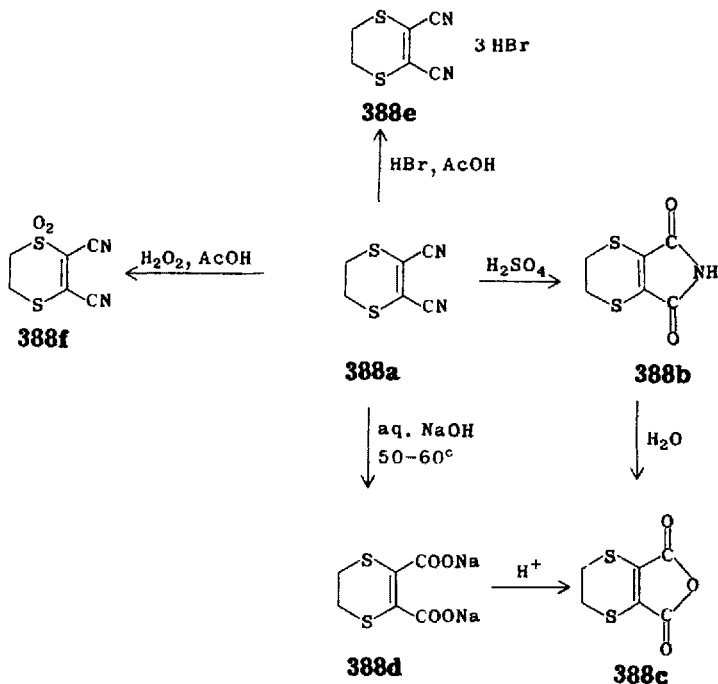


2, 3, 5, 6-Tetraphenyl-*p*-dithiin (**349**) appears to be somewhat different from 2, 5-diphenyl-*p*-dithiin in certain of its reactions. As already mentioned, it reacted like the 2, 5-diphenyl derivative on pyrolysis, yielding tetraphenylthiophene in the absence of oxidizing agents and either tetraphenylthiophene or the corresponding sulfone, depending on the reaction conditions, in the presence of peracetic acid.³⁰⁸ According to Mitra,³⁶² however, it yielded an unstable tetrabromide which reverted to **349** on heating. Since the *p*-dithiin ring in **349** cannot undergo electrophilic substitution, the tetrabromide may be formulated as **387**, although recent work indicates that compounds of this type might be better formulated as molecular complexes.^{339a} The compound tentatively formulated as 2-ethoxy-2, 3, 5, 6-tetraphenyl-2, 3-dihydro-*p*-dithiin (**350**) formed a pentabromide, perhaps **388**.



The ready availability of 2, 3-dihydro-5, 6-dicyano-*p*-dithiin (**388a**) has led to a study of its chemistry. According to Wolf, Degener, and Petersen^{510a} it gives a colorless solution in concentrated sulfuric acid, which turns red as the imide (**388b**) is formed. Pouring this into water yields the yellow anhydride (**388c**). The dinitrile is easily saponified to the dicarboxylic acid sodium salt (**388d**), acidification of which yields the anhydride. Thus, the dihydro-*p*-dithiin ring in these compounds is exceedingly stable. **388a** also forms a stable trihydrobromide (**388e**), and a monosulfone (**388f**).

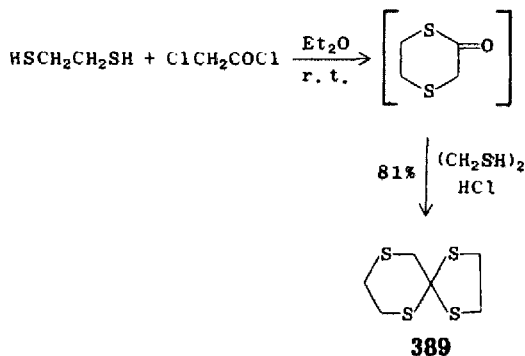
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Additional reactions are described in section III B.

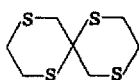
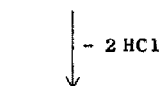
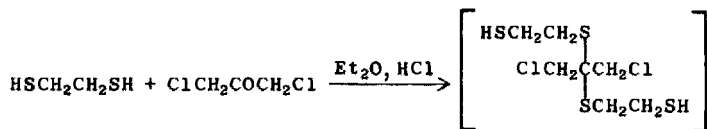
3. Spiro Derivatives

1, 4, 6, 9-Tetrathiaspiro[4.5]decane (**389**, RRI 1240), m.p. 98–99°, was prepared by Backer and Wiggerink²⁵ from 1, 2-dimercaptoethane and chloroacetyl chloride, presumably *via* the intermediate 2-*p*-dithianone, which was not isolated.



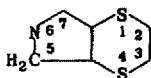
The same authors prepared 1, 4, 7, 10-tetrathiaspiro[5.5]undecane (390, RRI 1671), m.p. 103. 5-105°, by the reaction of 1, 3-dichloroacetone with 1, 2-dimercaptoethane.

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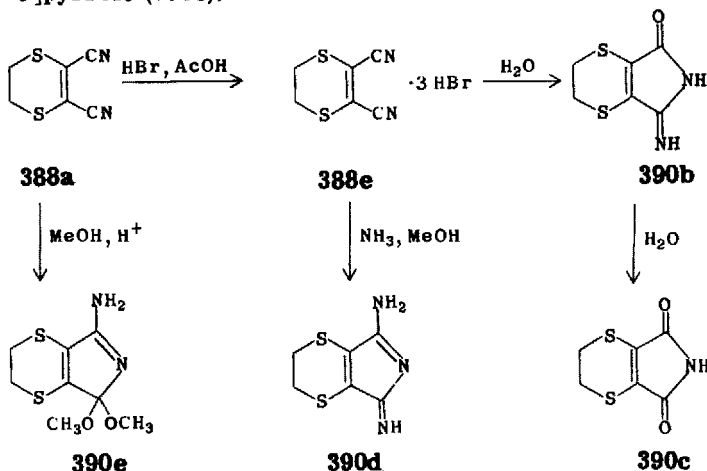
390

B. $\text{C}_4\text{N-C}_4\text{S}_2$ 5*H*-*p*-DITHIINO[2, 3-*c*]PYRROLE (**390a**)



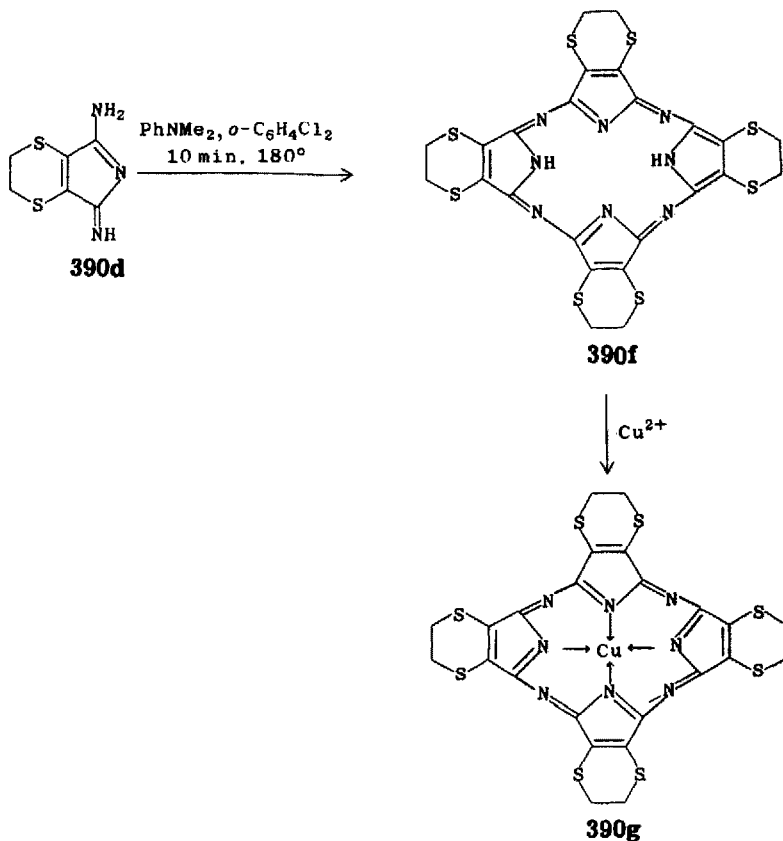
390a

This ring system is represented by the imide of 2, 3-dihydro-*p*-dithiin-5, 6-dicarboxylic acid (section III A-2c), 2, 3, 6, 7-tetrahydro-5*H*-*p*-dithiino[2, 3-*c*] pyrrole-5, 7-dione (**390c**), isolated by Wolf, Degener, and Petersen^{510a} as orange-yellow crystals, m.p. 217°. Treatment of 2, 3-dihydro-5, 6-dicyano-*p*-dithiin (**388a**) with hydrogen bromide in acetic acid yielded a trihydrobromide (**388e**). Hydrolysis of the trihydrobromide yielded first 2, 3, 6, 7-tetrahydro-5-imino-5*H*-*p*-dithiino[2, 3-*c*] pyrrol-7-one (**390b**), which then slowly hydrolyzed to the imide (**390c**). Methanolic ammonia converted the trihydrobromide into 2, 3-dihydro-5-imino-7-amino-5*H*-*p*-dithiino[2, 3-*c*] pyrrole (**390d**), also formed *via* the intermediate 2, 3-dihydro-5, 5-dimethoxy-7-amino-5*H*-*p*-dithiino[2, 3-*c*] pyrrole (**390e**).

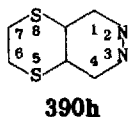


C₄S₂ Ring Systems

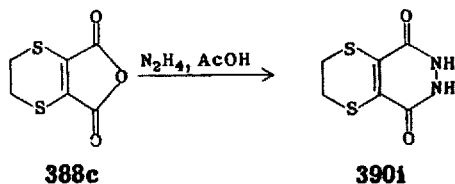
390d was isolated as a basic, yellow solid. It formed red salts and gave a deep violet solution in sulfuric acid. Heating with dimethylaniline yielded a tetrazaporphin (**390f**), which gave a new class of phthalocyanine pigment with nickel and copper salts (**390g**). Mixed porphins from **388a** and phthalonitrile were also prepared.



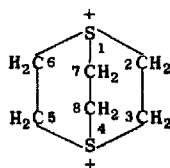
C. C₄N₂-C₄S₂ *p*-DITHIINO[2, 3-*d*]PYRIDAZINE (**390h**)



Wolf, Degener, and Petersen^{510a} reacted 2, 3-dihydro-*p*-dithiin-5, 6-dicarboxylic anhydride (**388c**) with hydrazine and isolated 1, 2, 3, 4, 6, 7-hexahydro-*p*-dithiino[2, 3-*d*]pyridazine-1, 4-dione (**390i**).

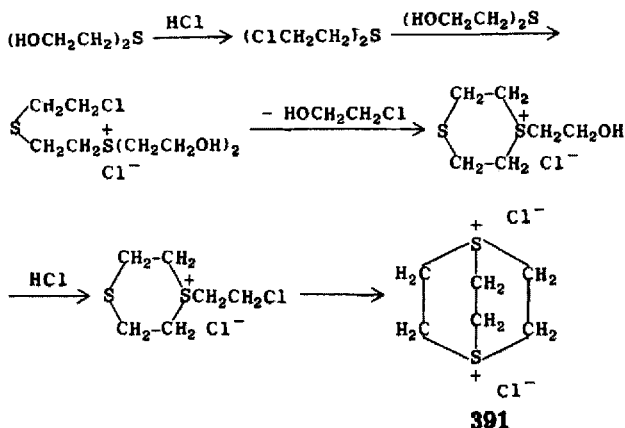
D. C₄S₂-C₄S₂

1. 1, 4-Dithioniabicyclo[2. 2. 2]octane (391)

**391**

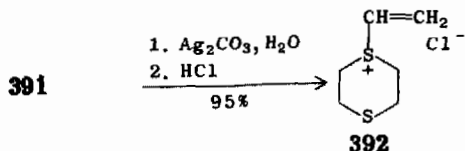
(RRI 1669)

In the course of their work on sulfonium derivatives of *p*-dithiane (see section III A-1g), Stahmann, Fruton, and Bergmann⁴⁶³ reacted bis(2-hydroxyethyl) sulfide with hydrochloric acid and zinc chloride at 100° and isolated **391**, indexed as 1, 4-dithiabicyclo[2. 2. 2] octa-1, 4-dianium in Chemical Abstracts, as the zinc chloride double salt, C₆H₁₂Cl₂S₂·ZnCl₂, in 4.5% yield. Its formation can be pictured as follows:

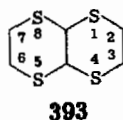


Treatment of the zinc chloride double salt with picrylsulfonic acid gave the dipicrylsulfonate as yellow leaflets, whereas silver carbonate gave 1-vinyl-1, 4-dithianium chloride (**392**).

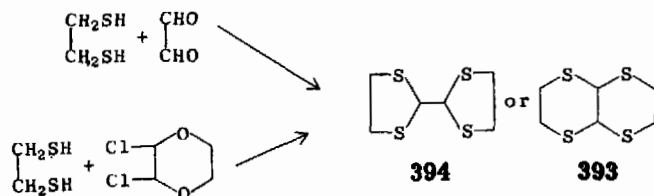
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2. *p*-Dithiino[2, 3-*b*]-*p*-dithiin (393)

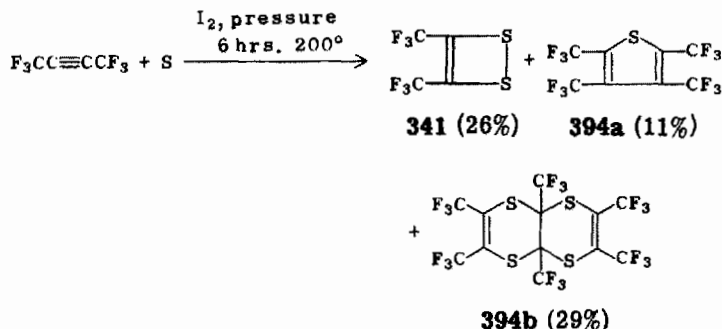


In 1888 Fasbender¹⁷⁴ reacted 1,2-dimercaptoethane with glyoxal in the presence of hydrogen chloride, and formulated the product as 2,2'-bis(1,3-dithiolane) (**394**). In 1952 Proštenik and Balenović⁴⁰⁰ prepared the same compound from 2,3-dichlorodioxane and 1,2-dimercaptoethane, and pointed out that the compound might be **393** instead.



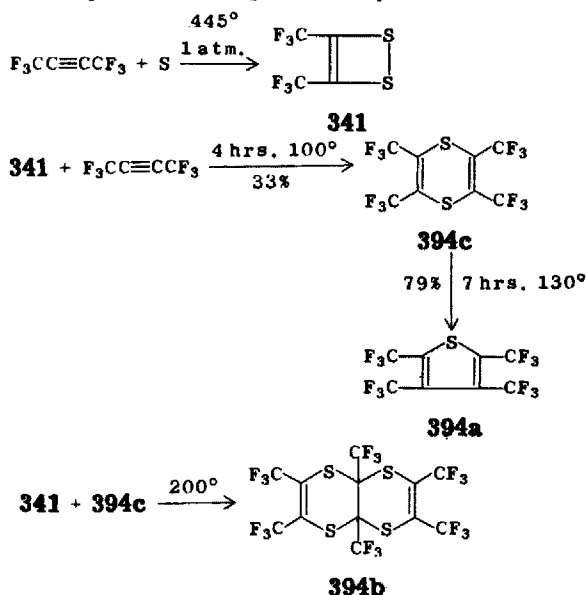
Brahde⁶¹ showed unequivocally, however, by X-ray diffraction that Fasbender's original assumption was correct (see Chapter 5, section II A-1a).

Recently, Krespan^{317a} found that the reaction of hexafluoro-2-butyne with sulfur under pressure yielded three products: 3,4-bis(trifluoromethyl)-1,2-dithietene (**341**), tetrakis(trifluoromethyl)thiophene (**394a**), and 2,3,4a,6,7,8a-hexakis(trifluoromethyl)-4a,8a-dihydro-*p*-dithiino[2, 3-*b*]-*p*-dithiin (**394b**), a yellow liquid boiling at 97-99° at 14 mm (see section III-A-2a).

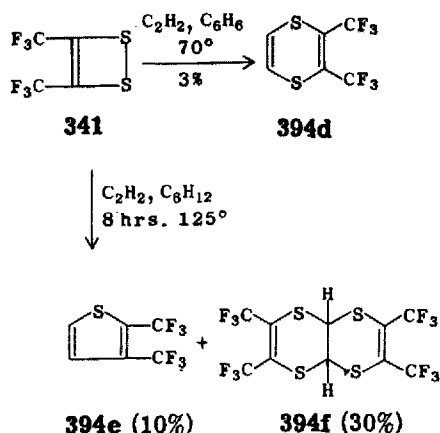


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The mechanism of the reaction was elucidated by showing that in a flow system the dithietene (**341**) was the sole product. Heating it with more hexafluoro-2-butyne yielded 2, 3, 5, 6-tetrakis(trifluoromethyl)-*p*-dithiin (**394c**) which, at a higher temperature eliminated sulfur to form the thiophene (**394a**) in a known type of reaction (section III A-2c). At a still higher temperature **341** presumably adds to **394c** to give **394b**.

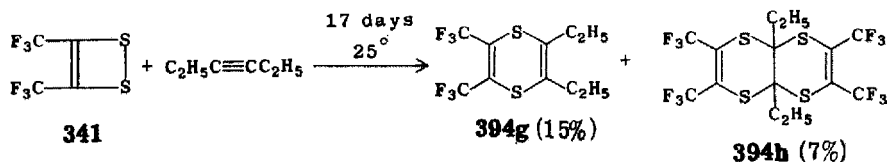


Further evidence was presented by Krespan and McKusick,^{317b} who showed that the 1,2-dithietene (**341**) could be heated with acetylene to yield either 2, 3-bis(trifluoromethyl)-*p*-dithiin (**394d**) or a mixture of 2, 3-bis(trifluoromethyl)thiophene (**394e**) and 2, 3, 6, 7-tetrakis(trifluoromethyl)-4a, 8a-dihydro-*p*-dithiino[2, 3-*b*]-*p*-dithiin (**394f**), m.p. 125-126°.



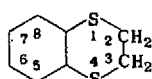
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At room temperature **341** and 3-hexyne yielded a mixture of 2, 3-diethyl-5, 6-bis(trifluoromethyl)-*p*-dithiin (**394g**) and 2, 3, 6, 7-tetrakis (trifluoromethyl)-4a, 8a-diethyl-*p*-dithiino[2, 3-*b*]-*p*-dithiin (**394h**), m.p. 132-133°.

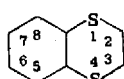


Structures were assigned on the basis of analyses and nuclear magnetic resonance spectra. Since the condensed ring compounds were considered to be formed by a Diels-Alder like addition of the 1, 2-dithietene to the *p*-dithiin, they were all assigned a *cis* configuration.

E. C₄S₂-C₆ 1, 4-BENZODITHIAN (**395**) AND 1, 4-BENZODITHIIN (**396**)



395



396

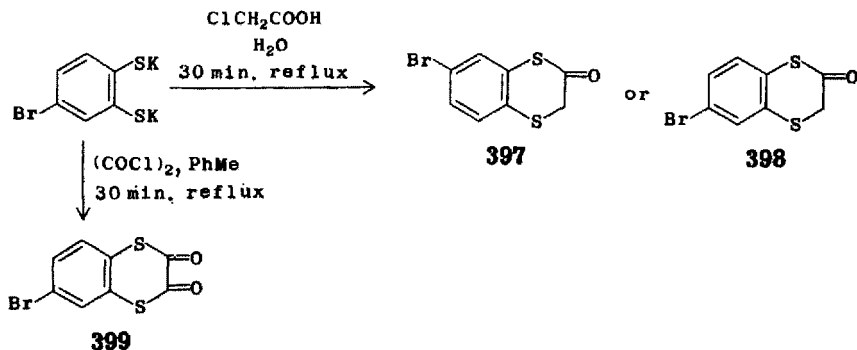
(RRI 1674)

Chemical Abstracts indexes these ring systems under the names shown. **396** is often referred to as benzo-1, 4-dithiadene.

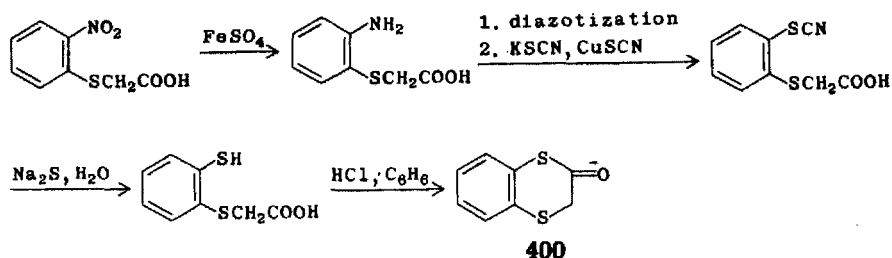
1. 1, 4-Benzodithian (**395**)

The first example of a compound of this type was reported by Guha and Chakladar,²³⁷ who reacted the dipotassium salt of 4-bromo-1, 2-dimercaptobenzene with chloroacetic acid, and isolated a compound, as a dihydrate, to which they assigned the structure 7-bromo-1, 4-benzodithian-2-one (**397**). It is quite apparent that this compound could be the 6-bromo derivative (**398**) instead. The sole evidence offered for the structural assignment was the solubility in aqueous sodium hydroxide, in agreement with the thiolactone structure. In the same type of reaction oxalyl chloride yielded 6-bromo-1, 4-benzodithian-2, 3-dione (**399**).

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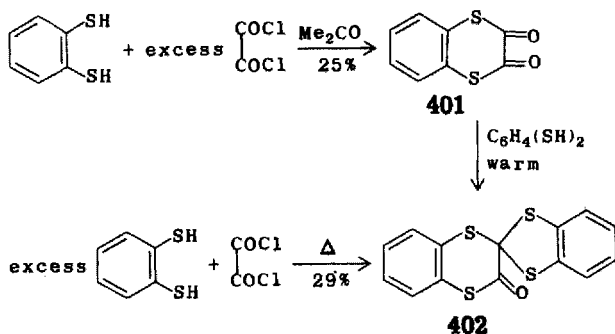


1,4-Benzodithian-2-one (**400**) was prepared by Ricci^{415,415a} by a straightforward synthesis from *o*-nitrophenylthioglycolic acid.



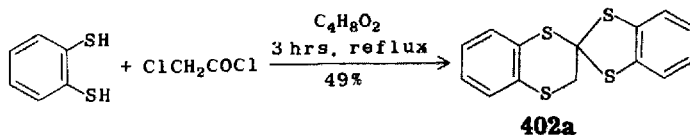
Polyphosphoric acid at 120–130° and sodium acetate-acetic anhydride at room temperature also converted the mercaptan acid into **400**.

The reaction of oxalyl chloride with dithiocatechol was investigated in greater detail by Hurtley and Smiles,²⁸⁵ who found that the product of the reaction depended on the conditions. With excess oxalyl chloride the product was the expected 1,4-benzodithian-2,3-dione (**401**), while with excess mercaptan this reacted further to form the spiro compound, spiro[1,3-benzodithiin-2(3*H*), 2'-[1,3]benzodithiole]-3-one (**402**), m.p. 168°. Under milder conditions other derivatives of 1,3-benzodithiole were formed (see Chapter 5, section II D-3). The structure of the spiro compound was indicated by its synthesis from **401** and dithiocatechol.

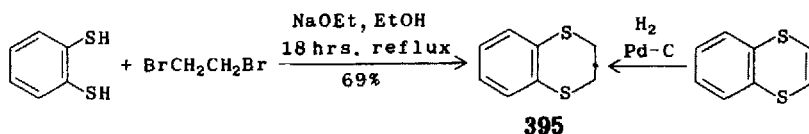


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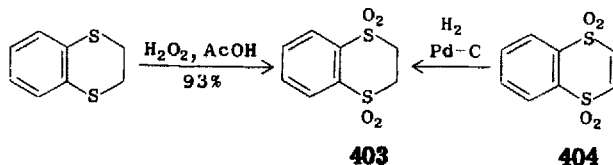
Spiro[1,4-benzodithiin-2(3*H*), 2'-[1,3]benzodithiole] (**402a**, RRI 4479), m.p. 250.5-251.5°, was prepared by Backer and Wiggerink²⁵ from dithiocatechol and chloroacetyl chloride.



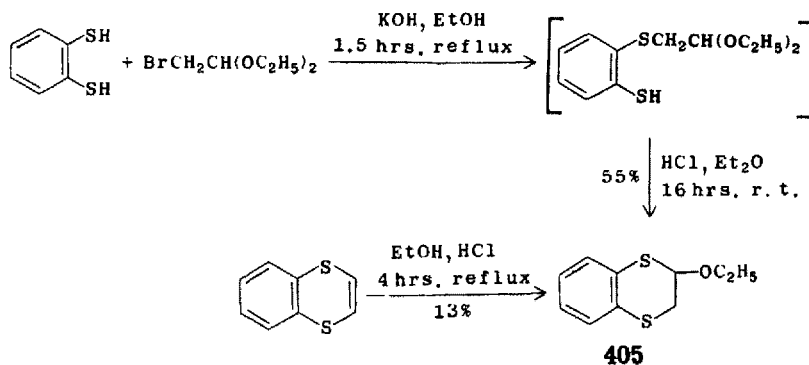
1,4-Benzodithian (**395**), the parent compound in this series, was prepared by Parham, Roder, and Hasek³⁷⁸ by the condensation of the disodium salt of dithiocatechol with ethylene bromide, and also by the catalytic reduction of 1,4-benzodithiin (see section III E-2).



Hydrogen peroxide in acetic acid oxidized it to the disulfone, 1,4-benzodithian 1,1,4,4-tetroxide (**403**), also prepared by reduction of 1,4-benzodithiin 1,1,4,4-tetroxide (**404**).

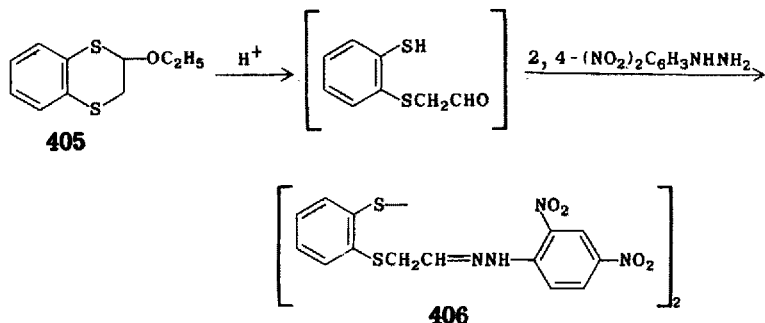


These same authors prepared 2-ethoxy-1,4-benzodithiane (**405**) from dithiocatechol and diethyl bromoacetal without isolating the intermediate diethyl *o*-mercaptophenylthioacetal. Treatment of 1,4-benzodithiin with alcoholic hydrogen chloride gave a small amount of **405**.



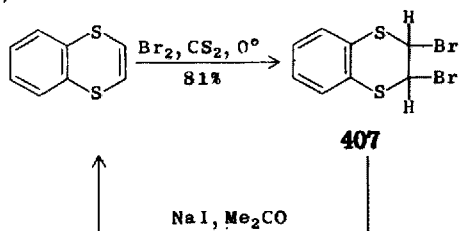
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2-Ethoxy-1,4-benzodithian (**405**) formed a solid derivative with trinitrobenzene. It reacted with 2,4-dinitrophenylhydrazine under the usual conditions to form the 2,4-dinitrophenylhydrazone of bis(*o*-phenylthioacetaldehyde) disulfide (**406**), indicating that **405** is, as expected, a thioacetal.



The conversion of 2-ethoxy-1,4-benzodithian into 1,4-benzodithiin is discussed in section III E-2.

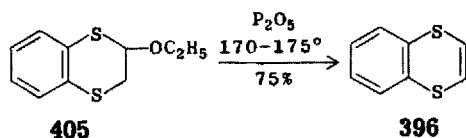
Parham and Jones³⁸⁰ found that 1,4-benzodithiin reacts with bromine to form an unstable dibromide, 2,3-dibromo-1,4-benzodithian (**407**). This lost hydrogen bromide readily to give, apparently, a purple polymeric sulfonium salt; reaction with sodium iodide in acetone regenerated 1,4-benzodithiin.



Derivatives of 1,4-benzodithian are listed in Table 19.

2. 1,4-Benzodithiin (396)

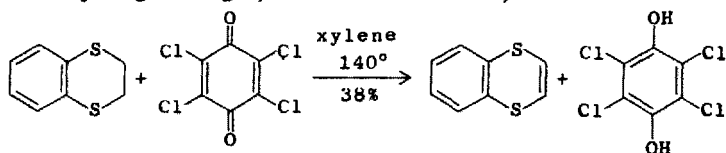
1,4-Benzodithiin was first prepared by Parham, Roder, and Hasek³⁷⁸ by the elimination of ethanol from 2-ethoxy-1,4-benzodithian (**405**) with phosphorus pentoxide.



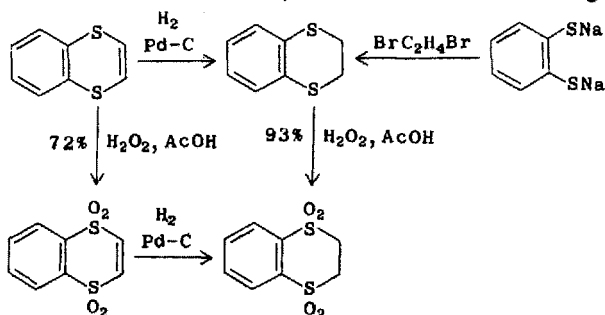
Hot 15% hydrochloric acid on **405** gave a small amount of 1,4-benzodithiin, while Parham and Jones³⁸⁰ found that passage of **405** over

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alumina at 250° gave a 58% yield. It is interesting that it was much more difficult to prepare 1,4-benzoxathiin by these procedures (see Chapter 11, section III F-1), presumably because of the greater degree of conjugation in the dithiin. Parham, Roder and Hasek³⁷⁸ also succeeded in dehydrogenating 1,4-benzodithian to 1,4-benzodithiin with chloranil.



1,4-Benzodithiin was isolated as a pale yellow-green oil with a brilliant green fluorescence; its ultraviolet absorption spectrum has been reported.³⁷⁸ Its structure was proved by comparison with an authentic sample of 1,4-benzodithian, as shown in the following sequences:



1,4-Benzodithiin is more aromatic than *p*-dithiin, undergoing a number of electrophilic substitutions in the heterocyclic ring. Thus, Parham, Roder, and Hasek³⁷⁸ prepared 2-nitro-1,4-benzodithiin (**408**) with nitric acid in acetic acid and 2-formyl-1,4-benzodithiin (**409**) by the Vilsmeier reaction; in both cases substitution in the heterocyclic ring was proved by oxidation to *o*-benzenedisulfonic acid.

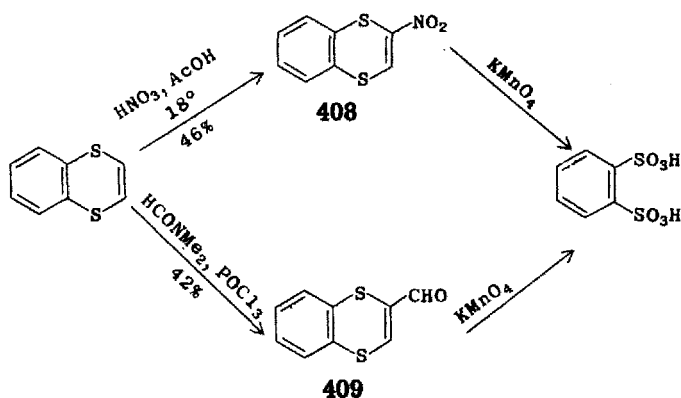


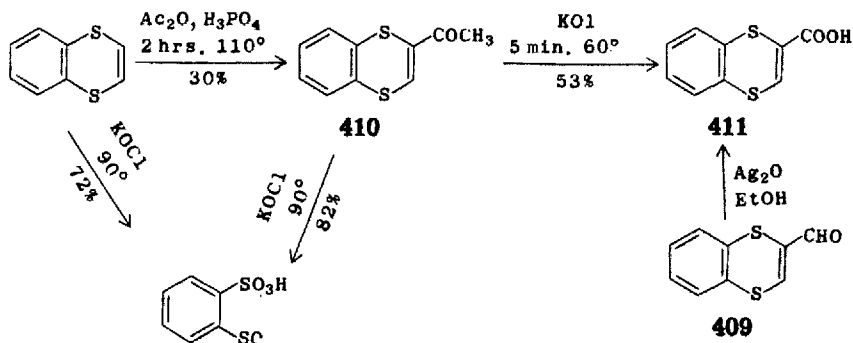
TABLE 19. 1, 4-Benzodithian Derivatives



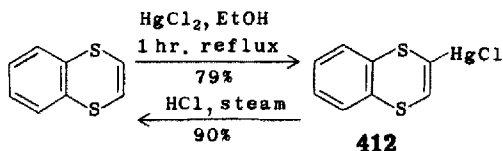
Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
None	69		82. 5-85	0. 18	n_D^{25} 1. 6713	378
1, 1, 4, 4-Tetroxide	93	269				378
2-C ₂ H ₅ O-	55		124-125	0. 9	n_D^{25} 1. 6229	378
2-C ₂ H ₅ O · 1, 3, 5 C ₆ H ₃ (NO ₂) ₃	88	103. 5-104				378
2, 3-Br ₂	81	106-108 (dec.)				380
2-(O=)		41				415, 415a
2-(HON=)		151				415, 415a
2-(H ₂ NCSNHN=)		191 (dec.)				415, 415a
2-(O=)-6(or 7)-Br · 2H ₂ O		191				237
2, 3-(O=) ₂	25	160 (dec.)			yellow prisms	285
2, 3-(O=) ₂ -6-Br		sublimes 150				237

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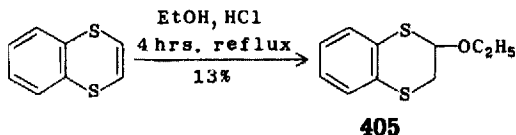
The formyl derivative (**409**) was identified by formation of an oxime and a phenylhydrazone. Parham, Wynberg, and co-workers,³⁸¹ succeeded in acetylating 1,4-benzodithiin with acetic anhydride and phosphoric acid. That the product was 2-acetyl-1,4-benzodithiin (**410**) was shown by oxidation with excess potassium hypochlorite to *o*-benzenedisulfonic acid. With potassium hypiodite, however, they were able to isolate 1,4-benzodithiin-2-carboxylic acid (**411**), identical with that prepared by the oxidation of **409**; the acid was unstable.



Parham, Stright, and Hasek³⁸⁹ mercurated 1,4-benzodithiin with mercuric chloride; no pure product could be isolated with mercuric acetate. The compound was assigned the structure 2-chloromercurin-1,4-benzodithiin (**412**) by analogy with other electrophilic substitution reactions; the ready conversion of **412** to 1,4-benzodithiin showed that the aromatic system was intact.



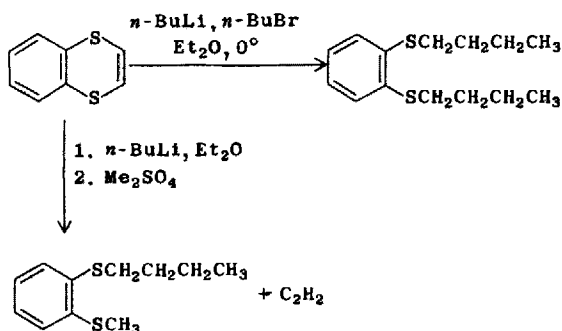
These reactions indicate the considerable stability of the double bond in the heterocyclic ring of 1,4-benzodithiin. Further evidence for this was the formation of only a small amount of 2-ethoxy-1,4-benzodithian (**405**) from 1,4-benzodithiin and alcoholic hydrogen chloride, the bulk of the dithiin being recovered unchanged.



Parham and Stright³⁸⁷ discovered an interesting reaction in the treatment of 1,4-benzodithiin with *n*-butyllithium, a small amount of 1,2-bis(*n*-butylthio)benzene being isolated. On the assumption that the product was formed because of excess *n*-butyl bromide in the *n*-butyllithium, they carried out the reaction in the presence of dimethyl sulfate

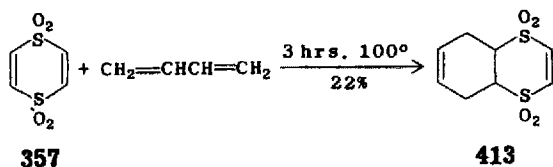
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and isolated acetylene plus a 46% yield of 1-*n*-butylthio-2-methylthio-benzene.



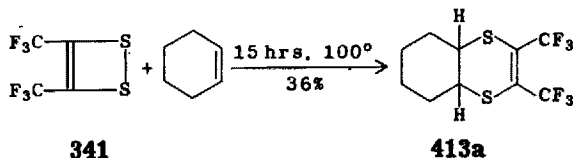
The mechanism has been discussed in connection with the analogous reaction of 2,5-diphenyl-*p*-dithiin, discovered subsequently by Parham and Kneller³⁸⁸ (see section III A-2c).

Parham, Wynberg, and co-workers³⁸¹ prepared 4a,5,8,8a-tetrahydro-1,4-benzodithiin 1,1,4,4-tetroxide (**413**) by the Diels-Alder reaction of *p*-dithiin 1,1,4,4-tetroxide (**357**) with butadiene. At higher temperatures both double bonds reacted.



Isoprene yielded 6-methyl-4a,5,8,8a-tetrahydro-1,4-benzodithiin 1,1,4,4-tetroxide, while 2,3-dimethylbutadiene yielded the 6,7-dimethyl derivative.

In connection with his work on 3,4-bis(trifluoromethyl)-1,2-dithietene (**341**) (see section III D-2), Krespan^{317b} prepared 2,3-bis(trifluoromethyl)-4a,5,6,7,8,8a-hexahydro-1,4-benzodithiin (**413a**) by the reaction of **341** with cyclohexene. Presumably the *cis* isomer is formed.

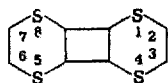


The derivatives of 1,4-benzodithiin which have been reported are listed in Table 20.

TABLE 20. 1, 4-Benzodithiin Derivatives

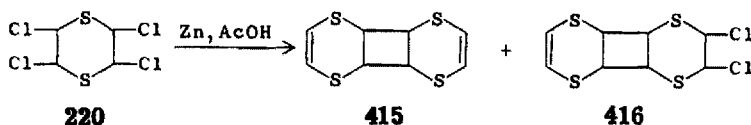


Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
None	75		67-70	0.1	n_D^{25} 1.6754, d_4^{20} 1.2789	378, 380
1, 1, 4, 4-Tetroxide	72	221.5-222.5				378
2-NO ₂	46	104.5-105.5	220	760	long red needles	378
		105-107				389
2-CHO	42				orange oil	378
2-(-CH=NOH)		166-169				378
2-(-CH=NNHC ₆ H ₅)		138.8-139.4				378
2-CH ₃ CO-	30	55-55.5	124-127	0.08	bright yellow	381
2-(CH ₃ C=NOH)		169-170			pale yellow	381
2-[2, 4-(NO ₂) ₂ C ₆ H ₃ NHN=CCH ₃]		248-248.5				381
2-CO ₂ H	53	134-137				381
2-ClHg-	79	127-130				389
4a, 5, 8, 8a-H ₄ 1, 1, 4, 4-tetroxide	22	195.5-200				381
2-CH ₃ -4a, 5, 8, 8a-H ₄ 1, 1, 4, 4-tetroxide	20	153-154				381
6, 7-(CH ₃) ₂ -4a, 5, 8, 8a-H ₄ 1, 1, 4, 4-tetroxide	60	152-153				381
2, 3-(F ₃ C)-4a, 5, 6, 7, 8, 8a-H ₆	36	67-68				317b

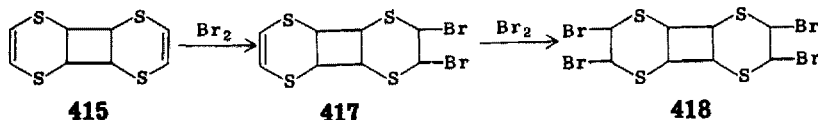
F. $C_4-C_4S_2-C_4S_2$ CYCLOBUTABIS-*p*-DITHIIN (414)**414**

(RRI 2188)

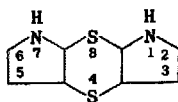
Varvoglis and Tsatsaronis⁴⁹⁹ dehalogenated 2, 3, 5, 6-tetrachloro-*p*-dithiane (**220**) with zinc and isolated two oily compounds, which they formulated as 4a, 4b, 8a, 8b-tetrahydrocyclobutabis-*p*-dithiin (**415**), b.p. 60° at 41 mm, and 2, 3-dichloro-2, 3, 4a, 4b, 8a, 8b-hexahydrocyclobutabis-*p*-dithiin (**416**).

**220****415****416**

Treatment of **416** with more zinc converted it into **415**. These structural assignments were based on the fact that **415** gave a green halochromism in sulfuric acid and **416** a red; halochromism is a characteristic of *p*-dithiins, but it is by no means limited to them. **415** gave a dibromide and a tetrabromide, 2, 3-dibromo-2, 3, 4a, 4b, 8a, 8b-hexahydrocyclobutabis-*p*-dithiin (**417**), b.p. 84° at 41 mm, and 2, 3, 6, 7-tetrabromo-2, 3, 4a, 4b, 6, 7, 8a, 8b-octahydrocyclobutabis-*p*-dithiin (**418**), m.p. 104° (dec.), respectively.

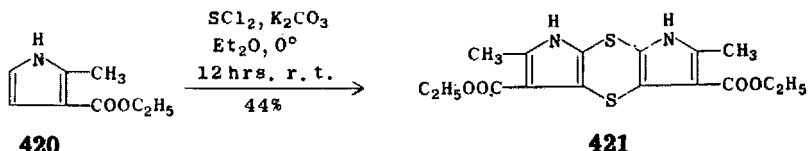
**415****417****418**

The dibromide showed green halochromism and the tetrabromide showed none. It would seem that more rigorous proof of the structure of these compounds, as well as that of the starting material, 2, 3, 5, 6-tetrachloro-*p*-dithiane (see section III A-1e), is required before their structures can be considered as established.

G. $C_4N-C_4N-C_4S_2$ 1*H*, 7*H*-*p*-DITHIINO[2, 3-*b*:6, 5-*b'*]DIPYRROLE (419)**419**

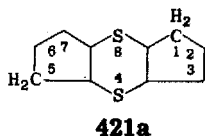
C₄S₂ Ring Systems

Treibs and Kolm⁴⁹³ reacted ethyl 2-methylpyrrole-3-carboxylate (**420**) with sulfur dichloride in the presence of base and isolated a pale yellow compound, m.p. 192°, which they formulated as diethyl 2,6-dimethyl-1*H*, 7*H*-*p*-dithiino[2, 3-*b*: 6, 5-*b'*]dipyrrole-3, 5-dicarboxylate (**421**).



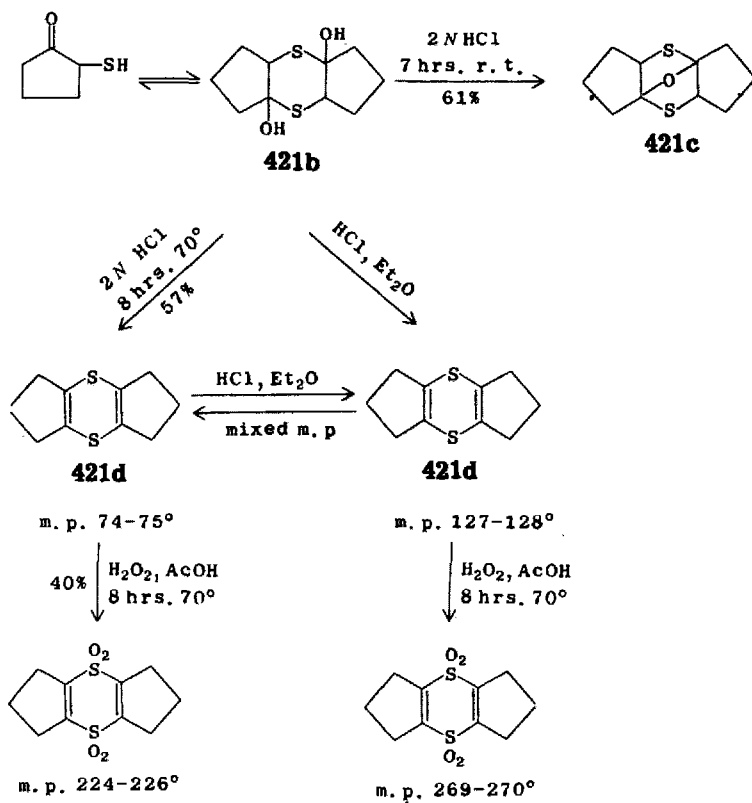
The reaction was successful only when it was carried out in the cold and the sulfur dichloride was added slowly. Otherwise an insoluble blue dye was formed. The structure of **421** was assigned by analogy with other pyrrole reactions.

H. C₅-C₅-C₄S₂ 1*H*, 5*H*-DICYCLOPENTA-*p*-DITHIIN (**421a**)



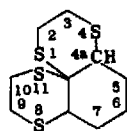
Asinger and co-workers^{15a} found 2-mercaptocyclopentanone to be monomeric in dioxane but dimeric in cyclohexane. The dimer, by analogy with other α -mercaptocarbonyl compounds (see section III A-1j), might be considered to be 4a, 8a-dihydroxyoctahydro-1*H*, 5*H*-dicyclopenta-*p*-dithiin (**421b**). 2-Mercaptocyclopentanone underwent three different reactions with acid the products, presumably derived from **421b**, varying with the reaction conditions. Aqueous hydrochloric acid at room temperature yielded an oxide (**421c**) (see Chapter 4, section IIJ). At 70° a compound, m.p. 74-75°, formulated as 2, 3, 6, 7-tetrahydro-1*H*, 5*H*-dicyclopenta-*p*-dithiin (**421d**), was formed. Ether saturated with dry hydrogen chloride yielded a still different compound, with the same formula as **421d** but melting at 127-128°. A mixture with the 75° melting isomer melted at 74-75°, while treatment of the low-melting isomer with ethereal hydrogen chloride converted it into the higher melting form. Both compounds yielded different disulfones on oxidation.

Chapter 12



The authors offered no explanation for this unusual behavior. That the two compounds are not dimorphous forms is indicated by the formation of two different disulfones. Positional double bond isomerism appears unlikely in view of the ready conversion of the high-melting to the low-melting form during a mixed melting point determination. Perhaps this is a case of *cis-trans* isomerism related to the non-planarity of the cyclopentene rings, but it is apparent that additional information is needed.

I. $C_4S_2-C_4S_2-C_6$ 4a*H*-BENZO[1,2-*b*:2,3-*b'*]BIS-*p*-DITHIIN (422)

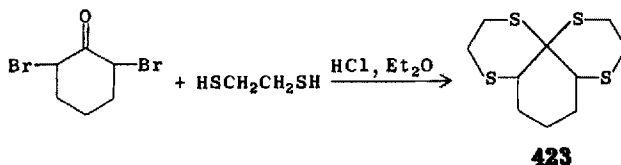


422

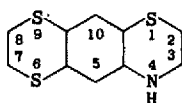
(RRI 3448)

C₄S₂ Ring Systems

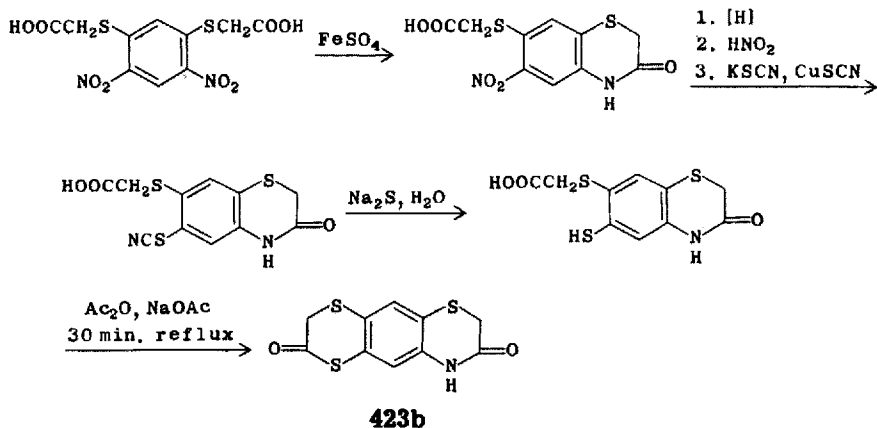
Backer and Wiggerink²⁵ prepared octahydro-4*aH*-benzo[1,2-*b*:2,3-*b'*]bis-*p*-dithiin (**423**), which they called 5,7-trimethylene-1,4,8,11-tetrathiaspiro[5.5]hendecane, by the reaction of 2,6-dibromocyclohexanone with 1,2-dimercaptoethane. It melts at 114.5-115.5°.



J. C₄S₂-C₄NS-C₆ 4*H*-*p*-DITHIINO[2,3-*g*]-1,4-BENZOTHAIAZINE (**423a**)

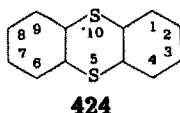


According to Ricci and Negri^{415a} 2,3,7-8-tetrahydro-4*H*-*p*-dithiino-[2,3-*g*]-1,4-benzothiazine-3,7-dione (**423b**), m.p. 274°, can be prepared in the following manner:



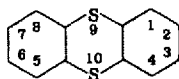
K. C₄S₂-C₆-C₆

1. Thianthrene (**424**)



(RRI 3449)

Thianthrene is listed as such in Chemical Abstracts, with the numbering shown above being used after 1936. Before that time Chemical Abstracts used the Richter numbering.

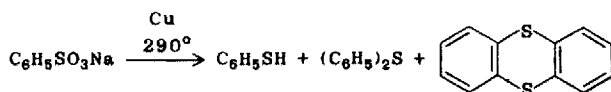


The Richter system has been used consistently in Beilstein, and is still used to a large extent in the non-American literature. In view of this, the literature must be read with caution; the present Chemical Abstracts numbering is used here.

Other names for thianthrene which have been used in the past, and still are in certain cases, are di-*o*-phenylene disulfide, diphenylene disulfide and dibenzo-1,4-dithiin.

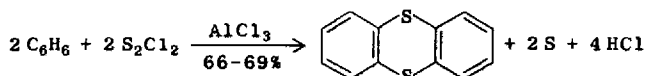
a. Preparation

Thianthrene was first prepared in 1869 by Stenhouse,⁴⁶⁵ who pyrolyzed sodium benzenesulfonate with copper and obtained thiophenol, diphenyl sulfide, and a white crystalline compound, which analyzed as C_6H_4S and which gave a purple solution in concentrated sulfuric acid. Graebe²³¹ determined the molecular weight and showed the compound to be $C_{12}H_8S_2$, and Kraft and Lyons³¹³ named it thianthrene by analogy with anthracene.



The yield in this initial preparation was undoubtedly quite low, and the mechanism of formation of thianthrene is obscure. More recently, Ura and Uno⁵¹⁴ decomposed sodium benzenesulfonate at about 400° with steam in the presence of the sodium salt of a carboxylic acid with essentially the same results.

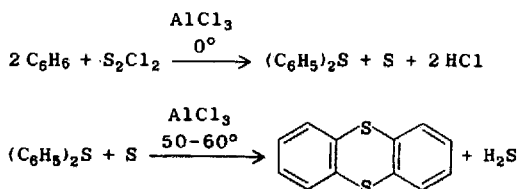
Probably the most convenient synthesis of thianthrene involves the reaction of benzene with sulfur monochloride. It was first carried out by Schmidt⁴²⁶ using zinc as the catalyst, and somewhat later by Cohen and Skirrow,¹²⁶ who used an aluminum-mercury couple. The preferred procedure, based on the work of Fleischer and Stemmer,¹⁸¹ involves the reaction of benzene, sulfur monochloride, and aluminum chloride under reflux. These authors claimed a yield of 64%, but Bergmann and Tschudnowsky^{46,455} obtained only 25-30% yields. Gilman and Swayampiat²¹⁹ modified the procedure by adding sulfur monochloride dropwise to a refluxing suspension of aluminum chloride in benzene and consistently obtained yields slightly better than reported by Fleischer and Stemmer.



C₄S₂ Ring Systems

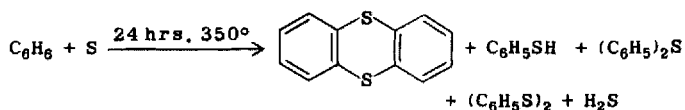
Koslov, Fruktova, and Shemyakina³¹¹ reported a 78.5% yield of thianthrene by this reaction, but details are not readily available.

The mechanism of this reaction is not very clear. When the reaction is carried out at 10-30° using one mole of sulfur monochloride and two of benzene, there is obtained, according to Hartman, Smith, and Dickey,^{246,247} an 83% yield of diphenyl sulfide. It would appear, therefore, that the reaction involves the intermediate formation of diphenyl sulfide, which then reacts with a second mole of sulfur monochloride to form thianthrene. However, Boeseken and van der Meulen⁵⁷ reacted two moles of benzene with one of sulfur monochloride at 0°, heated the reaction mixture for several days at 50-60°, and isolated thianthrene in 66.5% yield. Apparently on long heating diphenyl sulfide reacts with sulfur to give thianthrene.



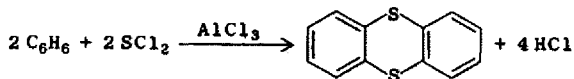
The procedure of Fries and Vogt,¹⁹⁴ also used by Sunner and Lundin,⁴⁷⁵ probably falls in this category.

There are numerous analogies for the latter reaction. Friedel and Crafts¹⁹¹ were apparently the first to show that benzene, sulfur, and aluminum chloride yielded some thianthrene, along with thiophenol and diphenyl sulfide. This was confirmed by Genvresse,^{210,211} who also isolated an insoluble "isothianthrene" from the reaction, probably a polymeric sulfide.²⁶⁰ Böeseken⁵⁵ isolated thianthrene from the reaction as its black complex with aluminum chloride, and Dougherty and co-workers^{163,164} investigated the reaction thoroughly and obtained a 36% yield of thianthrene. They reached the conclusion that the active intermediate in the reaction is diphenyl disulfide, since it plus sulfur and aluminum chloride gave an almost quantitative yield of thianthrene.^{56,163} Obolentsev, Netupskaya, and co-workers,^{374b} reported a 14% yield of thianthrene and a 31% yield of diphenyl sulfide from benzene, sulfur, and aluminum chloride. Ráy⁴⁰² prepared a complex between benzene, aluminum, and mercuric chloride and claimed that this reacted on heating with sulfur to give an 80% yield of thianthrene. Krafft and Lyons³¹³ showed that 20-30% yields of thianthrene could be obtained by heating diphenyl sulfide with sulfur in the absence of a catalyst, while Glass and Reid,²²⁶ on reacting benzene with sulfur, obtained similar results.



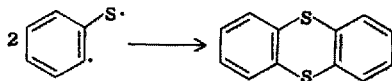
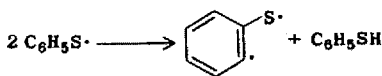
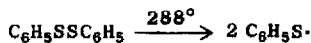
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There have been a number of references^{190,191,194,209,313} to the preparation of thianthrene from benzene, sulfur dichloride, and aluminum chloride. Genvresse²⁰⁹ claimed about a 50% yield by this procedure.



Shirley and Roussel⁴⁵⁴ isolated some thianthrene by carrying out this reaction under free radical conditions in the presence of benzoyl peroxide and ferrous ion.

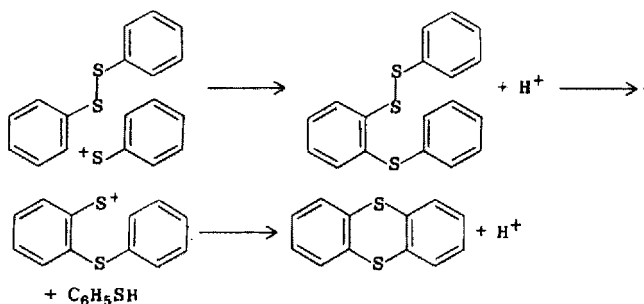
A number of sulfur-containing aromatics have been shown to form thianthrene under a variety of conditions. Deuss^{155,157} showed that thiophenol, diphenyl sulfide, and diphenyl disulfide all yielded thianthrene when warmed with aluminum chloride; diphenyl disulfide gave by far the best yields. Turner and Sheppard⁴⁹⁸ confirmed the reaction with diphenyl sulfide, although they used a high temperature of about 180°. Cullinane and Padfield¹³⁶ isolated a low yield of thianthrene from the treatment of thiophenol with litharge at 160°. Schönberg and co-workers^{437,438} claimed a 60% yield of thianthrene by the free-radical decomposition of diphenyl disulfide, which they formulated in the following manner:



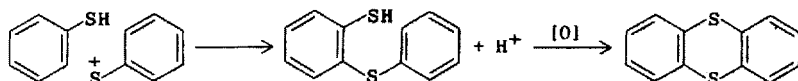
Fries and Volk¹⁹² and Hilditch²⁶⁰ prepared thianthrene by dissolving thiophenol in concentrated sulfuric acid; the first step in the reaction is apparently the formation of diphenyl disulfide. Both authors claimed yields of 10-20%. Kawahara³⁰⁰ started with diphenyl disulfide and obtained only a 7% yield of thianthrene with fuming sulfuric acid. Shine and Bear⁴⁵³ investigated the reaction more thoroughly and obtained only a small amount of thianthrene plus a large amount of water-soluble material with 100% sulfuric acid; with less than 100% sulfuric acid they obtained a polymeric disulfide, presumably the same product as isolated by Hilditch.

Fava, Sogo, and Calvin¹⁷⁵ postulated the following mechanism to explain the formation of thianthrene from diphenyl disulfide and sulfuric acid. A similar mechanism could be used to explain other thianthrene syntheses involving Friedel-Crafts catalysts.

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Alternatively, electrophilic attack might be on the thiophenol, in which case the final ring closure would involve an oxidation.

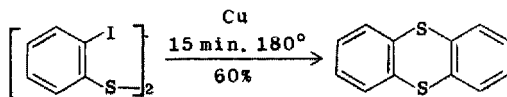


Tits-Skvortsova and co-workers⁴⁸⁸⁻⁴⁹⁰ described the formation of small amounts of thianthrene by passage of thiophenol, *m*-dimercaptobenzene, or diphenyl sulfide over an aluminosilicate catalyst at about 300°.

Kekulé and Szuch³⁰² formed thianthrene by heating phenol with phosphorus pentasulfide; Graebe^{230,231} showed that the yield of thianthrene in this reaction was very low. The formation of thianthrene from pyrocatechol and phosphorus pentasulfide has been patented.³²¹ Macallum^{337,338} described what appears to be a promising synthesis of thianthrene, a 75% yield being obtained by heating *o*-dichlorobenzene with calcium sulfide at 300-340°; the reaction takes place only if a small amount of sulfur is also present. Apparently the same results are obtained with a mixture of sulfur and sodium carbonate.³²⁵

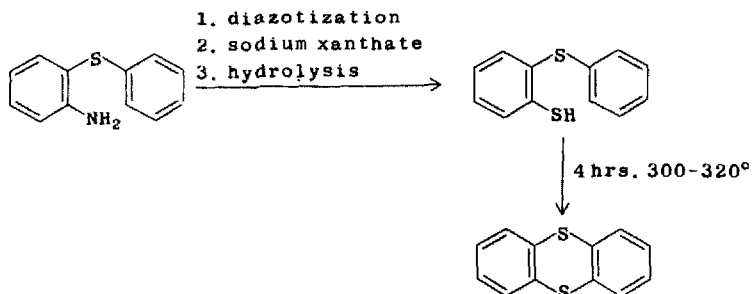
Bost and Borgstrom⁵⁸ isolated a small amount of thianthrene from the reaction of tetraphenyltin with sulfur at 250°.

Several syntheses of thianthrene have been reported which suffer from the unavailability of starting materials. Their value lies in their utility for the synthesis of substituted thianthrenes. Thus, Barber and Smiles³² prepared thianthrene by treatment of bis(*o*-iodophenyl) disulfide with copper, presumably a free-radical reaction.

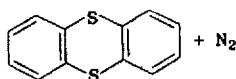
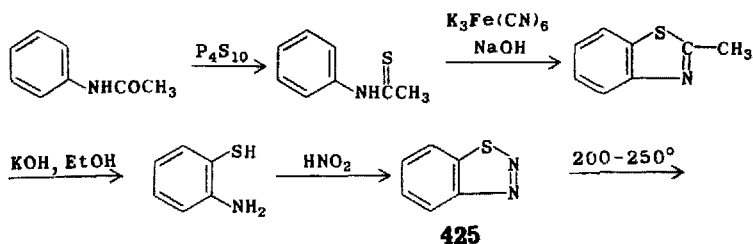


Cullinane and Davies¹³⁷ carried out a ring closure on 2-mercaptophenyl phenyl sulfide.

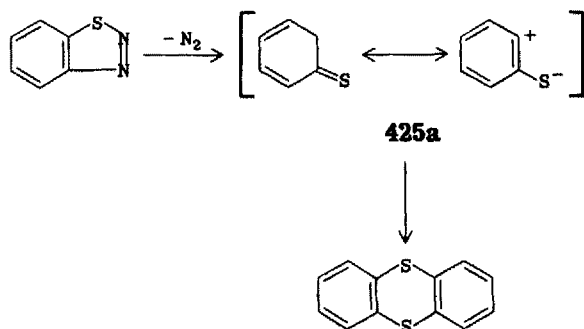
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One of the oldest and most versatile reactions in this category is the thermal elimination of nitrogen from 1,2,3-benzothiadiazole (**425**) developed by Jacobson and co-workers.^{290,291} **425** was synthesized as follows:

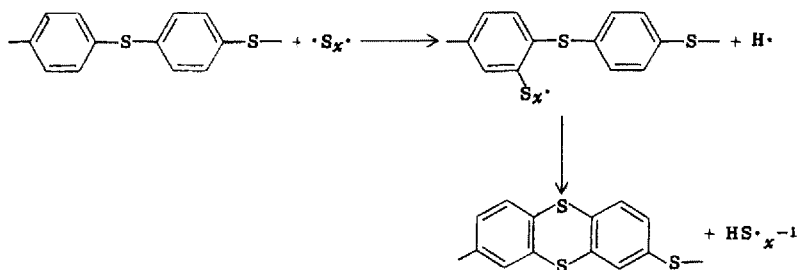


The reaction probably involves dimerization of the intermediate thio-ketocarbene (**425a**).^{283a}



Lenz and Handlovits³²⁵ concluded that thianthrene rings are present in polymer prepared from *p*-dichlorobenzene, sulfur, and sodium carbonate. The rings are introduced by radical substitution.

C₄S₂ Ring Systems



b. Structure and Properties

Thianthrene has been studied very thoroughly. It is a white, volatile solid belonging to the monoclinic system. Sunner and Lundin⁴⁷⁵ reported a melting point of 155.9° for a sample of 99.8 mole per cent purity, but Walls and Smyth⁵⁰⁴ reported a melting point of 157.5-157.8°. Several boiling points have been reported: 204° at 11 mm,¹⁵⁵ 210-211° at 15 mm,³¹³ 216-218° at 20 mm,¹⁹⁴ and about 360° at atmospheric pressure.^{191,313} The compound is insoluble in water, slightly soluble in ethanol, and quite soluble in most other organic solvents. The most characteristic property of thianthrene, first mentioned by Stenhouse,⁴⁶⁵ is the formation of a purple solution in concentrated sulfuric acid. Brill and Evans⁷⁰ reported a density of 1.706 for thianthrene.

One of the basic questions concerning the structure of thianthrene is whether or not it is a planar molecule. That the molecule is not planar was first shown by Bergmann and Tschudnowsky,⁴⁶ who found that thianthrene has a dipole moment of 1.68D; this was later corrected to 1.45D.⁴⁷ Walls and Smyth⁵⁰⁴ found a value of 1.41D, Bennett and Glasstone⁴⁴ found a value of 1.50D, and Campbell, Le Fèvre, and co-workers,⁹² 1.57D. This left little doubt that the molecule is not planar, being folded along the S-S axis. This was amply confirmed by X-ray investigations on thianthrene crystals. Preliminary determinations were made by Prasad, Shanker, and Peermohamed,³⁹⁶ by Crackston and Wood,^{128,511} and by Rowe and Post.⁴²¹ Detailed analyses by Lyn-ton and Cox³³⁶ and by Rowe and Post^{421a} showed excellent agreement. Thianthrene is folded on the S-S axis so that the benzene rings lie in two planes at an angle of 128°. The C-S-C valence angle is 100°, essentially the same as in diphenyl sulfide,⁴⁷⁹ so that the folding allows the sulfur atom to retain its normal valence angle. However, the C-S distance of 1.76Å is considerably less than the usually accepted value of 1.81Å, and some d- π conjugation has been suggested to explain this. Rowe and Post⁴²¹ estimated about 25% double bond character for the C-S bond.

Sunner and Lundin,⁴⁷⁵ Sunner,⁴⁷⁷ Hubbard, Katz, and Waddington,²⁸² and Keith and Mackle^{301a} have carried out thermochemical investigations on thianthrene. Sunner estimated 43.15 kcal/mole as being the best value for the standard heat of formation of solid thianthrene, and from thermochemical data Sunner⁴⁷⁷ calculated the resonance energy of thianthrene in excess of the two benzene rings to be 17 kcal/mole.

If thianthrene were a rigid non-planar molecule, monosubstituted derivatives should be resolvable. Bennett, Lesslie, and Turner⁴⁵ attempted to resolve a carboxylic acid, and Keats³⁰¹ an amine, but both were unsuccessful. Keats concluded that in solution thianthrene oscillates so rapidly through a mean planar position that it virtually possesses a plane of symmetry; Böeseken and van der Meulen⁵⁷ expressed the same view. However, Price^{396a} concluded, from an investigation of the dielectric relaxation time of 2, 7-dimethylthianthrene, that it behaves as a rigid molecule in tetrachloroethylene and in xylene. Whether these two views are really in conflict is uncertain.

Using the formation of solid solutions as a criterion, Cullinane and co-workers^{139,140} concluded that thianthrene and selenanthrene are isomorphous, but thianthrene and phenoxathiin are not. The ultraviolet absorption spectra of thianthrene and a number of derivatives have been reported,^{29,213,288} and the Raman spectrum of thianthrene has been determined under a number of conditions.^{368-370,456,457}

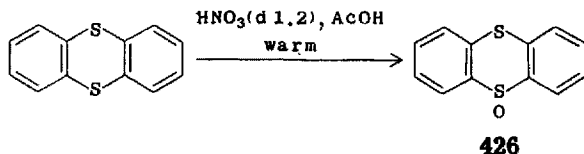
c. Oxides

Numerous oxides of thianthrene derivatives have been reported, many having been made for identification purposes. This section is devoted to the chemistry of the oxides of thianthrene itself; oxides of thianthrene derivatives are discussed under the corresponding derivatives.

Thianthrene should have one monosulfoxide, two disulfoxides, a sulfide-sulfone, and a disulfone, and all of these have been reported. Other oxides are possible because of the non-planar nature of thianthrene, but, in view of the lack of success in resolving thianthrene derivatives, it is not surprising that they have not been isolated.

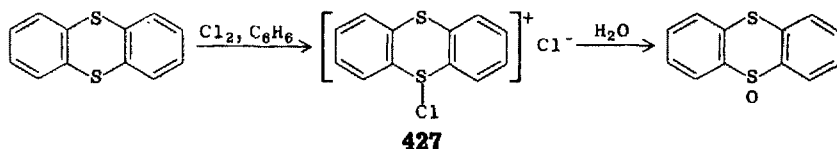
(1) Thianthrene 5-Oxide (426)

Thianthrene 5-oxide, m.p. 143-144°, was prepared by Hilditch²⁶⁰ and by Fries and Vogt¹⁹⁴ from thianthrene and dilute nitric acid in acetic acid.

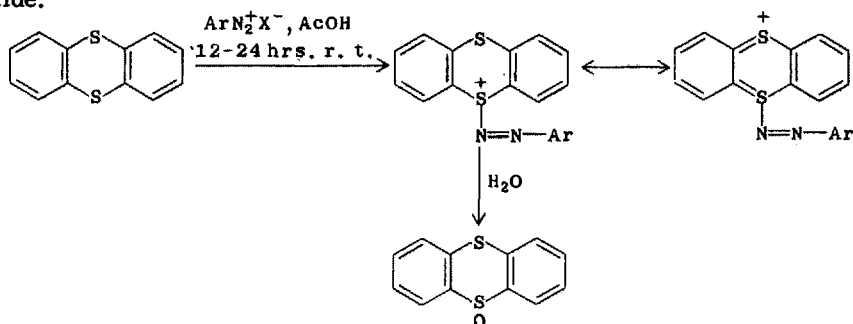


Böeseken and van der Meulen⁵⁷ reported an 83% yield by this procedure, while, by a minor modification, Gilman and Swayampati²¹⁷ obtained a yield of 98%; the reaction was also carried out by Fava, Sogo, and Calvin.¹⁷⁵ Fries and Vogt¹⁹⁴ proved that the compound was a sulfide by reducing it to thianthrene with hydrogen bromide in acetic acid. These same authors prepared the 5-oxide by hydrolyzing the reaction product of thianthrene and chlorine, the dichloride of thianthrene (427) presumably being an intermediate (see section III K-3).

C₄S₂ Ring Systems

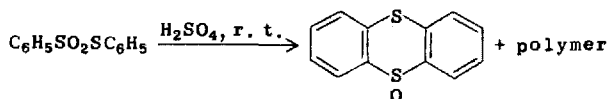


Gilman and Swayampati²¹⁹ found that negatively substituted diazonium salts oxidized thianthrene to the 5-oxide, a 98% yield being obtained with *o*-nitrobenzenediazonium sulfate. Phenyldiazonium chloride, on the other hand, gave no oxidation. The authors explained the reaction as involving attack on the electron-rich sulfur by the highly positive terminal nitrogen of the diazonium salt to give a thionium salt, analogous to the reaction of thianthrene with halogen; hydrolysis then gives the oxide.



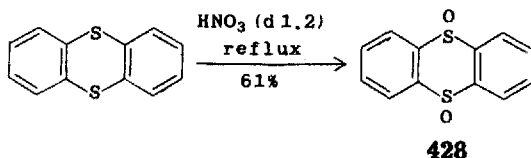
Evidence cited for the mechanism was the formation of an orange solution, similar in color to that formed in the reaction of thianthrene with chlorine or bromine in acetic acid, and the disappearance of the color on hydrolysis. The fate of the diazonium salt was not determined, but no nitrogen was evolved in the reaction. Böeseken and van der Meulen⁵⁷ investigated the oxidation of thianthrene with peracetic acid and reported that this reagent is not suitable for the preparation of the monoxide.

Hilditch²⁶¹ reported the formation of some thianthrene 5-oxide from the reaction of phenyl benzenethiolsulfonate with concentrated sulfuric acid, but the reaction is of no preparative value.



(2) Thianthrene 5,10-Dioxide (**428**)

Krafft and Lyons³¹³ oxidized thianthrene with dilute nitric acid to form a 5,10-dioxide.



The structure was proved by reducing the compound to thianthrene with zinc and acetic acid. Genvresse²⁰⁹ obtained the same compound with warm fuming nitric acid, while Friedel and Crafts¹⁹¹ used chromic anhydride in acetic acid, apparently some disulfone being formed simultaneously. However, the Krafft and Lyons procedure was preferred by a number of workers.^{36, 46, 57, 155, 175, 193} Actually, Krafft and Lyons did not have the compound completely pure; the best yield of pure isomer, melting at 249°, is 40-50%, reported by Bergmann and Tschudnowsky.⁴⁶

Both Krafft and Lyons³¹³ and Deuss¹⁵⁵ claimed that heating the 5, 10-dioxide at 270° gave a monosulfone melting at 279°. Fries and Vogt¹⁹³ were the first to show that thianthrene forms two isomeric 5, 10-dioxides and that the so-called sulfone was the other isomer, evidence being its reduction to thianthrene with hydrogen bromide or with zinc and acetic acid. Their preferred procedure for the preparation of the high-melting isomer involved the reaction of a solution of thianthrene in wet benzene with chlorine; the pure isomer melted at 284°. Several investigators^{36, 46, 57, 175} have used this procedure. Böeseken and van der Meulen⁵⁷ reported a 91% yield by passing the calculated quantity of chlorine into a solution of thianthrene in dry benzene and decomposing the resulting product with water.

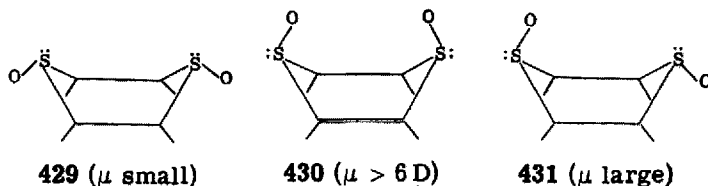
Fries and Vogt¹⁹³ reported that treatment of thianthrene with a mixture of nitric and sulfuric acids gave the high-melting isomer, as did Shirley and Roussel,⁴⁵⁴ while Bow, Bennett, and Dearn³⁶ claimed that the procedure of Krafft and Lyons³¹³ actually gave both isomers. Fries and Vogt¹⁹⁴ found that, as expected, treatment of thianthrene 5-oxide with chlorine followed by water gave the high-melting 5, 10-dioxide. There is little doubt that the chlorine oxidation of thianthrene is to be preferred for the synthesis of the high-melting isomer.

The thianthrene 5, 10-dioxide melting at 284° has been called the α -isomer. As already mentioned, the α -isomer is the more stable of the two, since heating the β -isomer above its melting point converts it into the α -isomer. However, the two are in equilibrium, since Fries and Vogt¹⁹³ found that the melting point of the α -isomer decreased in successive melting point determinations, and solution of either isomer in sulfuric acid followed by precipitation with water gave the same mixture. According to Bow, Bennett, and Dearn³⁶ the β -isomer is three times as soluble in acetic acid as the α -isomer, and Fries and Vogt¹⁹³ found the β -isomer to be more soluble than the α -isomer in nitric and hydrochloric acids; the acid solubility is a reflection of the well known basicity of sulfoxides.

The stereochemistry of the two isomeric 5, 10-dioxides has been a subject of interest for a considerable time. Bergmann and Tschudnowsky⁴⁶ attacked the problem by determining the dipole moments of the two isomers. The high-melting α -isomer has a moment of 1.7D, while the low-melting β -isomer has a moment of 4.2D. They concluded, therefore, on the assumption that the S-O bond is in the same plane as the other two bonds to sulfur, that the α -isomer is *trans* and the β -isomer

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cis; Baw, Bennett, and Dearn³⁶ reached the same conclusion on the basis of solubility data. Taylor,⁴⁸³ however, drew the opposite conclusion from the dipole moment data. He reasoned that, since the α -isomer has a moment only slightly greater than thianthrene itself, the two sulfoxide moments cancel each other. Taylor considered three possibilities based on an angle between the three covalencies of sulfur of 110°, which Hosoya and Wood²⁶⁸ named *anti-cis* (**429**), *syn-cis* (**430**), and *trans* (**431**), and estimated what their moments should be.



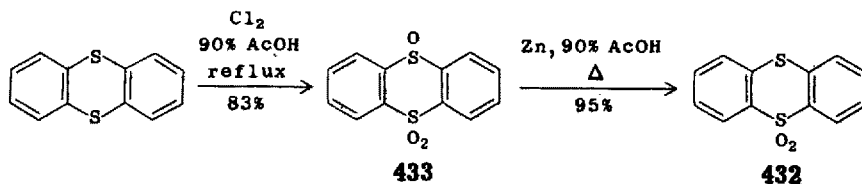
Taylor concluded that the α -isomer has the *anti-cis* structure (**429**) and the β -isomer the *trans* (**431**). This was completely confirmed by determinations of the crystal structures of the two isomers by Hosoya and Wood²⁶⁸ and by Hosoya.²⁶⁹ The dihedral angle of fold about the S-S axis is about 125°, close to the value found for thianthrene itself. The *anti-cis* and *syn-cis* forms are of course conformational isomers, and it is quite apparent that, because of the non-bonding interactions between the two oxygen atoms in the *syn-cis* form, the *anti-cis* form should be the more stable of the two. Thus, as in the *s*-trithianes (see Chapter 10, section II), this is another instance in which, of two geometrical isomers, the *cis* isomer has the greater symmetry, as shown by its higher melting point, lower solubility, and smaller dipole moment.

(3) Thianthrene 5, 5-Dioxide (**432**) and 5, 5, 10-Trioxide (**433**)

Fries and Vogt¹⁹⁴ claimed that treatment of a solution of thianthrene in aqueous acetic acid with excess chlorine gave the sulfone, thianthrene 5, 5-dioxide (**432**). Its structure was indicated by its lack of reactivity with hydrogen bromide or with zinc and acetic acid. **432**, on short heating with nitric acid (d 1.4), gave thianthrene 5, 5, 10-trioxide (**433**), which could also be formed by the reaction of thianthrene 5-oxide or 5, 10-dioxide with chlorine. Reduction of the 5, 5, 10-trioxide with hydrogen bromide gave the 5, 5-dioxide. Although there is little doubt, from the melting points reported, that Fries and Vogt obtained some of these oxides as impure compounds, neither Böeseken and van der Meulen⁵⁷ nor Fava, Sogo, and Calvin¹⁷⁵ could repeat their work.

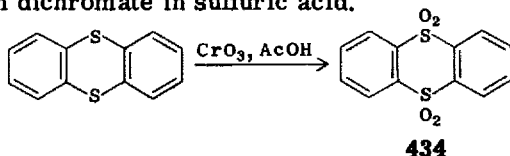
Gilman and Swayampati²¹⁸ investigated the chlorination of thianthrene in acetic acid and obtained an excellent yield of thianthrene 5, 5, 10-trioxide, melting at 221.5–222.5°. Reduction with zinc in acetic acid or with hydrobromic acid gave thianthrene 5, 5-dioxide, melting at 168–169°. The infrared spectra of the compounds agreed with these structures.

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(4) Thianthrene 5, 5, 10, 10-Tetroxide (**434**)

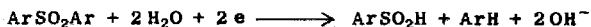
Melting points for thianthrene 5, 5, 10, 10-tetroxide have been reported ranging from 321^{311,313} to 337.5-340^o, the latter being a corrected value.^{165b} The disulfone was first prepared by Graebe²³¹ by the oxidation of thianthrene with chromic anhydride in acetic acid or with potassium dichromate in sulfuric acid.



The formation of a disulfone was cited by Graebe as evidence that thianthrene did not contain an S-S linkage. Several authors^{138,194,311,313} have used chromic anhydride in acetic acid on thianthrene or one of its oxides, and Kozlov, Fruktova, and Shemyakina³¹¹ reported a 92% yield by this procedure. Cohen and Skirrow¹²⁶ claimed a quantitative yield of disulfone from thianthrene and fuming nitric acid, but Böeseken and van der Meulen⁵⁷ reported only a 53% yield with concentrated nitric acid. Deuss¹⁵⁵ prepared the disulfone by oxidizing the 5, 10-dioxide with potassium permanganate, while Martin³⁴⁸ reported a 97% yield by the oxidation of thianthrene with hydrogen peroxide. It would thus appear that either chromic anhydride or hydrogen peroxide are the preferred oxidizing agents for the synthesis of the disulfone.

Hosoya and Wood²⁶⁸ suggested that thianthrene 5, 5, 10, 10-tetroxide might be planar to overcome the non-bonding interaction between the two "axial" oxygen atoms in the disulfone. However, a crystallographic determination of the structure of **434** by Hosoya²⁷⁰ has shown the molecule to have the same folded structure as thianthrene, the dihedral angle of 127^o being essentially the same in both compounds.

Drushel and Miller^{165b} investigated the polarographic reduction of diaryl sulfones, including thianthrene 5, 5, 10, 10-tetroxide. The reduction is a two-electron process, presumably following the path:



Thianthrene disulfone gave two waves, as expected. Aliphatic sulfones showed no reduction, and the authors used this procedure to determine the concentration of aromatic sulfides in petroleum.

d. Halochromism

Stenhouse,⁴⁶⁵ in his original paper on the synthesis of thianthrene,

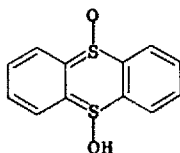
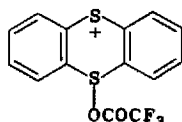
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noted that thianthrene gives a purple solution in concentrated sulfuric acid, and that thianthrene can be recovered unchanged on diluting the solution with water. Numerous authors used this as a test for thianthrene and its derivatives, and the phenomenon was studied intensively by Fries and his co-workers.^{192,194-196}

Fries found that a wide variety of thianthrene derivatives dissolve in sulfuric acid to give red, purple, or blue solutions. That the color is related to some reaction involving the sulfur atoms was demonstrated by the fact that only the disulfones give no color in this reaction. Halochromism is not limited to sulfuric acid; it was also shown with nitric, perchloric, hydrochloric, and trichloroacetic acids, and with a number of Lewis acids—stannic chloride, zinc chloride, antimony pentachloride, aluminum chloride, and ferric chloride. In certain cases 1 : 1 adducts could be isolated.

Fries noted that the solution of thianthrene in sulfuric acid involves an oxidation, since sulfur dioxide was evolved, and assumed that air was the oxidizing agent in other cases. According to Fries, dilution with water yields a mixture of thianthrene and thianthrene 5-oxide. Substitution of electron-donating groups, such as methoxyl, on the thianthrene nucleus stabilizes the color obtained with sulfuric acid so that it is not discharged immediately on adding a small amount of water. Inasmuch as a solution of thianthrene 5-oxide in concentrated sulfuric acid yielded thianthrene if it were allowed to stand for some time before the addition of water, it must be assumed that a disproportionation took place, the other product being a thianthrene dioxide.

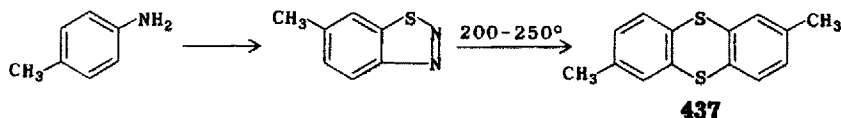
In spite of a considerable amount of work in several laboratories, there is still no clear agreement as to the identity of the species responsible for the color shown by thianthrene and its derivatives with strong acids. Several workers^{264, 339b, 506, 513a} had shown by electron spin resonance that paramagnetic compounds are present in solutions of thianthrene in concentrated sulfuric acid, and MacLean and van der Waals^{339b} showed the absence of paramagnetic species in solutions in hydrogen fluoride. Fava, Sogo, and Calvin¹⁷⁵ correlated the visible absorption spectrum with the intensity of the spin resonance signal and showed that the color is characteristic of the radical present. Trifluoroacetic acid was used instead of sulfuric acid because it is a non-oxidizing acid, and solutions of thianthrene 5-oxide and 5,10-dioxide in it showed that a maximum amount of free radical is present in a mixture of the two oxides. The authors concluded, therefore, that the free radical is an intermediate oxidation state between thianthrene 5-oxide and 5,10-dioxide, with a structure such as **435**. However, using the same general approach with concentrated sulfuric acid Shine and Piette^{453a} concluded that the paramagnetic species is formed by a one-electron oxidation of thianthrene and has the structure **436**.

**435****436**

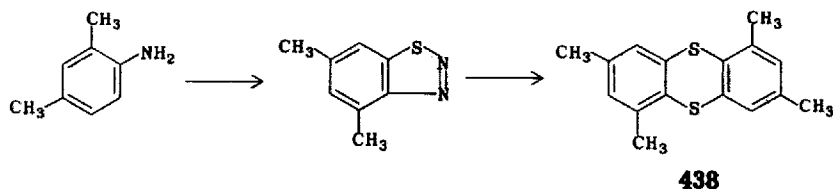
Lucken^{332a} arrived at the same conclusion as a result of studying the 1 : 1 complex of thianthrene with antimony pentachloride, which has the same electron spin resonance spectrum. He also found that 2, 5-di-phenyl-*p*-dithiin and 6-methyl-1, 4-benzodithiin form 1 : 1 paramagnetic complexes with antimony pentachloride, and concluded that this is a general property of the *p*-dithiin ring system.

2. Alkyl Derivatives

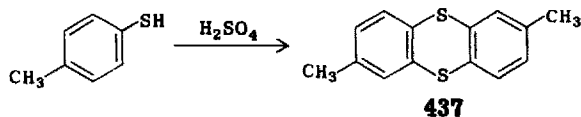
Relatively few alkyl-substituted thianthrenes have been reported; these are listed in Table 21. The preparations were generally carried out using the same procedures as those used for thianthrene itself. Thus, Jacobson and Ney^{290,292} applied their 1, 2, 3-benzothiadiazole procedure to *p*-toluidine to obtain 2, 7-dimethylthianthrene(**437**).



Since there is no reason for doubting that the sulfur couples at the position previously occupied by the nitrogen, this synthesis serves to fix the position of the methyl groups. Similarly, 2, 4-dimethylaniline yielded 1, 3, 6, 8-tetramethylthianthrene (**438**).



Numerous other preparations of 2, 7-dimethylthianthrene (**437**) have been reported. Fries and Volk¹⁹² reacted *p*-thiocresol with sulfuric acid, also an unequivocal synthesis, and reported a 47% yield by this procedure; Rumpf⁴²⁴ claimed a 50% yield with fuming sulfuric acid.



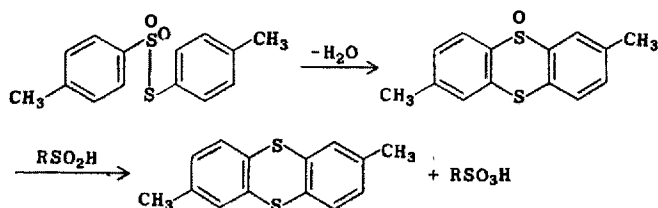
However, Tits-Skvortsova, Leonova, and co-workers,⁴⁹⁰ obtained only a

TABLE 21. Alkyl Derivatives of Thianthrene

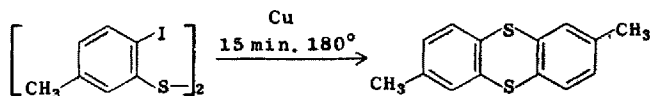
Substituents	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Ref.
2, 7-(CH ₃) ₂		116			290, 292
	47	123			32, 192
	15	117			490
		122.8	183-188	1-3	144
			230-235	60	126
			244	17	181
		117-118	228-231	14	313
			248-250	13	209
		120			36
		124			423
		94			192
2, 7-(CH ₃) ₂ 5-Oxide		195.5 (202.5 corr.)			36
2, 7-(CH ₃) ₂ α-5, 10-dioxide		194			192
2, 7-(CH ₃) ₂ β-5, 10-dioxide		168.5 (174 corr.)			36
2, 7-(CH ₃) ₂ 5, 5-dioxide		171			36
2, 7-(CH ₃) ₂ 5, 5, 10-trioxide		223			36
2, 7-(CH ₃) ₂ 5, 5, 10, 10-tetroxide		286			192
2, 7-(?)-(C ₆ H ₅ CH ₂) ₂		196			403
2, 3, 7, 8-(CH ₃) ₄		125-128	197-202	1-3	144
1, 3, 6, 8-(CH ₃) ₄		118			290, 292
1, 4, 6, 9-(CH ₃) ₄		242			450

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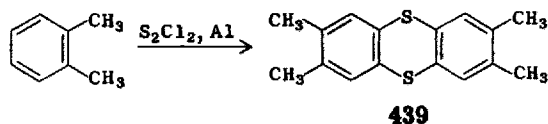
15% yield. Runge, Jumar, and Held⁴²³ found that 2, 7-dimethylthianthrene is formed on treatment of α -pyridyl *p*-tolyl disulfide with sulfuric acid. Brederick and co-workers⁶⁹ used the formation of 2, 7-dimethylthianthrene to explain the decrease in catalytic activity for radical polymerization of vinyl monomers which *p*-toluenesulfinic acid underwent on standing in a desiccator over concentrated sulfuric acid. The crystals turned blue, indicating the formation of a thianthrene complex.



Several investigators reacted toluene with sulfur monochloride. Fleischer and Stemmer¹⁸¹ used aluminum chloride for the reaction, Cohen and Skirrow¹²⁶ used aluminum amalgam, and Damanski and Kostić¹⁴⁴ used pure aluminum. Genvresse²⁰⁹ and Krafft and Lyons³¹³ reacted toluene with sulfur dichloride and aluminum chloride to form 2, 7-dimethylthianthrene. In view of the variation in melting points reported and the difficulty noted by several authors in obtaining the compound crystalline, it may be suspected that some of these reactions formed isomeric dimethylthianthrenes in addition to the 2, 7-derivative. Barber and Smiles³² dehalogenated bis(4-iodotolyl-3) disulfide with copper to obtain 2, 7-dimethylthianthrene.

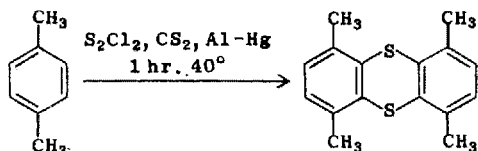


Damanski and Kostić¹⁴⁴ applied the sulfur monochloride-aluminum synthesis to *o*-xylene and isolated a compound which they formulated as 2, 3, 7, 8-tetramethylthianthrene (**439**). In view of the number of isomers possible, it is not surprising that they reported a rather broad melting point range for the sample.



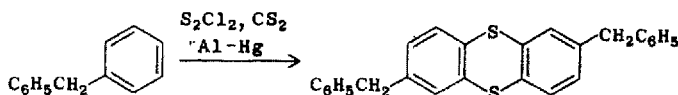
Sen and Rây⁴⁵⁰ used sulfur monochloride and aluminum amalgam on *p*-xylene to prepare 1, 4, 6, 9-tetramethylthianthrene (**440**). Only one isomer should be possible in this case, but the 242° melting point is surprisingly high.

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440

Rây⁴⁰³ used the same procedure on diphenylmethane and isolated a compound which he formulated as dibenzylthianthrene, presumably the 2, 7-isomer (**441**).



441

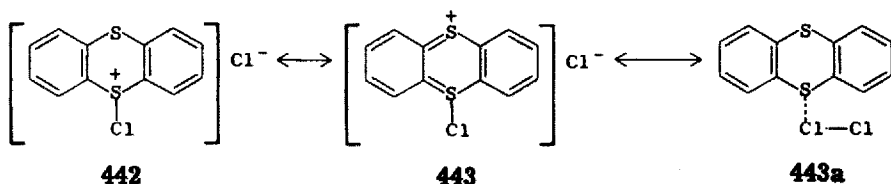
Various oxides of 2, 7-dimethylthianthrene have been reported. Fries and Volk¹⁹² prepared the 5-oxide by oxidizing 2, 7-dimethylthianthrene with dilute nitric acid in acetic acid at room temperature. Dilute nitric acid under reflux yielded the 5, 10-dioxide; Fries and Volk isolated only one form, the α -isomer. Baw, Bennett, and Dearn³⁶ oxidized 2, 7-dimethylthianthrene with the calculated quantity of hydrogen peroxide in acetic acid at 75-80° and obtained a mixture of the two isomeric 5, 10-dioxides. By analogy with thianthrene itself, it is reasonable to assume that the higher melting, less soluble α -isomer is the *cis* isomer and the lower melting β -isomer is the *trans*. The same authors prepared 2, 7-dimethylthianthrene 5, 5, 10-trioxide with three moles of hydrogen peroxide; reduction with zinc in acetic acid gave the 5, 5-dioxide. Fries and Volk¹⁹² prepared 2, 7-dimethylthianthrene 5, 5, 10, 10-tetroxide with excess hydrogen peroxide in acetic acid at 100°; according to these authors neither Cohen and Skirrow¹²⁶ nor Genvresse²⁰⁹ had prepared the pure disulfone.

3. Halogen Derivatives

Thianthrene forms two types of halogen derivatives, compounds with halogen on sulfur and compounds with halogen on the aromatic rings.

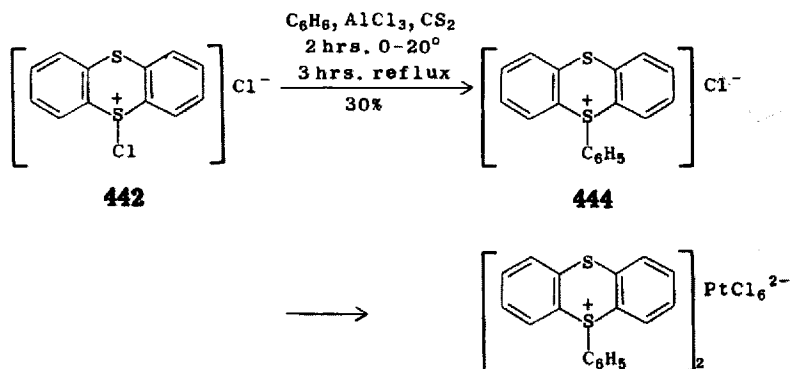
The sulfur-halogen derivatives were investigated by Fries and co-workers.¹⁹⁴⁻¹⁹⁶ Stenhouse⁴⁶⁵ reported, in his original paper on the synthesis of thianthrene, that thiathrene reacts with bromine in carbon disulfide to give a tetrabromide as black prisms. Since the compound was decomposed by water, it presumably contained S-Br bonds, but this work has not been confirmed. On the contrary, Fries and Vogt¹⁹⁴ found that treatment of thianthrene with chlorine in dry benzene gave an unstable red dichloride, isolated as red prisms. Since it has been claimed⁵⁴ that the bromine adduct of dimethyl sulfide has the structure $[(\text{CH}_3)_2\text{SBr}]^+\text{Br}^-$, thianthrene dichloride may have an analogous structure (**442**), perhaps with some contribution from the resonance form **443** to account for the color of the adduct and the lack of reactivity with

excess chlorine.¹⁹⁵ However, in view of the finding that iodine forms a molecular complex with sulfides,^{228a} a simple molecular complex (**443a**) cannot be eliminated.



As already mentioned, hydrolysis leads to thianthrene 5-oxide. Fries and co-workers^{194,195} claimed that the hydrolysis is reversible, but, in view of the reaction of the 5-oxide with hydrogen bromide (*vide infra*), it is more reasonable to assume that the 5-oxide reacts with hydrogen chloride to yield thianthrene and chlorine, the two combining to give the adduct. Fries and co-workers^{195,196} reported that the halogen adducts are stabilized toward hydrolysis when methoxyl groups are substituted on the benzene rings.

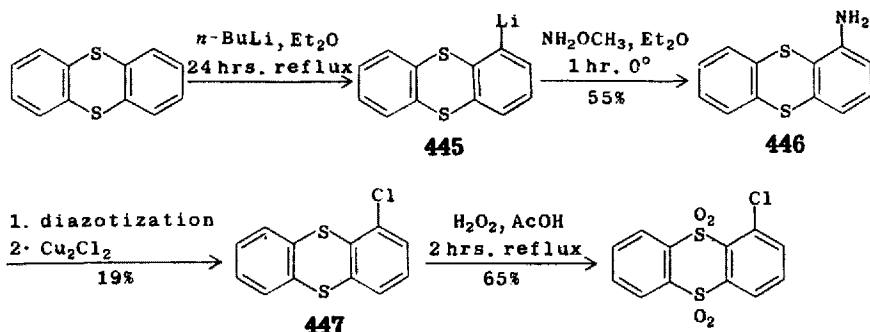
Dougherty and Hammond¹⁶⁵ carried out a Friedel-Crafts reaction between thianthrene dichloride (**442**) and benzene and obtained a product which they formulated as 5-phenylthianthrenium chloride (**444**). The same reaction took place with phenetole, both compounds being isolated as their chloroplatinates.



It is interesting that these are the only sulfonium derivatives of thianthrene which have been reported. Jacobson and Janssen²⁹¹ were unable to alkylate thianthrene with methyl iodide at 100°, indicating a considerable amount of resonance involving the sulfur atoms, in agreement with the calculations of Sunner⁴⁷⁷ (see section III K-1b).

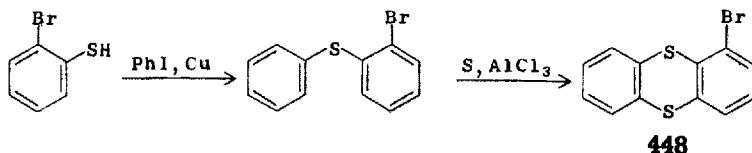
Simple halogenated derivatives of thianthrene in which the halogen is substituted on sulfur or on the aromatic rings are listed in Table 22; halogenated thianthrenes containing other functional groups on the aromatic rings are described under the corresponding functional groups. 1-Chlorothianthrene (**447**) was prepared by Gilman and Swayampati²²¹ from 1-aminothianthrene (**446**), prepared in turn by the metalation of thianthrene.²¹⁵

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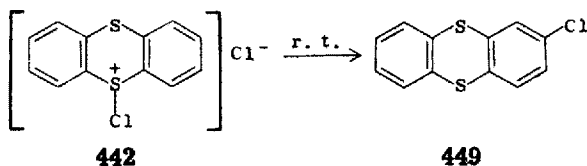
That thianthrene metalates in the 1-position, in accord with the metalation of dibenzofuran and dibenzothiophene, was shown by the non-identity of 1-aminothianthrene (**446**) and a sample of 2-aminothianthrene prepared by an unequivocal synthesis. Furthermore, carbonation of 1-thianthrenyllithium (**445**) yielded an acid different from the known 2-thianthrenecarboxylic acid.

1-Bromothianthrene (**448**) was prepared by Gilman and Stuckwisch²¹⁵ by an unequivocal ring closure synthesis.



Martin³⁴⁸ prepared 1-iodothianthrene in very low yield by the reaction of 1-thianthrenyllithium (**445**) with iodine.

2-Chlorothianthrene (**449**) was first prepared by Fries and Vogt,¹⁹⁴ who found that thianthrene dichloride (**442**), on standing, yielded a mono-chloro compound which they formulated as 2-chlorothianthrene.



Their structural assignment was based apparently only on the reasonable assumption that substitution should take place *para* to the sulfur atom. Although the reported melting point of 2-chlorothianthrene is practically identical with that reported by Gilman and Swayampati²²¹ for 1-chlorothianthrene, the work of Gilman and Swayampati^{218,221} on the bromination of thianthrene leaves little doubt that direct bromination of thianthrene yields 2-bromothianthrene; there appears to be no reason for assuming that chlorine reacts differently. Kozlov, Fruktova,

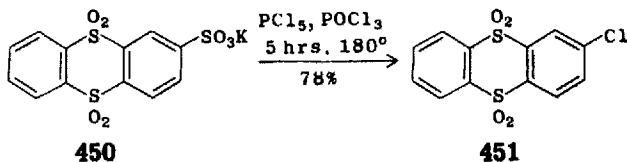
TABLE 22. Halogen Derivatives of Thianthrene

Substituents	Yield (%)	M.p.(°C)	Ref.
1-Cl	19	85-85.5	221
1-Cl 5, 5, 10, 10-tetroxide	65	242	221
1-Br		145	215
1-I	4.6	187.5-188.5	348
2-Cl		84	194
2-Cl 5, 5, 10, 10-tetroxide	78	120	311
2-Br	36	88-89	218
2-Br 5, 5, 10, 10-tetroxide	92	226-227	218
1, 6-Cl ₂		174.5	143
2, 7-Cl ₂	49	181.5 (186 corr.)	36
		171	194
		147 (?)	403
2, 7-Cl ₂ 5-oxide		235-237 (dec.)	36
2, 7-Cl ₂ α -5, 10-dioxide		301 (313 corr.)	36
2, 7-Cl ₂ β -5, 10-dioxide		256.5 (267.5 corr.)	36

2, 7-Cl ₂ 5, 5-dioxide	215	36
2, 7-Cl ₂ 5, 5, 10-trioxide	281	36
2, 7-Cl ₂ 5, 5, 10, 10-tetroxide	293 (305 corr.)	36
2, 7- and 2, 8-Br ₂	140-149	218
2, 7- and 2, 8-Br ₂ 5, 5, 10, 10-tetroxide	246-280	218, 225
2, 3, 7, 8-Br ₄	291-292	225
2, 3, 7, 8-Br ₄ 5, 5, 10, 10-tetroxide	357-358 (dec.)	225
Cl ₂ -(CH ₃ -) ₂	145	403
1, 6-Cl ₂ -4, 9-(CH ₃ -) ₂ or 1, 9-Cl ₂ -4, 6-(CH ₃ -) ₂	195-197	403
1, 6-Cl ₂ -4, 9-(CH ₃ -) ₂ or 1, 9-Cl ₂ -4, 6-(CH ₃ -) ₂ 5, 5, 10, 10-tetroxide	>250	403

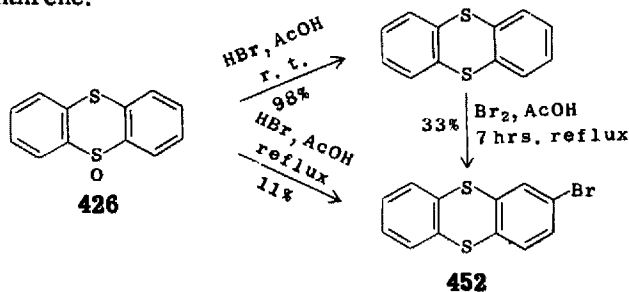
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and Shemyakina³¹¹ prepared 2-chlorothianthrene 5, 5, 10, 10-tetroxide (**451**) from potassium 2-thianthrenesulfonate (**450**).

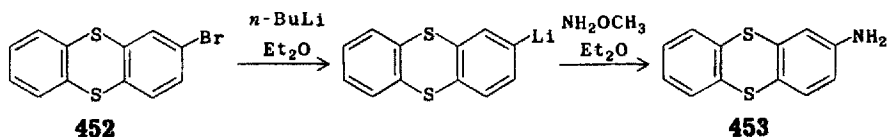


The melting point of 120° reported for **451** is surprisingly low for a compound of this type; however, according to these authors oxidation of 2-chlorothianthrene, prepared presumably according to the procedure of Fries and Vogt,¹⁹⁴ yielded the same disulfone.

The discovery by Fries and Vogt¹⁹⁴ that thianthrene 5-oxide (**426**) is reduced by hydrogen bromide to thianthrene has already been mentioned. This reaction was investigated more thoroughly by Gilman and Swayampati,²¹⁸ who found the reaction to be essentially quantitative at room temperature. However, in refluxing acetic acid a small amount of 2-bromothianthrene (**452**) was formed. This latter reaction they called reductive bromination, and they demonstrated that bromine is formed as an intermediate. The same product was formed by bromination of thianthrene.



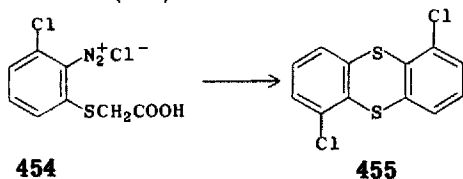
The maximum yield (36%) of 2-bromothianthrene was obtained by refluxing thianthrene 5-oxide with 32% aqueous hydrobromic acid for ten hours. Thus, chlorination and bromination appear to be completely analogous reactions. The position of the bromine was proved by the following sequence, the 2-aminothianthrene (**453**) formed being identical with that prepared by the unequivocal procedure of Krishna.³¹⁸



It is rather interesting that thianthrene 5, 5-dioxide could not be brominated. Thus, Gilman and Swayampati²¹⁸ reduced thianthrene 5, 5, 10-trioxide with hot hydrobromic acid and isolated a 92% yield of the 5, 5-dioxide; this resisted attack by bromine.

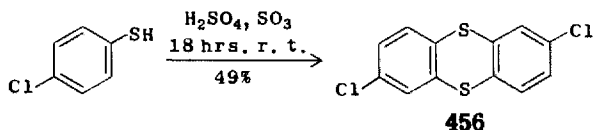
C₄S₂ Ring Systems

1, 6-Dichlorothianthrene (**455**) was isolated by Dalglish and Mann¹⁴³ as a by-product in the synthesis of 4-chlorothiindoxyl. The authors assumed it to be formed from diazotized 3-chloro-2-aminophenylthioglycolic acid (**454**).



The mode of formation of **455** is obscure, and the authors made no attempt to prove its structure. Although its melting point is suspiciously close to that of 2, 7-dichlorothianthrene (**456**), it is difficult to see how the latter could have been formed, unless 4- or 5-chloro-2-aminophenylthioglycolic acid were present as an impurity in the material used by Dalglish and Mann.

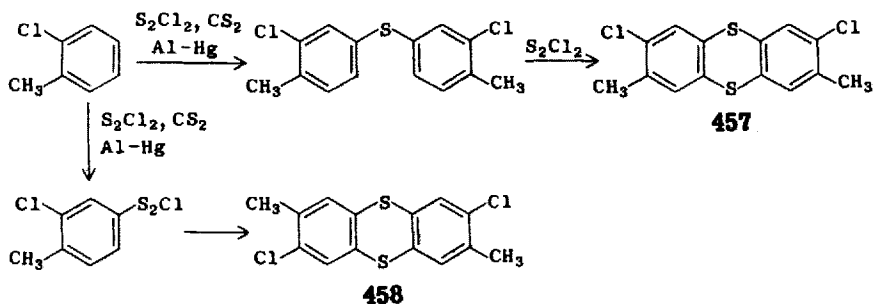
2, 7-Dichlorothianthrene (**456**) was first prepared by an unequivocal synthesis by Baw, Bennett, and Dearn, ³⁶ involving the reaction of *p*-chlorothiophenol with sulfuric acid.



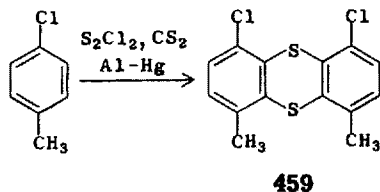
456 had been prepared previously by Fries and Vogt¹⁹⁴ by several different procedures, and mistakenly identified by them as 2, 8-dichlorothianthrene. Their syntheses involved the reaction of chlorobenzene with sulfur monochloride and aluminum chloride (confirmed by Baw, Bennett, and Dearn), the direct chlorination of thianthrene or 2-chlorothianthrene, and the reaction of thianthrene 5, 10-dioxide with hydrogen chloride in acetic acid. Inasmuch as Gilman and Swayampati^{218, 225} have shown that bromination of thianthrene gives a mixture of 2, 7- and 2, 8-dibromothianthrene, it is reasonable to assume that chlorination would also give a mixture; the 171° melting point reported by Fries and Vogt is 10° lower than that reported by Baw, Bennett, and Dearn. Rây⁴⁰³ condensed chlorobenzene with sulfur monochloride using an aluminum amalgam catalyst; in view of his reported melting point of 147°, the numerous syntheses reported by this procedure must be viewed with suspicion, since it appears rather unlikely that aluminum chloride and aluminum amalgam would give different isomers in this reaction. He also reacted *o*-chlorotoluene under these conditions. Actually, very little is known about this reaction. If sulfur monochloride reacts with two moles of *o*-chlorotoluene *para* to the methyl group, the initial product would probably be a sulfide, which would then react with more sulfur monochloride to give the unsymmetrical derivative, 2, 8-dichloro-3, 7-dimethylthianthrene (**457**). If sulfur monochloride reacts with one mole of *o*-chlorotoluene *para* to the methyl group, condensation of this reaction product would be expected to yield the symmetrical derivative,

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2, 7-dichloro-3, 8-dimethylthianthrene (**458**). No evidence is available at present to choose between these two alternatives, although the first seems more likely. It may be suspected that in many cases isomeric mixtures were obtained.



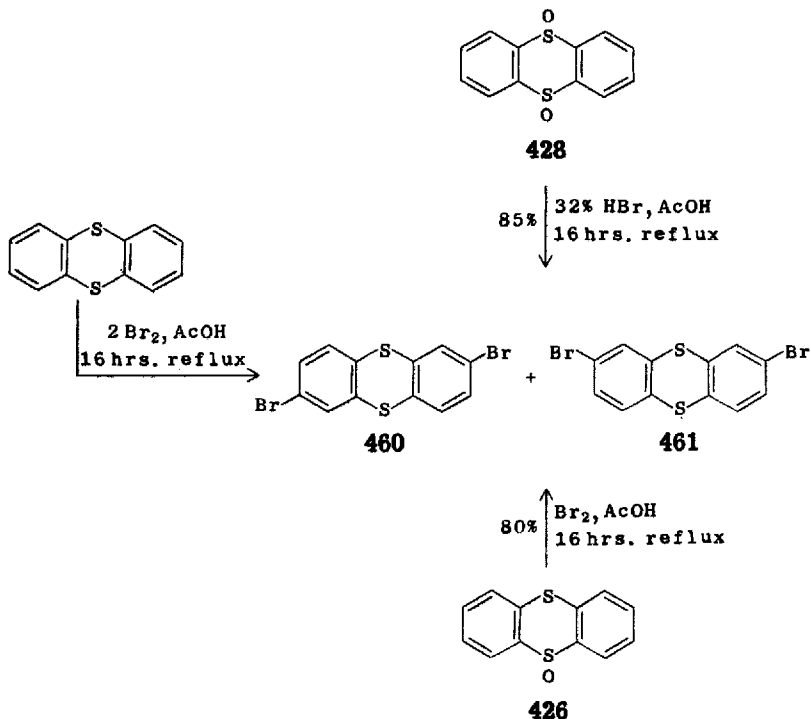
Rây also reacted *p*-chlorotoluene under these conditions and formulated the compound as 1, 9-dichloro-4, 6-dimethylthianthrene (**459**) rather than as the isomeric 1, 6-dichloro-4, 9-dimethyl compound.



Baw, Bennett, and Dearn³⁶ prepared all the possible oxides of 2, 7-dichlorothianthrene. By using one mole of hydrogen peroxide in acetic acid, they isolated and separated a mixture of the 5-oxide and 5, 5-dioxide. Two moles of hydrogen peroxide gave the two isomeric 5, 10-dioxides, whose structures were proved by zinc reduction to 2, 7-dichlorothianthrene. Three moles of hydrogen peroxide gave the 5, 5, 10-trioxide, reduction of which with zinc and acetic acid gave the 5, 5-dioxide, while chromic anhydride in acetic acid gave the 5, 5, 10, 10-tetroxide.

Several patents^{107,108} describe the bromination of thianthrene with bromine in nitrobenzene to give a dibromothianthrene. The reaction product was shown to be a mixture of 2, 7- (**460**) and 2, 8-dibromothianthrene (**461**) by Gilman and Swayampati,^{218,225} although they were unable to separate either the mixture of the two dibromo compounds or their corresponding disulfones, prepared by oxidation with hydrogen peroxide in acetic acid. Gilman and Swayampati found that the same mixture is formed by direct bromination of thianthrene in acetic acid, by reductive bromination of thianthrene 5, 10-dioxide (**428**), and by bromination of thianthrene 5-oxide (**426**).

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That thianthrene, like dibenzothiophene, brominates *para* to the S-atoms had already been demonstrated by the isolation of 2-bromothianthrene. That the second bromine attacks the unsubstituted ring was indicated by the infrared spectrum of the mixture, which showed that both rings were substituted in the 1, 2, 4-positions. Further evidence was the bromination of thianthrene or its 5,10-dioxide with excess bromine to give a tetrabromide, undoubtedly 2, 3, 7, 8-tetrabromothianthrene (**462**).

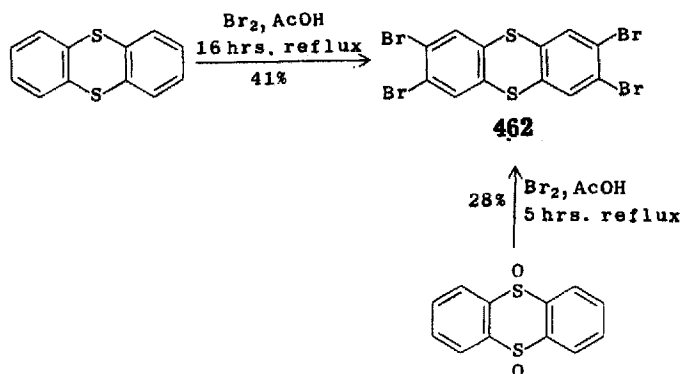


TABLE 23. Hydroxyl Derivatives of Thianthrene

Substituents	Yield (%)	M.p.(°C)	Ref.
1-HO-	2.5	117-118	216
1-HO- 5, 5, 10, 10-tetroxide	46	117-118	222
1-CH ₃ O-	82	239-240	222
1-CH ₃ O- 5, 5, 10, 10-tetroxide	67	81-81.5	222
1-HO ₂ CCH ₂ O-	98	246-247	222
1-C ₂ H ₅ O ₂ CCH ₂ O-	30	174-175	222
2-HO-	24	90-90.5	222
2-HO- 5, 5, 10, 10-tetroxide		145	401
2-CH ₃ CO ₂ - 5, 5, 10, 10-tetroxide	25-30	160 (dec.)	312
1, 2-(HO-) ₂ 5, 5, 10, 10-tetroxide		>360	312
2, 7-(HO-) ₂	48	197	312
2, 7-(HO-) ₂ 5-oxide		233	195
2, 7-(CH ₃ O-) ₂		>300	195
	30	131	195
		133	36
2, 7-(CH ₃ O-) ₂ 5-oxide		154-155	195
2, 7-(CH ₃ O-) ₂ α-5, 10-dioxide		266-268	36, 195
2, 7-(CH ₃ O-) ₂ β-5, 10-dioxide		198-200	36
2, 7-(CH ₃ O-) ₂ 5, 5, 10, 10-tetroxide		282	195
2-HO-1, 3(?) -Br ₂ 5, 5, 10, 10-tetroxide		159.5	312
2. 3. 7. 8-(HO-),	50	273	196

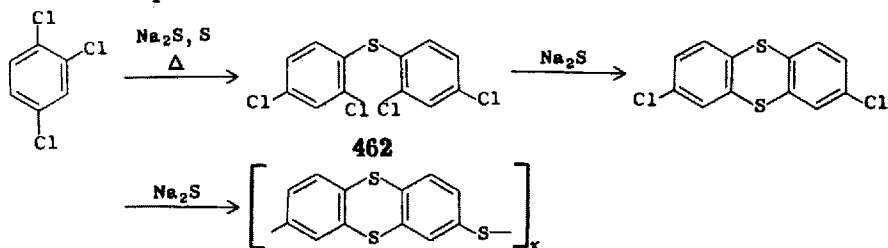
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2, 3, 7, 8-(HO-) ₄ 5, 5-dioxide	dec. > 300	196
2, 3, 7, 8-(HO-) ₄ 5, 5, 10, 10-tetroxide	> 300	196
2, 3, 7, 8-(CH ₃ O-) ₄	176	196
	18	501
	175-176	196
2, 3, 7, 8-(CH ₃ O-) ₄ 5-oxide	196	196
2, 3, 7, 8-(CH ₃ O-) ₄ 5, 10-dioxide	259	196
2, 3, 7, 8-(CH ₃ O-) ₄ 5, 5-dioxide	253	196
2, 3, 7, 8-(CH ₃ O-) ₄ 5, 5, 10-trioxide	275	196
2, 3, 7, 8-(CH ₃ O-) ₄ 5, 5, 10, 10-tetroxide	296	196
	294-295	501
2, 3, 7, 8-(CH ₃ O-) ₄ perbromide	220-222 (dec.)	196
2, 7-(HO-) ₂ -3, 8-(CH ₃ O-) ₂	202	450
2, 7-(CH ₃ CO ₂ -) ₂ -3, 8-(CH ₃ O-) ₂	165	450
2, 3, 7, 8-(CH ₃ CO ₂ -) ₄	224	196
2, 3, 7, 8-(CH ₃ CO ₂ -) ₄ 5-oxide	213	196
2, 3, 7, 8-(CH ₃ CO ₂ -) ₄ 5, 5-dioxide	203	196
2, 7-(CH ₃ O-) ₂ -3, 8-(?) -Br ₂	235	195
2, 7-(HO-) ₂ -1, 3, 6, 8-Cl ₄	> 300	192
2, 7-(HO-) ₂ -1, 3, 6, 8(?) -Br ₄	291	195
2, 3, 7, 8-(HO-) ₄ -1, 4, 6-Br ₃ 5, 5, 10, 10-tetroxide	> 340	196
2, 3, 7, 8-(HO-) ₄ -1, 4, 6, 9-Br ₄ 5, 5, 10, 10-tetroxide	> 350	196
2, 3, 7, 8-(CH ₃ CO ₂ -) ₄ -1, 4, 6, 9-Br ₄ 5, 5, 10, 10-tetroxide	300 (dec.)	196

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As already mentioned, a sulfone group deactivates the benzene rings toward bromination, and neither thianthrene 5, 5-dioxide nor 5, 5, 10-trioxide reacts with bromine.

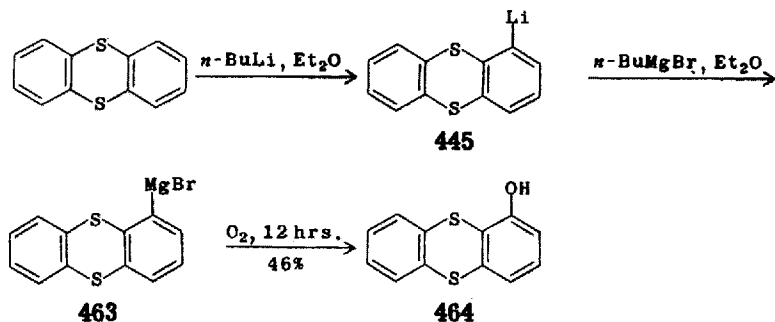
Lenz and Handlovits³²⁵ postulated thianthrene repeating units in the polymer formed from 1, 2, 4-trichlorobenzene and sodium sulfide at elevated temperature.



Presumably 2, 7-disubstituted thianthrene rings should be formed as well.

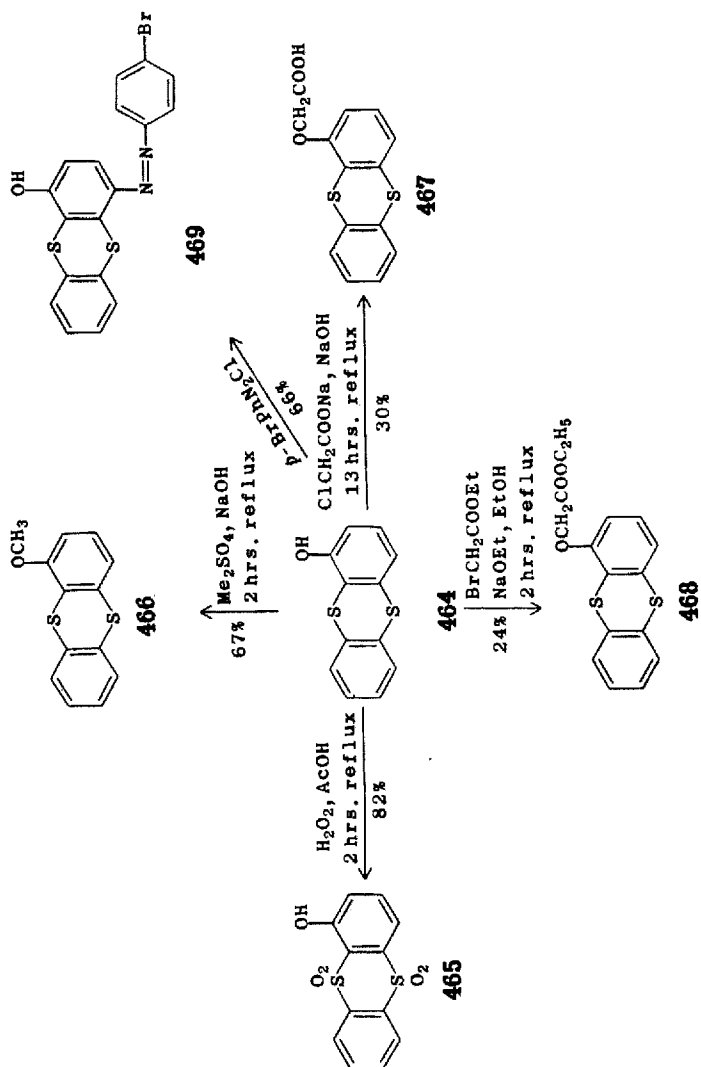
4. Hydroxyl Derivatives

Hydroxyl derivatives of thianthrene are listed in Table 23. Thianthren-1-ol (464) was first prepared in low yield by Gilman and Esmay²¹⁶ by metalation of thianthrene with *n*-butyllithium, conversion of the lithium derivative (445) to the Grignard derivative (463), and air oxidation; the metalation of thianthrene in the 1-position has already been described. The yield was improved considerably by Gilman and Swayampati.²²²



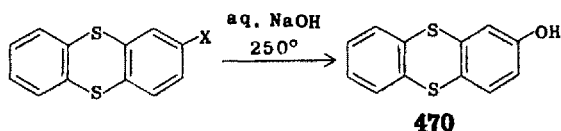
Oxidation of 464 with hydrogen peroxide in acetic acid gave the disulfone (465). Treatment of thianthren-1-ol with dimethyl sulfate and base yielded 1-methoxythianthrene (466), sodium chloroacetate yielded thianthren-1-oxyacetic acid (467), while ethyl bromoacetate yielded ethyl thianthren-1-oxyacetate (468). Coupling with *p*-bromobenzenediazonium chloride yielded 4-(4'-bromobenzeneazo)-thianthren-1-ol (469), showing the phenolic nature of the hydroxyl group. The compound could also be nitrated (see section III K-5).

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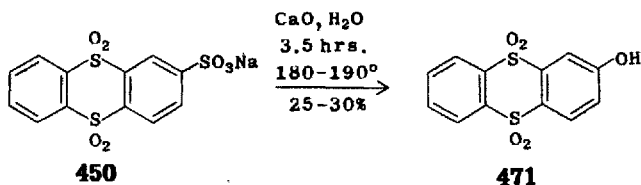


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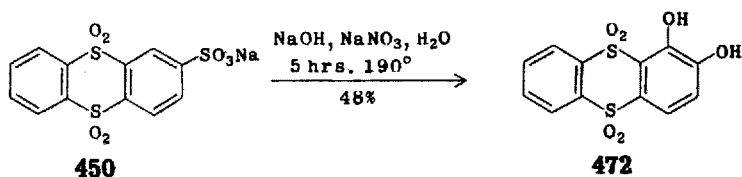
Pützer and Muth⁴⁰¹ patented the hydrolysis of a 2-halothianthrene to thianthren-2-ol (**470**).



According to Kozlov and Stakhovskaya,³¹² hydrolysis of sodium thianthrene-2-sulfonate 5, 5, 10, 10-tetroxide (**450**) with aqueous calcium hydroxide yielded thianthren-2-ol 5, 5, 10, 10-tetroxide (**471**).

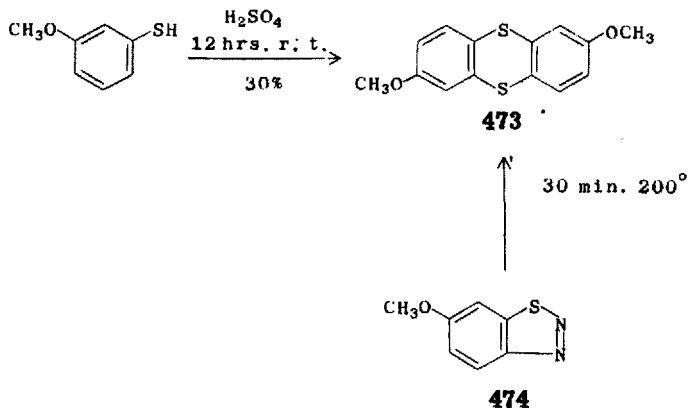


471 was reported to melt at 160° with decomposition, while esterification with acetic anhydride gave the corresponding acetate melting above 360°. It is difficult to reconcile these melting points with the postulated structure. Bromine in acetic acid gave a dibromo derivative, presumably 1, 3-dibromothianthren-2-ol 5, 5, 10, 10-tetroxide if the structure assigned to the hydroxy derivative is correct, and diazotized *p*-nitroaniline gave a red-orange dye. The same authors claimed that hydrolysis of **450** in the presence of sodium nitrate yielded thianthrene-1, 2-diol 5, 5, 10, 10-tetroxide (**472**), but no proof of structure was given.



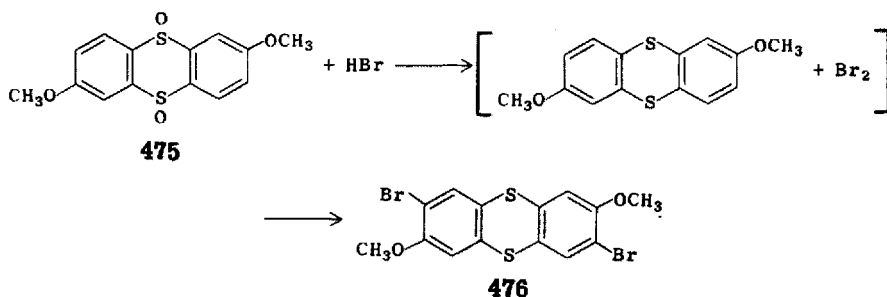
Fries and Engelbertz¹⁹⁵ prepared 2, 7-dimethoxythianthrene (**473**) by two procedures, the reaction of *m*-methoxythiophenol with sulfuric acid and the pyrolysis of 6-methoxy-1, 2, 3-benzothiadiazole (**474**) according to the procedure of Jacobson;^{290,291} the latter synthesis served to fix the position of the methoxyl groups.

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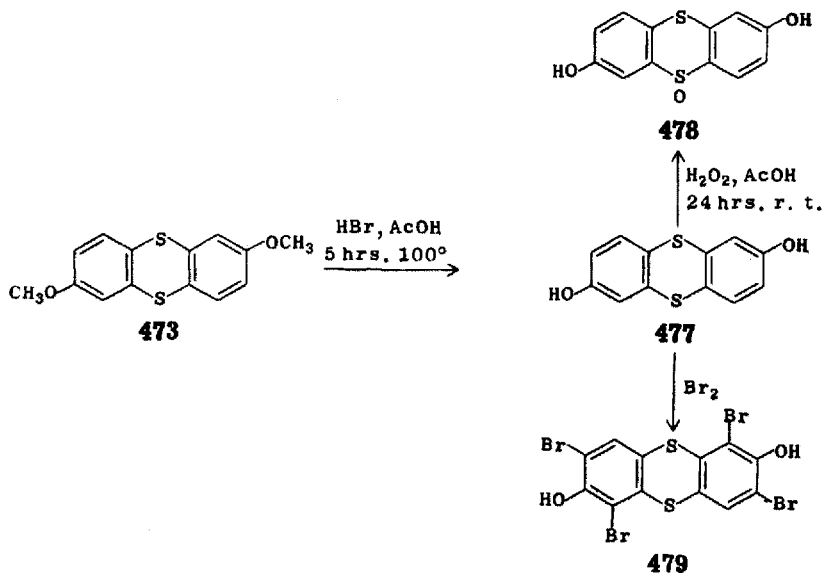


Fries and Engelbertz prepared 2,7-dimethoxythianthrene 5-oxide by treatment of **473** with dilute nitric acid. Refluxing **473** with more concentrated nitric acid gave 2,7-dimethoxythianthrene α -5,10-dioxide (**475**), and Baw, Bennett, and Dearn³⁶ were able to isolate the β -5,10-dioxide from the reaction mixture. Wet chlorine¹⁹⁵ and hydrogen peroxide³⁶ both gave the α -5,10-dioxide. Both dioxides gave 2,7-dimethoxythianthrene when reduced with zinc and hydrochloric acid. Treatment of 2,7-dimethoxythianthrene with hydrogen peroxide in hot acetic acid gave, according to Fries and Engelbertz,¹⁹⁵ 2,7-dimethoxythianthrene 5,5,10,10-tetroxide.

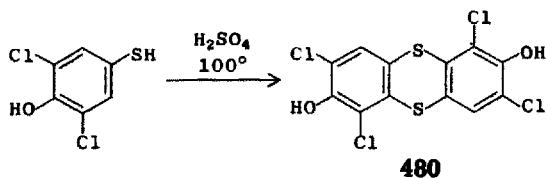
Fries and Engelbertz¹⁹⁵ attempted the reduction of 2,7-dimethoxythianthrene α -5,10-dioxide (**475**) with hydrogen bromide. The product was a dibromo derivative, however, formulated tentatively as 2,7-dimethoxy-3,8-dibromothianthrene (**476**); it is not at all surprising that the bromine formed in the reduction brominated the activated aromatic rings.



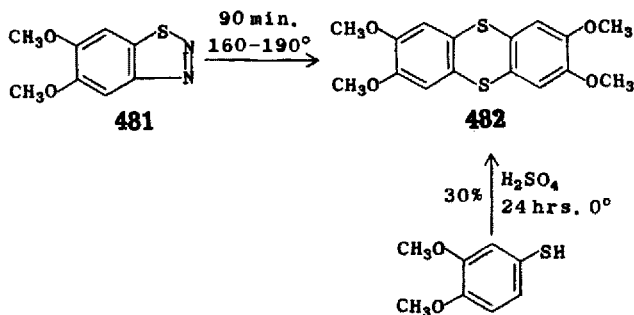
Fries and Engelbertz¹⁹⁵ were able to demethylate 2,7-dimethoxythianthrene (**473**) with hydrogen bromide to thianthrene-2,7-diol (**477**). Hydrogen peroxide gave thianthrene-2,7-diol 5-oxide (**478**), and bromine gave a tetrabromide, presumably 1,3,6,8-tetrabromothianthrene-2,7-diol (**479**).



The corresponding tetrachloro derivative, 1, 3, 6, 8-tetrachlorothianthrene-2, 7-diol (**480**), was reported by Fries and Volk¹⁹² as being formed by the reaction of 3, 5-dichloro-4-hydroxythiophenol with sulfuric acid.

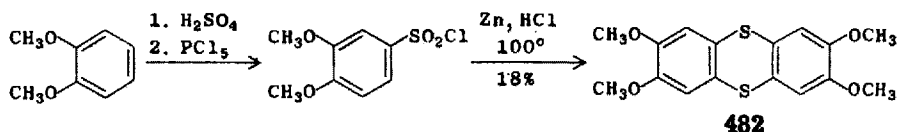


Fries, Koch, and Stukenbrock¹⁹⁶ carried out a thorough investigation of the chemistry of 2, 3, 7, 8-tetramethoxythianthrene (**482**). Two syntheses were used; one involved pyrolysis of 6, 7-dimethoxy-1, 2, 3-benzothiadiazole (**481**), which located the methoxyl groups, while the preferred procedure involved the reaction of 3, 4-dimethoxythiophenol with sulfuric acid.



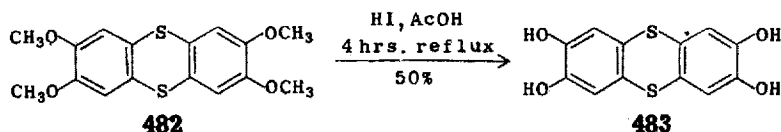
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3, 4-Dimethoxythiophenol was prepared by reduction of 3, 4-dimethoxybenzenesulfonyl chloride. Vinkler and Szabó⁵⁰¹ found that, by modifying the conditions somewhat, some 2, 3, 7, 8-tetramethoxythianthrene was formed during the reduction. Apparently zinc chloride in hydrochloric acid is sufficiently acidic to effect the condensation.



Fries, Koch, and Stukenbrock¹⁹⁶ investigated the oxidation of **482**. Dilute nitric acid gave the 5-oxide which, with hydrogen bromide in hot acetic acid, gave a tribromide of unknown constitution. Since sodium bisulfite regenerated 2, 3, 7, 8-tetramethoxythianthrene, the bromines must be connected to sulfur in the perbromide. In view of the ready ring bromination of 2, 7-dimethoxythianthrene, the lack of ring substitution with the tetramethoxy derivative is surprising. Treatment of **482** with more concentrated nitric acid at a higher temperature gave the 5, 10-dioxide, only one isomer being isolated; reduction with hydrogen bromide followed by sodium bisulfite showed the compound to be the disulfoxide. 2, 3, 7, 8-Tetramethoxythianthrene 5, 5, 10-trioxide was prepared by oxidizing **482** with chlorine in hot aqueous acetic acid; the structure was indicated by isolation of the 5, 5-dioxide after reduction with hydrogen bromide followed by treatment with sodium bisulfite. The monosulfone was also formed by dissolving the trioxide in concentrated sulfuric acid and allowing the solution to stand before diluting it with water. Apparently the oxidation of the tetramethoxythianthrene is more difficult than that of thianthrene itself, since reaction of the monosulfone with concentrated nitric acid in hot acetic acid gave the trioxide. The disulfone, 2, 3, 7, 8-tetramethoxythianthrene 5, 5, 10, 10-tetroxide, was prepared with hydrogen peroxide in hot acetic acid.

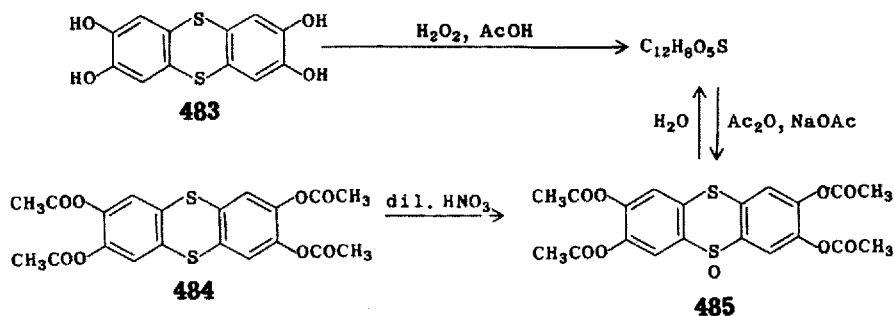
Fries, Koch, and Stukenbrock¹⁹⁶ isolated thianthrene-2, 3, 7, 8-tetrol (**483**) from the demethylation of 2, 3, 7, 8-tetramethoxythianthrene with hydrogen iodide.



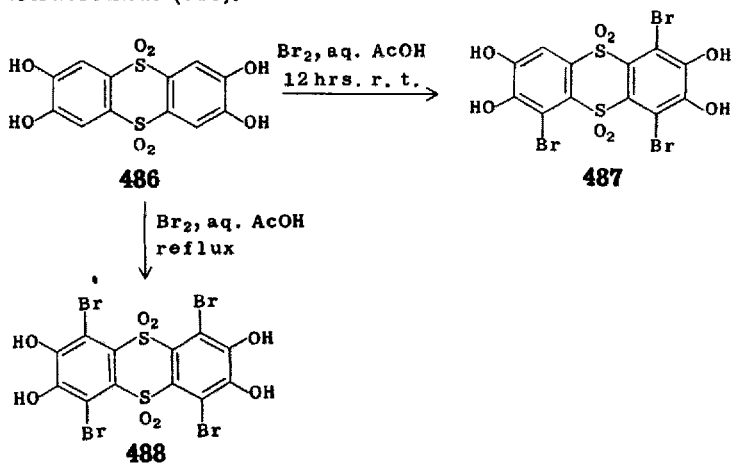
483 was not as stable as the other thianthrene derivatives and slowly turned blue in air; the tetraacetate (**484**) was apparently like the tetramethoxy compound. Treatment of the tetrol with one mole of hydrogen peroxide in acetic acid gave a blue compound of indeterminate structure, presumably not the 5-oxide, which should be colorless. Esterification of the blue compound with acetic anhydride gave 2, 3, 7, 8-tetraacetoxythianthrene 5-oxide (**485**), a colorless compound, also formed by

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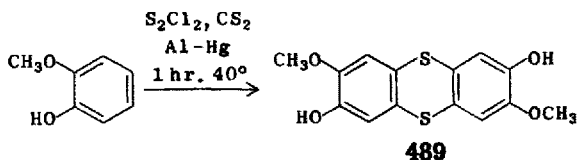
oxidation of 2, 3, 7, 8-tetraacetoxythianthrene (**484**), while hydrolysis regenerated the blue compound. The authors postulated a quinoid structure to explain the color.



Other oxidized derivatives of **483** were prepared from the corresponding tetramethoxy derivatives by demethylation with hydrogen iodide. In this way were prepared thianthrene-2, 3, 7, 8-tetrol **5, 5-dioxide** and **5, 5, 10, 10-tetroxide (486)**. The tetroxide could be brominated at room temperature to a tribromide (**487**) and at elevated temperatures to a tetrabromide (**488**).



Sen and Rây⁴⁵⁰ condensed guaiacol with sulfur monochloride in the presence of an aluminum-mercury couple and obtained a compound which they formulated as 3, 8-dimethoxythianthrene-2, 7-diol (**489**).

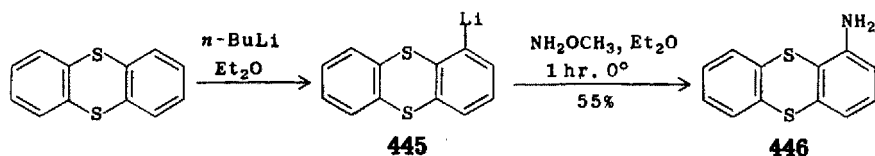


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Alternatively, this could be the unsymmetrical compound, 3, 7-dimethoxy-thianthrene-2, 8-diol. The questionable nature of this synthesis has already been mentioned in connection with the synthesis of halogenated thianthrenes. Fries and Engelbertz¹⁹⁵ were unable to isolate a thianthrene derivative from the reaction of anisole with sulfur, sulfur monochloride, or sulfur dichloride, using an aluminum chloride catalyst. However, it is not uncommon for a Friedel-Crafts reaction to succeed with a mild catalyst and fail with an active one.

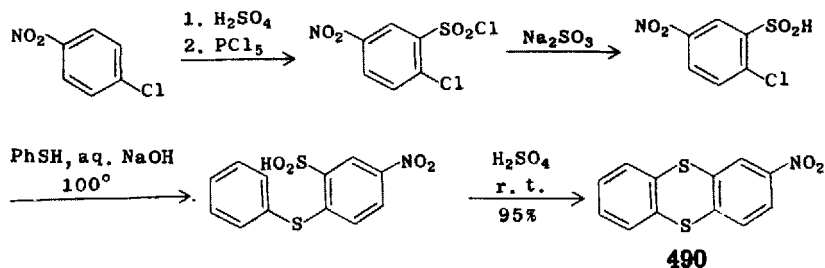
5. Nitrogen Derivatives

A variety of nitro and amino derivatives of thianthrenes are known; these are listed in Table 24. Gilman and co-workers^{215,221} prepared 1-aminothianthrene (**446**) from 1-thianthrenyllithium (**445**) and hydroxylamine *O*-methyl ether. The fact that thianthrene is metalated in the 1-position has already been discussed, part of the evidence being that the aminothianthrene formed by this procedure is different from 2-aminothianthrene prepared by the unequivocal synthesis of Krishna,³¹⁸ discussed below.



Reaction with *p*-acetamidobenzenesulfonyl chloride yielded 1-(*N*⁴-acetylsulfanilamido)thianthrene, hydrolysis of which gave 1-sulfanilamidothianthrene. A Sandmeyer reaction on 1-aminothianthrene gave 1-chlorothianthrene.

2-Nitrothianthrene (**490**) was prepared by Krishna³¹⁸ by ring closure of 2-phenylthio-5-nitrobenzenesulfinic acid, a synthesis which locates the position of the nitro group unequivocally. Keats³⁰¹ and Gilman and Stuckwisch²¹⁵ confirmed the synthesis, the latter authors reporting a 95% yield in the ring closure step. The starting material was *p*-chloronitrobenzene.



According to Krishna, the product of the reaction was the expected 10-oxide if the ring closure was carried out at 50°. However, in view of the fact that **490** was formed at a lower temperature, and that dilute nitric

TABLE 24. Nitrogen Derivatives of Thianthrene

Substituent	Yield (%)	M.p.(°C)	Ref.
1-NH ₂	55	120-121	215, 221
1-NH ₂ · HCl	75	231 (dec.)	215, 221
1-(<i>p</i> -CH ₃ CONHC ₆ H ₄ SO ₂ NH-)	58	154	215
1-(<i>p</i> -H ₂ NC ₆ H ₄ SO ₂ NH-)	80	dec. >120	215
2-NO ₂	95	128	318
			215
2-NO ₂ 5(or 10)-oxide		134-135, 5	348
2-NO ₂ 5, 10-dioxide		166	318
2-NO ₂ 5, 5, 10, 10-tetroxide		226	318
		255	318
2-NH ₂	69	160, 5-161	218
	78		215
	95	160	301
2-NH ₂ <i>d</i> -camphorsulfonate		278	45
2-CH ₃ CONH-		185	218, 318
	59	186	301
2-(<i>p</i> -CH ₃ CONHC ₆ H ₄ SO ₂ NH-)	62	163	215
2-(<i>p</i> -H ₂ NC ₆ H ₄ SO ₂ NH-)	85	dec. >125	215

C₄S₂ Ring Systems

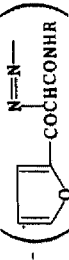
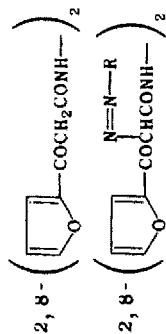
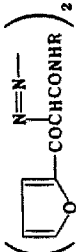
2-()	198-200	95a
2-()		
R = C ₆ H ₅ -	179-180	95a
p-CH ₃ C ₆ H ₄ -	185-186	95a
p-CH ₃ OC ₆ H ₄ -	179-181	95a
p-C ₂ H ₅ OC ₆ H ₄ -	212-214	95a
p-ClC ₆ H ₄ -	232-233	95a
p-BrC ₆ H ₄ -	239-240	95a
2,5-Cl ₂ C ₆ H ₃ -	250-251	95a
2-Naphthyl-	200-202	95a
Dibenzofuranyl-	274-275	95a
2-Thianthrenyl-	245-246	95a
2-()		
R = C ₆ H ₅ -	198-199	95a
p-CH ₃ C ₆ H ₄ -	195-197	95a
p-CH ₃ OC ₆ H ₄ -	186-187	95a
p-C ₂ H ₅ OC ₆ H ₄ -	177-179	95a
p-ClC ₆ H ₄ -	235-236	95a

TABLE 24. Nitrogen Derivatives of Thianthrene (contd)

Substituent	Yield (%)	M.p.(°C)	Ref.
<i>p</i> -BrC ₆ H ₄ -		248-250	95a
2, 5-Cl ₂ C ₆ H ₃ -		243-245	95a
2-Naphthyl-		225-226	95a
Dibenzofuranyl-		239-240	95a
2-[(CH ₃) ₃ N] ⁺ Cl ⁻		181	301
2-[(CH ₃) ₃ N] ⁺ I ⁻	58	190	301
2-[(CH ₃) ₃ N] ⁺ NO ₃ ⁻		201	301
2-[(CH ₃) ₃ N] ⁺ <i>d</i> -camphor-10-sulfonate			301
2-[(CH ₃) ₃ N] ⁺ α -bromo- <i>d</i> -camphor- π -sulfonate		224	301
2-[(CH ₃) ₃ N] ⁺ hydrogen <i>d</i> -diacetyltartrate		171	301
2-NO ₂ -8-CH ₃ -		157	196
		159-160	319
2-NO ₂ -8-CH ₃ -5, 5, 10, 10-tetroxide		256	319
2-NH ₂ -8-CH ₃ -		130	196
2-NH ₂ -8-CH ₃ - · HCl		256	319
2-CH ₃ CONH-8-CH ₃ -		180	196
2-NO ₂ -8-Cl		215	319
2-NO ₂ -8-Cl 5, 5, 10, 10-tetroxide		251-253	319
2-NH ₂ -8-Cl · HCl		272	319
1-HO-4-(<i>p</i> -BrC ₆ H ₄ N=N-)	66	199-200	222

2-NH ₂ -8-NO ₂	198	196
2-CH ₃ CONH-8-NO ₂	205	196
1, 7-(NO ₂) ₂	45	222-223
1, 7-(NO ₂) ₂ 5, 5, 10, 10-tetroxide	58	311 (dec.)
2, 7(or 1, 8)-(NO ₂) ₂	50	214-215
2, 7-(NH ₂) ₂		102-104
		120
		238
2, 7-(NH ₂) ₂ · 2HCl		190-191
2, 7-(CH ₃ CONH-) ₂		328 (dec.)
		477a
		403
		297-298
		477a
2, 7-(p-CH ₃ CONHC ₆ H ₄ SO ₂ NH-) ₂		180 (dec.)
		238
2, 8-(NO ₂) ₂	52	242
2, 8-(NO ₂) ₂ 5, 5, 10, 10-tetroxide	75	335
2, 8-(NH ₂) ₂		192
2, 8-(NH ₂) ₂ 5, 5, 10, 10-tetroxide		>340
2, 8-(CH ₃ CONH-) ₂		246-247
2, 8-(CH ₃ CONH-) ₂ 5, 5, 10, 10-tetroxide	93	300a
	50	336-338 (dec.)
		300a
		203-205
		95b

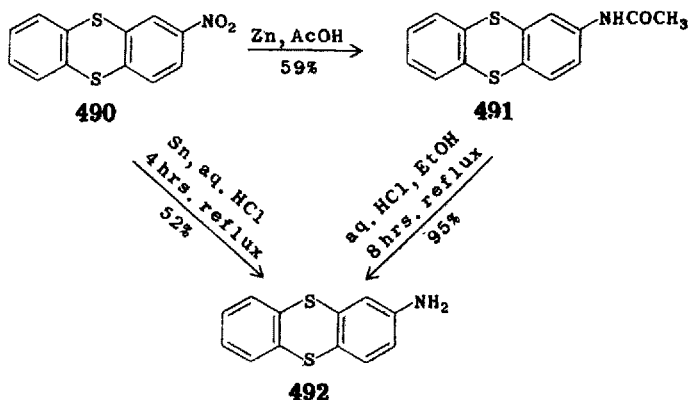


R= <i>p</i> -CH ₃ C ₆ H ₄ -	160-162	95b
<i>p</i> -C ₂ H ₅ OC ₆ H ₄ -	202-204	95b
<i>p</i> -ClC ₆ H ₄ -	283-284	95b
2,5-Cl ₂ C ₆ H ₃ -	264-266	95b
2-Naphthyl-	266-268	95b
Dibenzofuranyl-	292-293	95b
2,8-() ₂		
R= <i>p</i> -CH ₃ C ₆ H ₄ -	291-292	95b
<i>p</i> -CH ₃ OC ₆ H ₄ -	288-289	95b
<i>p</i> -C ₂ H ₅ OC ₆ H ₄ -	280-281	95b
<i>p</i> -ClC ₆ H ₄ -	>320	95b
<i>p</i> -BrC ₆ H ₄ -	>320	95b
2,5-Cl ₂ C ₆ H ₃ -	>320	95b
2-Naphthyl-	293-294	95b
Dibenzofuranyl-	310-312	95b
2-Thianthrenyl-	306-308	95b
1,3-(CH ₃) ₂ -7-NO ₂	142-144	319
1,4-Cl ₂ -7-NO ₂	220	319

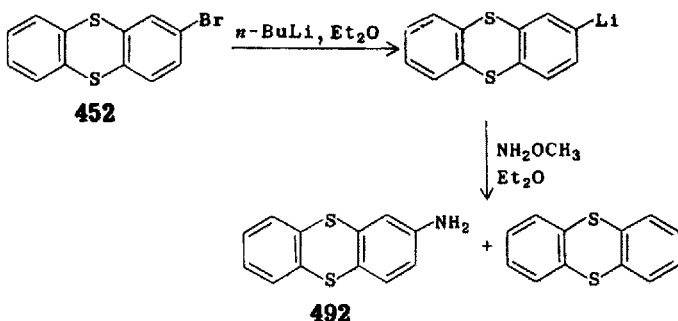
1, 4-Cl ₂ -7-NO ₂ 5, 5, 10, 10-tetroxide	251-253	319
1-CH ₃ O-4-CH ₃ -7-NO ₂	189-190	319
1-CH ₃ O-4-CH ₃ -7-NH ₂ · HCl	221	319
2, 3-(CH ₃ O-) ₂ -7-NO ₂	194	196
2, 3-(CH ₃ O-) ₂ -7-NH ₂	149	196
2, 3-(CH ₃ O-) ₂ -7-CH ₃ CONH-	180	196
1-HO-2, 4-(NO ₂) ₂	234	222
1-HO-2, 4-(NO ₂) ₂ 5(or 10)-oxide	192 (dec.)	222
1-HO-2, 4-(NO ₂) ₂ 5, 10, 10-trioxide	209-210 (dec.)	222
1-HO-2, 4-(NO ₂) ₂ 5, 5, 10, 10-tetroxide	287 (dec.)	222
1, 3-(NO ₂) ₂ -7(or 8)-CH ₃ -8(or 7)-NH ₂	203	197
1, 3-(NO ₂) ₂ -7(or 8)-CH ₃ -8(or 7)-[(CH ₃ CO) ₂ N-]	168	197
1, 3, 8-(or 7)-(NH ₂) ₃ -7(or 8)-CH ₃ -		197

acid reacted with it to give the same oxide, the position of the oxygen cannot be considered to be proved. Reduction of the monoxide with hydrogen bromide in hot acetic acid regenerated 2-nithrothianthrene, no bromination of the unsubstituted ring taking place in spite of the high temperature of the reaction. More concentrated nitric acid gave 2-nitrothianthrene 5,10-dioxide, only one form being isolated, while chromic anhydride gave the 5, 5, 10, 10-tetroxide.

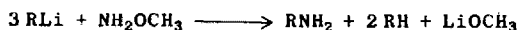
Krishna³¹⁸ reported the formation of 2-aminothianthrene (**492**) by reduction of the nitro compound with zinc and acetic acid. However, Keats³⁰¹ claimed that the compound was actually 2-acetamidothianthrene (**491**), and this was confirmed by Gilman and co-workers.^{215,218} Acid hydrolysis of the amide gave 2-aminothianthrene,^{218,301} as did reduction of 2-nitrothianthrene with tin and aqueous hydrochloric acid.²¹⁸



Gilman and Swayampati²¹⁸ also prepared 2-aminothianthrene from 2-bromothianthrene (**452**) by metalation and reaction with hydroxylamine O-methyl ether.



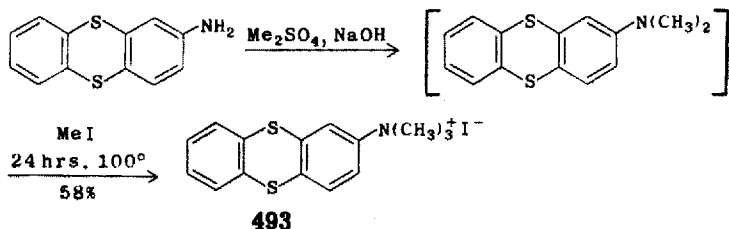
A 63% yield of 2-aminothianthrene and a 76% yield of thianthrene were obtained based on the following equation:



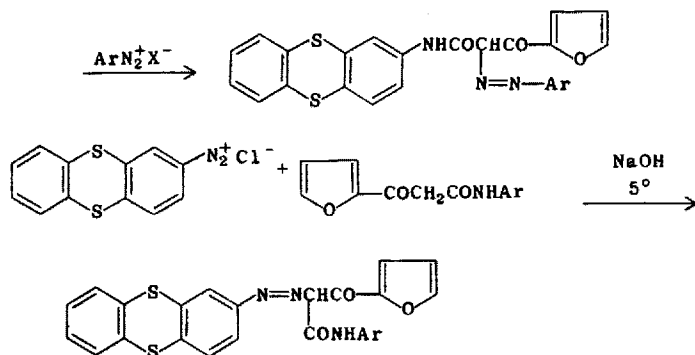
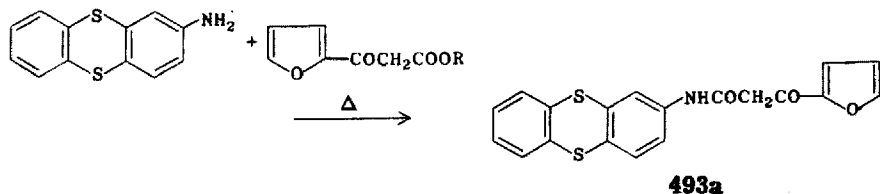
C₄S₂ Ring Systems

The identity of the amine and amide with those prepared according to Krishna³¹⁸ and Keats³⁰¹ served to prove the structure of 2-bromothianthrene, since it has been shown in numerous instances that metalation takes place without rearrangement.

Bennett, Lesslie, and Turner⁴⁵ prepared the *d*-camphorsulfonate salt of 2-aminothianthrene but, as already mentioned, it could not be resolved. Keats³⁰¹ methylated 2-aminothianthrene, but was unable to resolve a number of salts of the quaternary ammonium compound (493) with optically active acids.



2-Aminothianthrene reacts as a typical aromatic amine. Thus, both Krishna³¹⁸ and Keats³⁰¹ diazotized it and coupled the diazonium salt with compounds such as β -naphthol; in Krishna's case the amide must have been hydrolyzed during diazotization. Krishna succeeded also in deaminating the diazonium salt to thianthrene with ethanol. Cerniàni^{95a} prepared two types of cotton and rayon dyes, reportedly of good wash fastness, one by coupling a diazonium salt with 2-(2-furoylacetamido)-thianthrene (493a), and the second by coupling 2-thianthrenyl diazonium chloride with 2-furoylacetanilides.

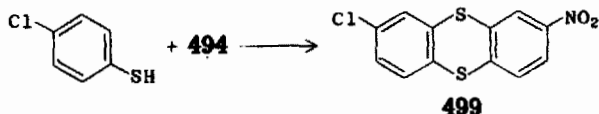


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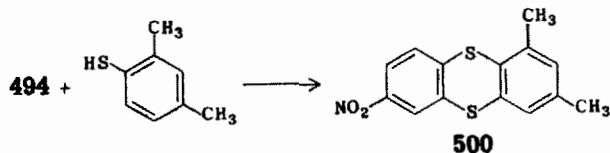
A number of azo wool dyes were prepared by coupling 2-thianthrenyl diazonium chloride with substituted naphthols—chromotropic acid, H-acid, and R-acid.^{95c}

Krishna³¹⁹ applied the sulfinic acid synthesis to the preparation of a number of substituted nitrothianthrenes, starting in each case with 2-chloro-5-nitrobenzenesulfinic acid (**494**). Thus, *p*-methylthiophenol gave 2-nitro-8-methylthianthrene (**495**), reduced with zinc and hydrochloric acid to 2-amino-8-methylthianthrene (**496**) and oxidized with potassium permanganate to 2-nitro-8-methylthianthrene 5, 5', 10, 10'-tetroxide (**497**). Fries, Koch, and Stuckenbrock¹⁹⁶ claimed that solution of the amine (**496**) in concentrated sulfuric acid converted it into 2-amino-8-methylthianthrene-1-sulfonic acid (**498**), but they offered no evidence to prove the position of the sulfonate group. (See p. 1199).

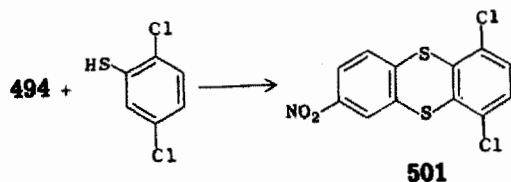
In a similar fashion Krishna³¹⁹ found that *p*-chlorothiophenol with **494** gave 2-chloro-8-nitrothianthrene (**499**)



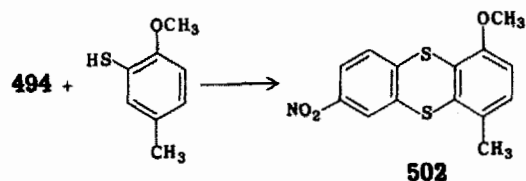
With 2, 4-dimethylthiophenol the product was 1, 3-dimethyl-7-nitrothianthrene (**500**).



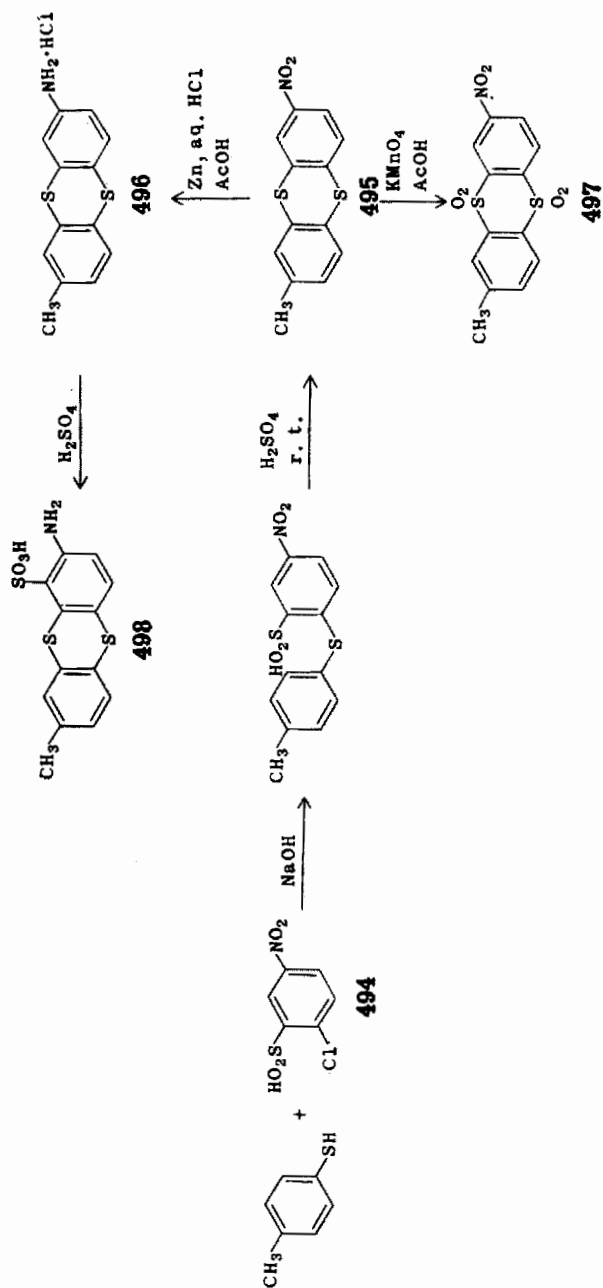
With 2, 5-dichlorothiophenol the product was 1, 4-dichloro-7-nitrothianthrene (**501**).



With 2-methoxy-5-methylthiophenol the product was 1-methoxy-4-methyl-7-nitrothianthrene (**502**).

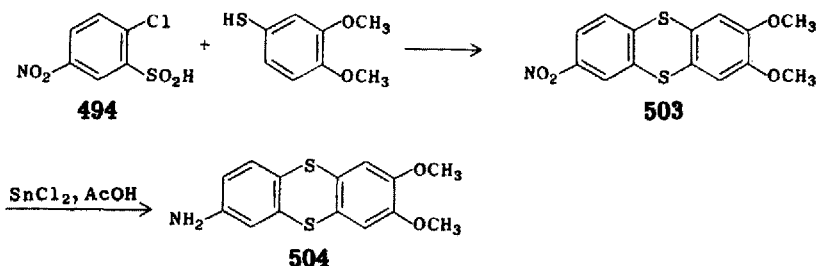


C_4S_2 Ring Systems



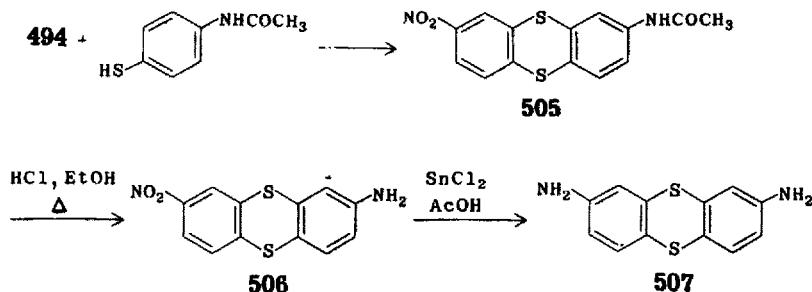
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In each case the synthesis appears to be unequivocal. Ring closure was carried out in sulfuric acid at room temperature for 0.5-3 hours, and sulfoxide in the products was removed by treatment with hydrogen bromide in acetic acid. All the thianthrenes were reduced to the amine hydrochlorides and oxidized to the nitro disulfones. Fries, Koch, and Stuckenbrock¹⁹⁶ applied the same synthesis to 2,3-dimethoxy-7-nitrothianthrene (503). This was reduced to the corresponding amine (504).



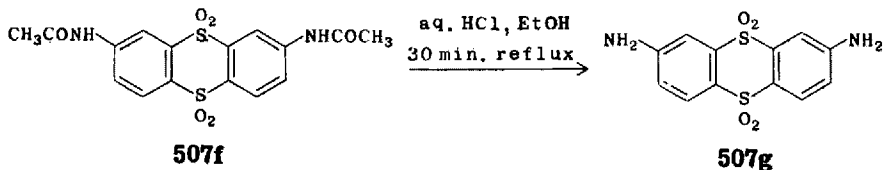
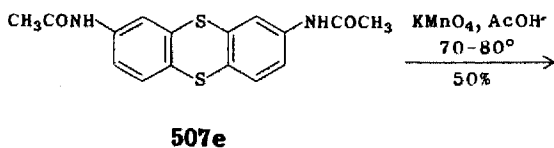
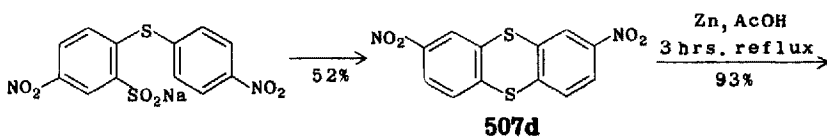
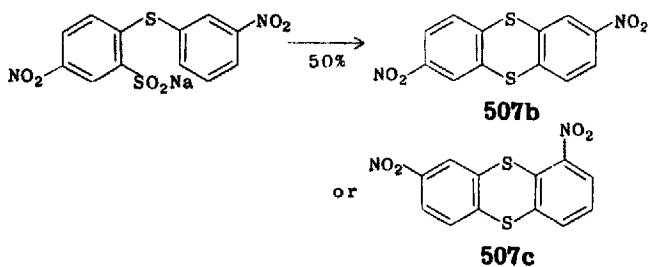
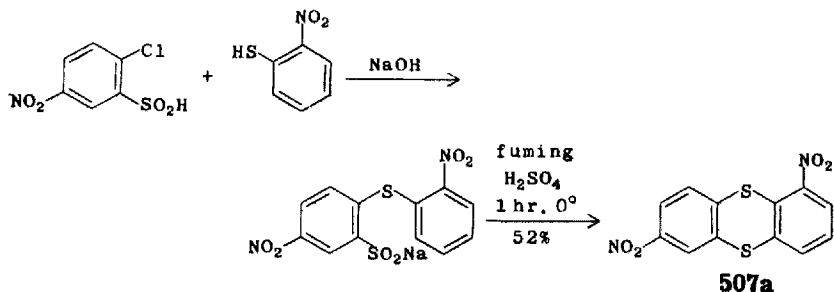
It is conceivable, of course, that ring closure took place to give 1,2-dimethoxy-7-nitrothianthrene instead.

The identity of the diaminothianthrenes is in a considerable state of confusion. Fries, Koch, and Stuckenbrock¹⁹⁶ condensed 494 with *p*-acetamidothiophenol to form, presumably, 2-acetamido-8-nitrothianthrene (505), which was hydrolyzed to the nitro-amine (506) and reduced to 2,8-diaminothianthrene (507), m.p. 192°.



Kawai and Ueda^{300a} condensed 494 with *o*-, *m*-, and *p*-nitrothiophenol and isolated 1,7-dinitrothianthrene (507a), 2,7- (507b) or 1,8-dinitrothianthrene (507c), and 2,8-dinitrothianthrene (507d), respectively. The 2,8-dinitro compound was reduced to 2,8-diacetamidothianthrene (507e), m.p. 246-247°, which was oxidized to the disulfone (507f). The disulfone was hydrolyzed to the 2,8-diamino disulfone (507g). Although there is no reason for doubting these syntheses, it is unfortunate that Kawai and Ueda prepared no derivatives which could have been compared with the compounds prepared by Fries and co-workers.¹⁹⁶

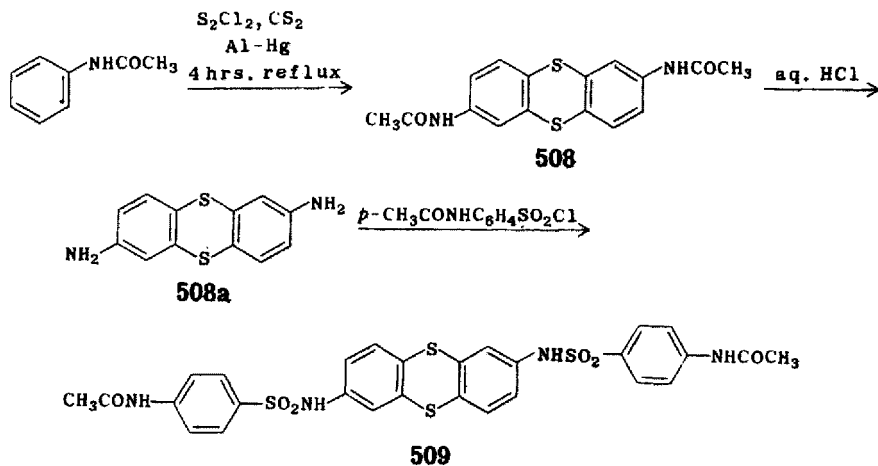
C_4S_2 Ring Systems



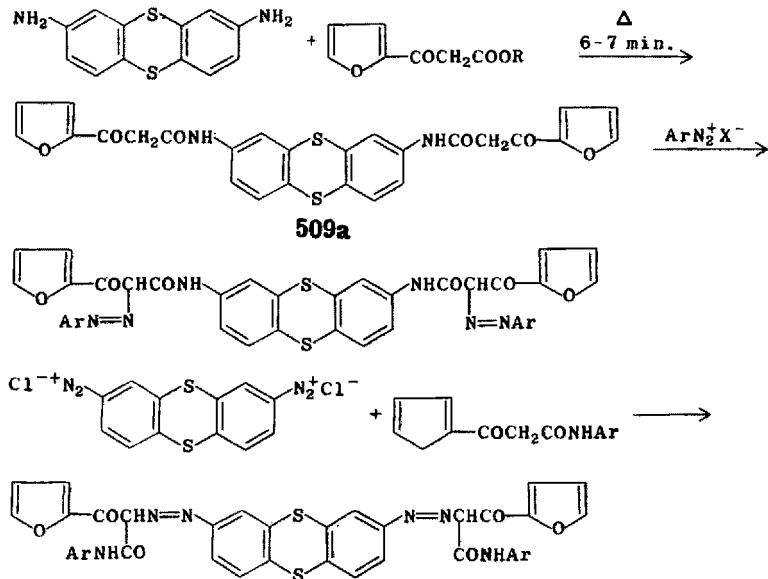
Rây⁴⁰³ condensed acetanilide with sulfur monochloride using his aluminum-mercury couple as catalyst. His diacetamidothianthrene, m.p. 198-200°, and diaminothianthrene, m.p. 102-104°, are apparently different from the 2,8-derivatives described above and should therefore be the

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2, 7-derivatives (**508** and **508a**). Guha and Dokras²³⁸ described the hydrolyzed product as 2, 7-diaminothianthrene (**508a**), m.p. 120°; treatment with *p*-acetamidobenzenesulfonyl chloride yielded, presumably, 2, 7-bis-(*N*⁴-acetylsulfanilamido)thianthrene (**509**).

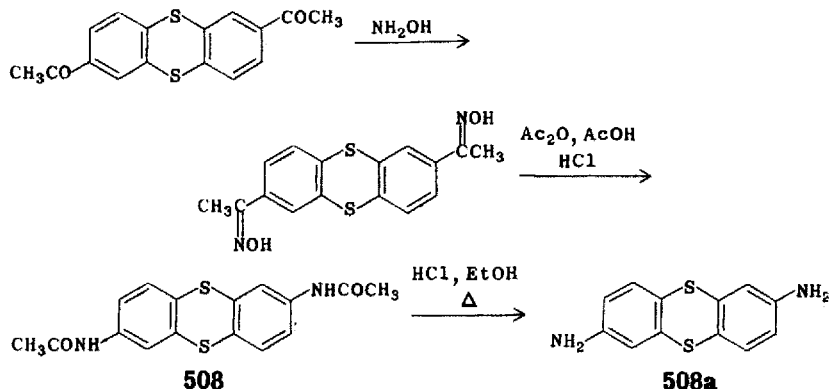


Sen and Rây⁴⁵⁰ described several coupling reactions of the diazotized diaminothianthrene (**508a**) with β -naphthol, resorcinol, and sulfanilic acid. The products were useless as dyes. Cerniâni^{95b} reported the synthesis of two types of useful washfast cotton and rayon dyes, one by the coupling of aryl diazonium salts with 2, 8-bis(2-furoylacetamido)-thianthrene (**509a**), and the other by coupling of tetrazotized 2, 8-diaminothianthrene with 2-furoylacetanilides.



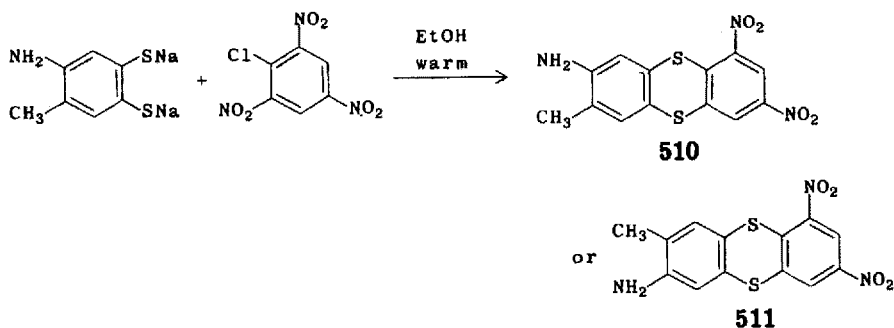
C₄S₂ Ring Systems

Suszko and Ratajczak^{477a} recently described the synthesis of 2, 7-diacetamidothianthrene (**508**) by a Beckmann rearrangement of 2, 7-diacetylthianthrene dioxime. Unfortunately, the source of the diacetyl derivative is not given in Chemical Abstracts, and its melting point does not agree with the reported melting point of 2, 7-diacetylthianthrene. Hydrolysis of the amide yielded 2, 7-diaminothianthrene (**508a**).



The melting point of **508**, 297-298°, does not agree with previously reported melting points of either 2, 7- or 2, 8-diacetamidothianthrene, and, although the melting point of **508a**, 190-191°, agrees with the melting point of 2, 8-diaminothianthrene reported by Fries and co-workers,¹⁹⁶ the authors claim that the two compounds are different. It is quite apparent that no unequivocal conclusions can be drawn about the structures of these compounds without additional work.

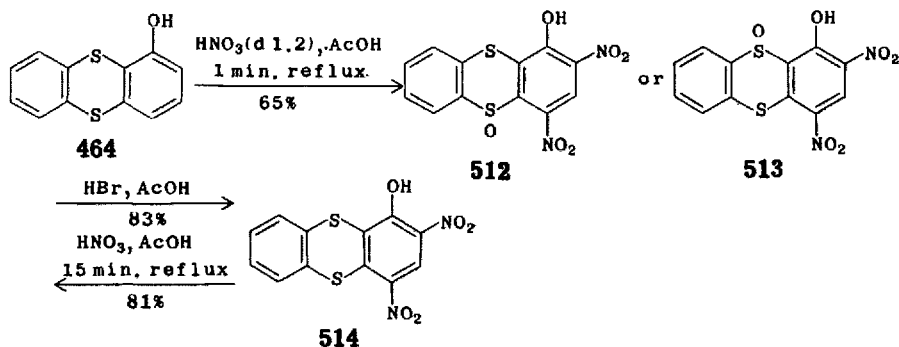
Frölich¹⁹⁷ described an interesting thianthrene synthesis which involved the basic condensation of picryl chloride with 2-methyl-4, 5-dimercaptoaniline, both a chlorine and a nitro group being displaced from the picryl chloride to yield either 1, 3-dinitro-7-methyl-8-aminothianthrene (**510**) or 1, 3-dinitro-7-amino-8-methylthianthrene (**511**).



The author claimed that treatment with acetic anhydride and sodium acetate gave an imide with two acetyl groups on the amine nitrogen.

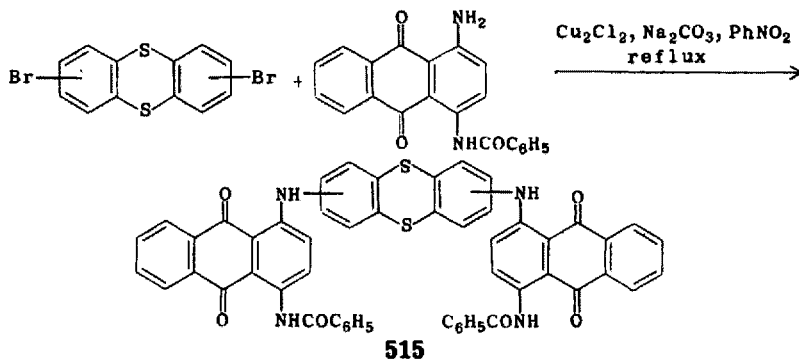
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The inability to nitrate thianthrene has been mentioned on numerous occasions; oxidation occurs instead. Gilman and Swayampati²²² found that even at -30° the product is thianthrene α -5,10-dioxide. These authors found, however, that thianthren-1-ol (**464**) could be nitrated, the product being very probably 2,4-dinitrothianthren-1-ol 5-oxide (**512**) or the corresponding 10-oxide (**513**). Infrared analysis showed that both nitro groups are on the same ring; the most likely positions are *ortho* and *para* to the hydroxyl group. The location of the oxide group could not be determined. Reduction with hydrogen bromide yielded 2,4-dinitrothianthren-1-ol (**514**). It is interesting that oxidation of **514** yielded the same monoxide as was formed by nitration of thianthren-1-ol and not a mixture of the two possible oxides.



Oxidation of 2,4-dinitrothianthren-1-ol 5 (or 10)-oxide with hydrogen peroxide in acetic acid stopped at the trioxide stage. The compound was formulated as 2,4-dinitrothianthren-1-ol 5,10,10-trioxide, the assumption being made that the nitro group in the 4-position offers steric hindrance to oxidation of the sulfur in the 5-position. The disulfone, 2,4-dinitrothianthren-1-ol 5,5,10,10-tetroxide was prepared by nitration of thianthren-1-ol 5,5,10,10-tetroxide.

A mixture of 2,7- and 2,8-dibromothianthrene was reacted with 1-amino-4-benzamidoanthraquinone to give a bis(4-benzamido-1-anthraquinonylamino)thianthrene (**515**), which dyed cotton violet.⁴⁶⁰



6. Acyl Derivatives

Few acyl derivatives of thianthrene have been reported; these are listed in Table 25. Burtner and Brown⁸¹ claimed that thianthrene reacts with succinic anhydride in the presence of aluminum chloride to give γ -oxo- γ -2-thianthrenylbutyric acid (**516**); substitution in the 2-position appears to be a reasonable assumption. According to Burtner⁸² bromination of **516** yielded β -bromo- γ -oxo- γ -2-thianthrenylbutyric acid (**517**) which, on dehydrohalogenation, gave γ -oxo- γ -2-thianthrenylcrotonic acid (**518**); however, properties of the last two compounds were not given.

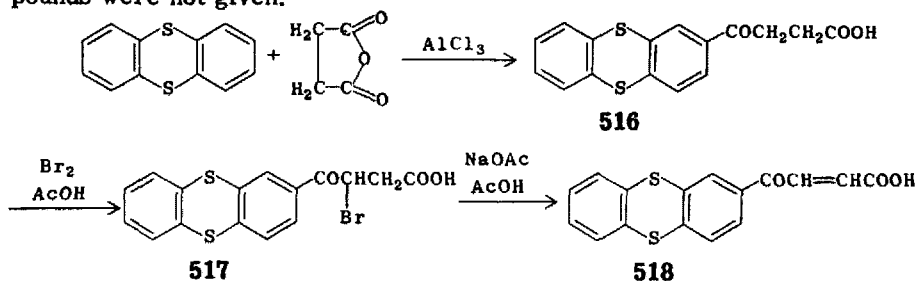
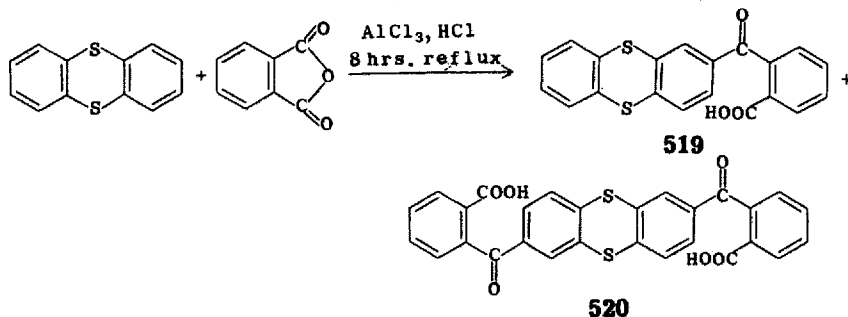


TABLE 25. Acyl Derivatives of Thianthrene

Substituents	Yield (%)	M.p.(°C)	Ref.
2-(HO ₂ CCH ₂ CH ₂ CO-)		167-169	81
2-(HO ₂ CCH=CHCO-)			82
2-(<i>o</i> -HO ₂ CC ₆ H ₄ CO-)	48	219-221	439
(?)-(CH ₃ CO-) ₂		88-91	403
2, 7-(CH ₃ CO-) ₂		157	491
2, 7-(CH ₃ CO-) ₂ 5, 5, 10, 10-tetroxide		247-248	477a
2, 7-(CH ₃ C(=NOH) ₂)		234-235	477a
2, 7-(CH ₃ C(=NOCOCH ₃) ₂)		156-158	477a
2, 7-(CH ₃ C(=NNHC ₆ H ₅) ₂)		284-286	477a
2, 7-(ClCH ₂ CO-) ₂		177	491
2, 7-(ClCH ₂ CO-) ₂ 5, 5, 10, 10-tetroxide		209-213	492
2, 7-(C ₅ H ₁₀ NCH ₂ CO-) ₂		129	491

Substituents	Yield (%)	M.p.(°C)	Ref.
2, 7- $\left(\text{C}_5\text{H}_{10}\text{NCH}_2\underset{\text{OH}}{\text{CH}}-\right)_2$		141	491
2, 7-($o\text{-HO}_2\text{CC}_6\text{H}_4\text{CO-}$) ₂	47		439
2, 7-($o\text{-HO}_2\text{CC}_6\text{H}_4\text{CO-}$) ₂ -3, 8-($\text{CH}_3\text{-}$) ₂	73		439

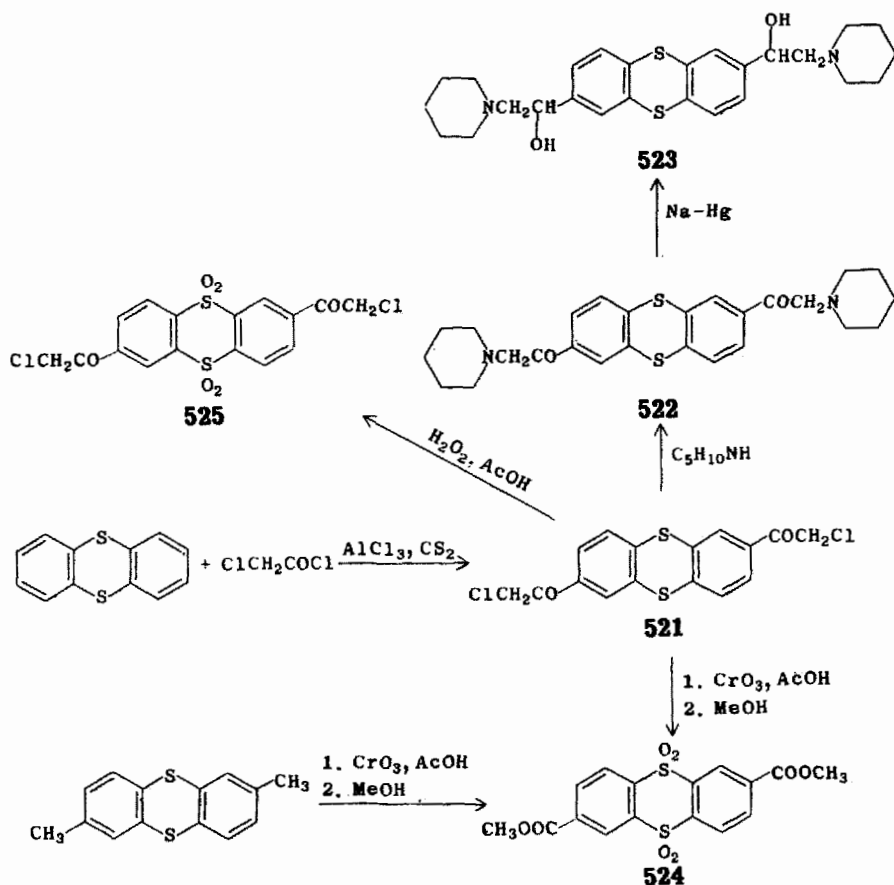
Scholl and Seer⁴³⁹ carried out a Friedel-Crafts reaction between thianthrene and phthalic anhydride and isolated a mixture of 2-(*o*-carboxybenzoyl)thianthrene (**519**) and 2, 7-bis(*o*-carboxybenzoyl)thianthrene (**520**). The latter was not obtained pure; by analogy with the bromination of thianthrene, it presumably contained some of the 2, 8-isomer.



The same reaction with 2, 7-dimethylthianthrene yielded 2, 7-bis(*o*-carboxybenzoyl)-3, 8-dimethylthianthrene.

Tomita⁴⁹¹ reacted thianthrene with acetyl chloride to give 2, 7-diacetylthianthrene (**525a**) and with chloroacetyl chloride to give 2, 7-bis(chloroacetyl)thianthrene (**521**). **521** reacted with piperidine to give 2, 7-bis(piperidylacetyl)thianthrene (**522**), reduction of which yielded 2, 7-bis(α -hydroxy- β -piperidylethyl)thianthrene (**523**). The position of acyl groups was proved by oxidation with chromic anhydride to thianthrene-2, 7-dicarboxylic acid 5, 5, 10, 10-tetroxide. The dimethyl ester (**524**) was shown to be identical with that prepared by esterification of the oxidation product of 2, 7-dimethylthianthrene. Oxidation of 2, 7-bis(chloroacetyl)thianthrene with hydrogen peroxide yielded 2, 7-bis(chloroacetyl)thianthrene 5, 5, 10, 10-tetroxide (**525**).

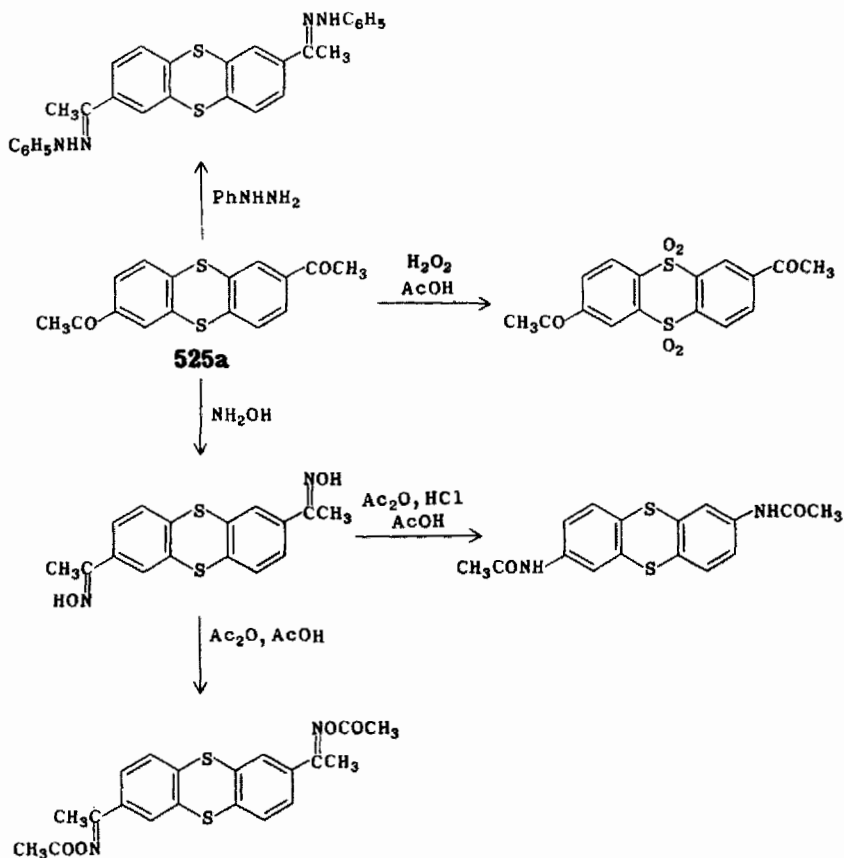
C₄S₂ Ring Systems



According to Tomita and Ikeda⁴⁹² thianthrene 5, 5, 10, 10-tetroxide cannot be acylated, the sulfone groups inactivating the rings.

Tomita's synthesis of 2, 7-diacetylthianthrene (525a) would appear to be unequivocal. It is difficult to reconcile his reported melting point of 157° with the melting point of 179-181° reported by Suszko and Ratajczak^{477a} for 2, 7-diacetylthianthrene prepared by an unstated procedure, unless Tomita's compound was quite impure. The importance of this question to the structure of the diaminothianthrenes has already been discussed (see section III K-5). Unfortunately, here too, Suszko and Ratajczak made no attempt to prepare derivatives which could be compared with reported derivatives (see section III K-7), although several reactions were carried out.

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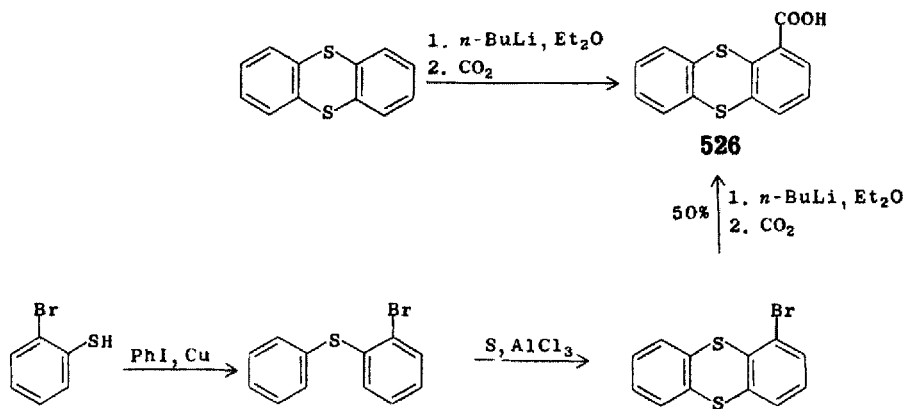
The only reported synthesis of an acylthianthrene by ring closure is that of Rây,⁴⁰³ who described the reaction of acetophenone with sulfur monochloride using an aluminum amalgam catalyst, the product being presumably a diacetylthianthrene. That the reaction occurred at all is surprising, in view of the deactivating effect of the acetyl group, and it is difficult to predict the positions of the acetyl groups. The compound was reported to form a phenylhydrazone, which melted with decomposition, and oxidation with nitric acid yielded benzoic acid. In view of the results obtained by Tomita⁴⁹¹ on oxidizing 2,7-bis(chloroacetyl)thianthrene, the formulation of Rây's compound as a thianthrene derivative appears to require confirmation; certainly it is not the 2,7-derivative.

7. Carboxylic Acids

Thianthrenecarboxylic acids which have been reported in the literature are listed in Table 26. Gilman and Stuckwisch²¹⁵ prepared thianthrene-1-carboxylic acid (**526**) by two routes, metalation of thianthrene

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followed by carbonation and reaction of 1-bromothianthrene with *n*-butyllithium followed by carbonation; the acids prepared by the two routes were identical, melting at 217-218°.



Other evidence agreed with the conclusion reached here that thianthrene metalates in the 1-position. Further work by Gilman and Swayampati²²¹ on the metalation of thianthrene showed that the thianthrenecarboxylic acid prepared in the early work was not completely pure; the pure acid is yellow and melts at 224-225°. Thermal decarboxylation regenerated thianthrene.²¹⁵

Gilman and Swayampati^{217,220,221} also investigated the metalation of thianthrene 5-oxide and 5,5-dioxide. The sulfoxide reacted with *n*-butyllithium to give a low yield of thianthrene-1-carboxylic acid, the major reaction being one of cleavage of the thianthrene ring (see section III K-10). The sulfone (432), on the other hand, metalated more readily than thianthrene and, at -70°, gave a 41% yield of thianthrene-1-carboxylic acid 10,10-dioxide (527). The structure was assigned on the following basis. Oxidation with hydrogen peroxide gave thianthrene-1-carboxylic acid 5,5,10,10-tetroxide (528), identical with a specimen prepared by the oxidation of thianthrene-1-carboxylic acid (526).

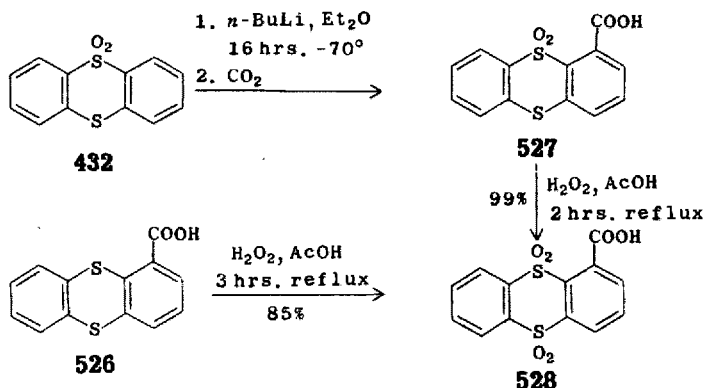
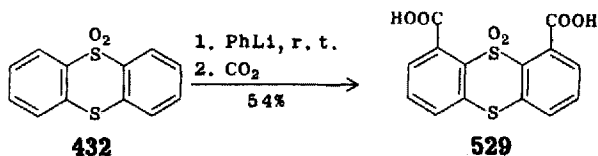


TABLE 26. Thianthrenecarboxylic Acids

Substituent	Yield (%)	M.p. (°C)	Ref.
1-CO ₂ H	28	224-225	215, 217, 220, 221
1-CO ₂ H 10, 10-dioxide	23	255-256	221
1-CO ₂ H 5, 5, 10, 10-tetroxide	99	307-308	221
2-CO ₂ H	6	224	45
	70	227-228	221
2-CO ₂ H <i>l</i> -α-phenylethylamine salt		286-288	45
2-CO ₂ H 5, 5, 10, 10-tetroxide	87	302-303	221
2-CONH ₂		227	45
2-CONHC ₆ H ₅		200-201	45
1, 9-(CO ₂ H) ₂ 10, 10-dioxide	54	364 (dec.)	221
(?)-(CO ₂ H) ₂		204	404
2, 7-(CO ₂ H) ₂		350	477a
2, 7-(CO ₂ H) ₂ 5, 5, 10, 10-tetroxide		>300	491
2, 7-(CO ₂ CH ₃) ₂		185-186	477a
2, 7-(CO ₂ CH ₃) ₂ 5, 5, 10, 10-tetroxide		202	491
2 (or 1)-CO ₂ H-7 (or 8)-NO ₂		272-273	319
2 (or 1)-CO ₂ H-7 (or 8)-NO ₂ 5, 5, 10, 10-tetroxide		>285	319
2 (or 1)-CO ₂ H-7 (or 8)-NH ₂ · HCl		239	319

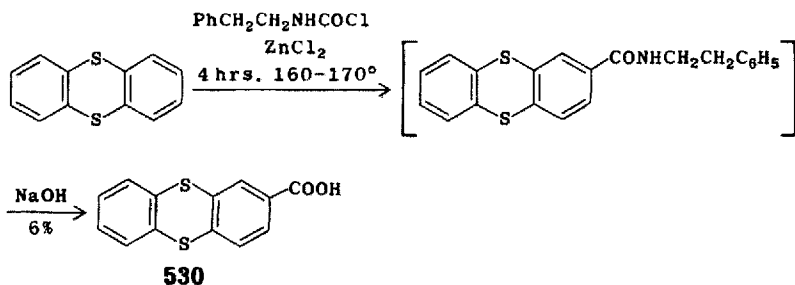
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This showed that metalation occurred at either the 1-position or the 4-position. Thianthrene is unattacked by *n*-butyllithium at -70° , indicating that no metalation *ortho* to a sulfur atom takes place at this low temperature. Furthermore, dibenzothiophene 5,5-dioxide is metalated at -30° , whereas dibenzothiophene is unattacked at -10° , showing that metalation *ortho* to a sulfone group takes place more readily than *ortho* to a sulfur atom. Thus, the assignment of structure is reasonable. When thianthrene 5,5-dioxide was metalated at a higher temperature, some dicarboxylic acid was formed as well. The preferred procedure for the preparation of the dicarboxylic acid was metalation with phenyllithium at room temperature.

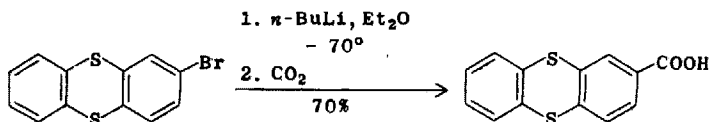


The compound was assigned the structure thianthrene-1,9-dicarboxylic acid 10,10-dioxide (**529**) on the basis of the infrared spectrum, which showed substitution in both rings. Since the first carboxyl group is *ortho* to the sulfone group, it is reasonable to assume that the second carboxyl group also enters *ortho* to the sulfone.

Thianthrene-2-carboxylic acid (**530**) was first prepared by Bennett, Lesslie, and Turner⁴⁵ by the acylation of thianthrene with phenylethyl-carbamyl chloride followed by hydrolysis.



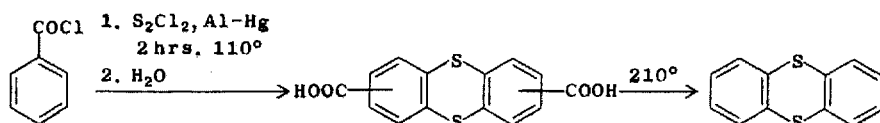
Bennett, Lesslie, and Turner made no attempt to locate the position of the carboxyl group, but Gilman and Stuckwisch²¹⁵ repeated the preparation and claimed that the acid is different from that prepared by carbonation of 1-thianthrenyllithium. Gilman and Swayampati²²¹ prepared thianthrene-2-carboxylic acid from 2-bromothianthrene.



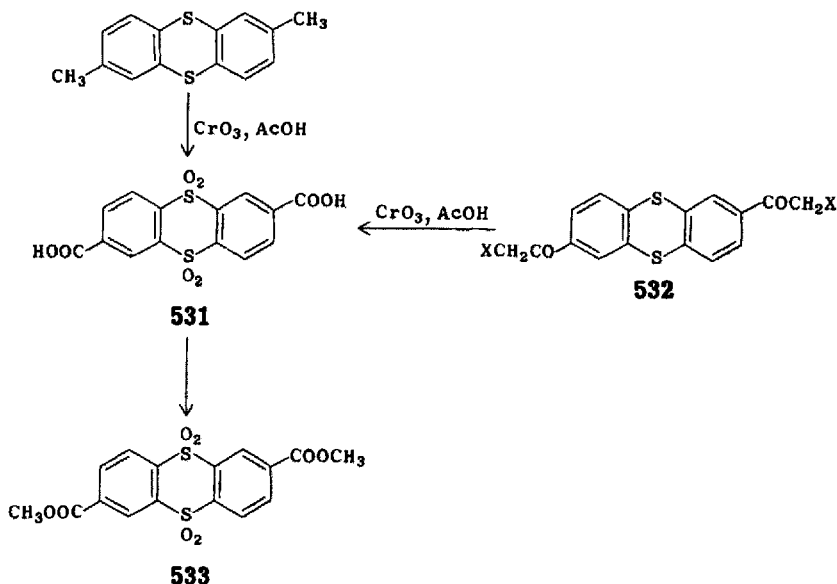
In spite of the similarity in melting points of thianthrene-1-carboxylic acid and thianthrene-2-carboxylic acid, as well as of their disulfones,

Gilman and Swayampati believed the two to be different; the 1-acid is yellow, while the 2-acid is white. The formation of thianthrene-2-carboxylic acid by a Friedel-Crafts reaction is in agreement with other reported acylations of thianthrene (see section III K-6). Bennett, Lesslie, and Turner⁴⁵ prepared several derivatives of the carboxyl group; the salt with 1- α -phenylethylamine could not be resolved, a further indication of the facile inversion of the thianthrene nucleus.

Rây⁴⁰³ reacted benzoyl chloride with sulfur monochloride using an aluminum amalgam catalyst and isolated, after hydrolysis, a thianthrenedicarboxylic acid melting at 204°. The compound lost carbon dioxide at 210° and yielded thianthrene. The location of the carboxyl groups was not determined.

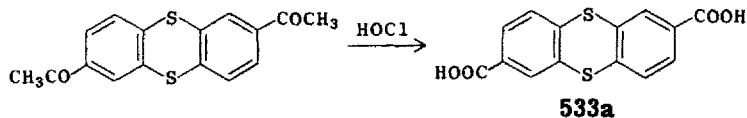


Tomita⁴⁹¹ oxidized 2, 7-dimethylthianthrene, 2, 7-diacetylthianthrene (532, X = H), and 2, 7-bis(chloroacetyl)thianthrene (532, X = Cl) with chromic anhydride, all three derivatives yielding thianthrene-2, 7-dicarboxylic acid 5, 5, 10, 10-tetroxide (531), identified as the dimethyl ester (533).

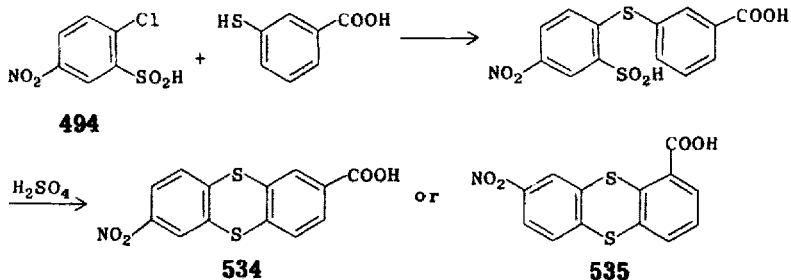


Suszko and Ratajczak^{447a} oxidized their 2, 7-diacetylthianthrene, prepared by an unspecified procedure (see section III K-6), to, presumably, thianthrene-2, 7-dicarboxylic acid (533a); the dimethyl ester was also prepared.

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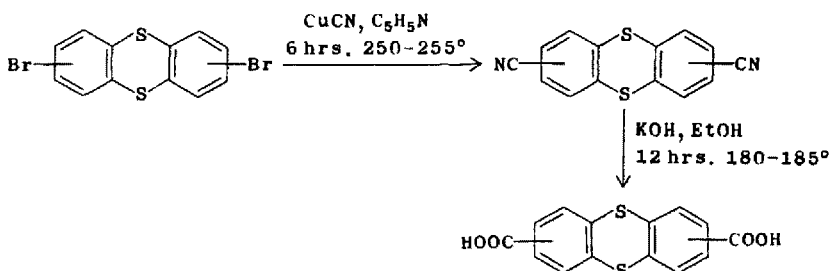


Krishna³¹⁹ prepared a nitrothianthrenecarboxylic acid from *m*-mercaptobenzoic acid and 2-chloro-5-nitrobenzenesulfonic acid (**494**). The compound is either 7-nitrothianthrene-2-carboxylic acid (**534**) or 8-nitrothianthrene-1-carboxylic acid (**535**), the former being more likely.



Oxidation with potassium permanganate gave the disulfone and reduction with zinc and hydrochloric acid gave the hydrochloride of the amino-acid.

Several Ciba patents^{107,108} describe the preparation of a mixture of thianthrene-2, 7- and -2, 8-dicarboxylic acids from a mixture of the two dibromothianthrenes (see section III K-3).



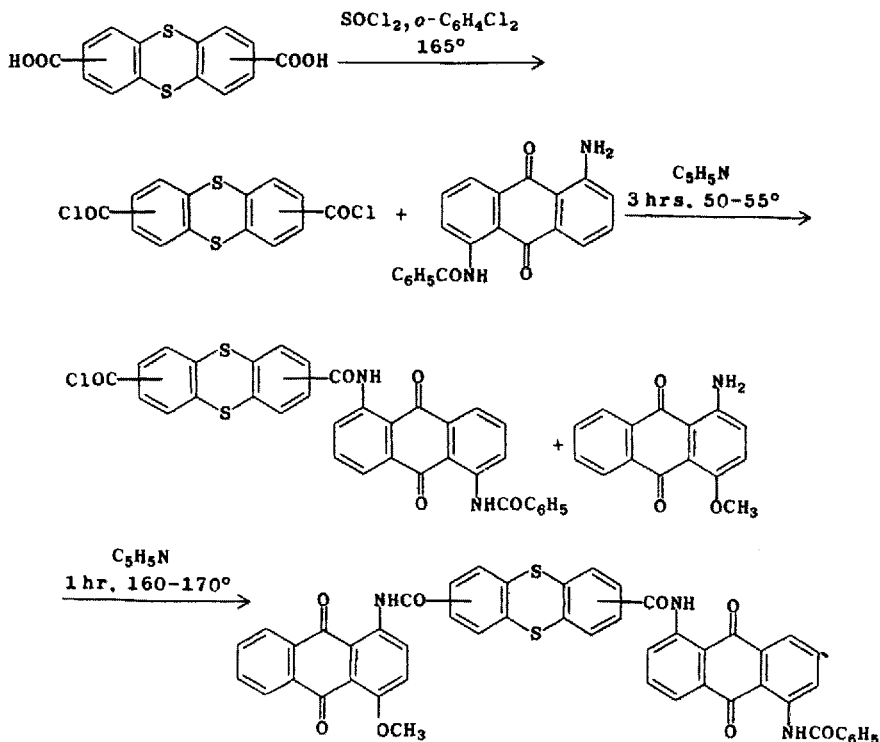
The dicarboxylic acids, or their partially oxidized derivatives formed by treatment with sodium hypochlorite, were condensed with aminoanthraquinones to form vat dyes.^{102-120,306,307,363-365,461,478} These dyed cotton various shades of yellow. The compounds which have been described are listed in Table 27.

TABLE 27. Thianthrenedicarboxamide Vat Dyes

Compound	Dyes cotton	Ref.
<i>N,N'</i> -Bis(4-methoxy-1-anthraquinonyl)	fast orange	102
<i>N,N'</i> -Bis(3-benzoyl-1-anthraquinonyl)	yellow	103
<i>N,N'</i> -Bis(1-anthraquinonyl)	fast yellow	104
<i>N,N'</i> -Bis(4-benzamido-1-anthraquinonyl)	scarlet-red	105
<i>N,N'</i> -Bis(5-benzamido-1-anthraquinonyl)	fast yellow	461
<i>N,N'</i> -Bis(5-benzamido-1-anthraquinonyl), monoxide	fast golden yellow	106
<i>N,N'</i> -Bis[5-(3-methylsulfonylbenzamido)-1-anthraquinonyl]		307
<i>N,N'</i> -Bis(5-benzamido-1-anthraquinonyl), oxides	fast yellow	107
<i>N</i> -(5-Benzamido-1-anthraquinonyl)- <i>N'</i> -(4-methoxy-1-anthraquinonyl)		108
<i>N</i> -(5-Benzamido-1-anthraquinonyl)- <i>N'</i> -(5-methoxy-1-anthraquinonyl)	yellow	109
<i>N</i> -(1-Anthraquinonyl)- <i>N'</i> -(5-methoxy-1-anthraquinonyl)	greenish yellow	110
<i>N</i> -(5-Benzamido-1-anthraquinonyl)- <i>N'</i> -(2-anthraquinonyl)	yellow	111
<i>N</i> -(5-Methoxy-1-anthraquinonyl)- <i>N'</i> -(2-anthraquinonyl)	greenish yellow	112
<i>N,N'</i> -Bis(6-chloro-1-anthraquinonyl)	fast yellow	113-115, 478
<i>N,N'</i> -Bis(6-chloro-1-anthraquinonyl), oxides	fast yellow	113, 116, 478
<i>N,N'</i> -Bis(7-chloro-1-anthraquinonyl)	fast yellow	115, 478
<i>N</i> -(6-Chloro-1-anthraquinonyl)- <i>N'</i> -(7-chloro-1-anthraquinonyl)	fast yellow	113, 478

<i>N, N'</i> -Bis(4-amino-3- <i>p</i> -chlorobenzoyl)-1-anthraquinonyl)	363
<i>N, N'</i> -Bis(5- <i>o</i> -chlorobenzamido-1-anthraquinonyl)	fast yellow
<i>N, N'</i> -Bis(5- <i>o</i> -fluorobenzamido-1-anthraquinonyl)	golden yellow
<i>N, N'</i> -Bis[5-(4-chloro-2-fluorobenzamido)-1-anthraquinonyl]	fast yellow
<i>N, N'</i> -Bis[5-(5-chloro-2-fluorobenzamido)-1-anthraquinonyl]	fast yellow

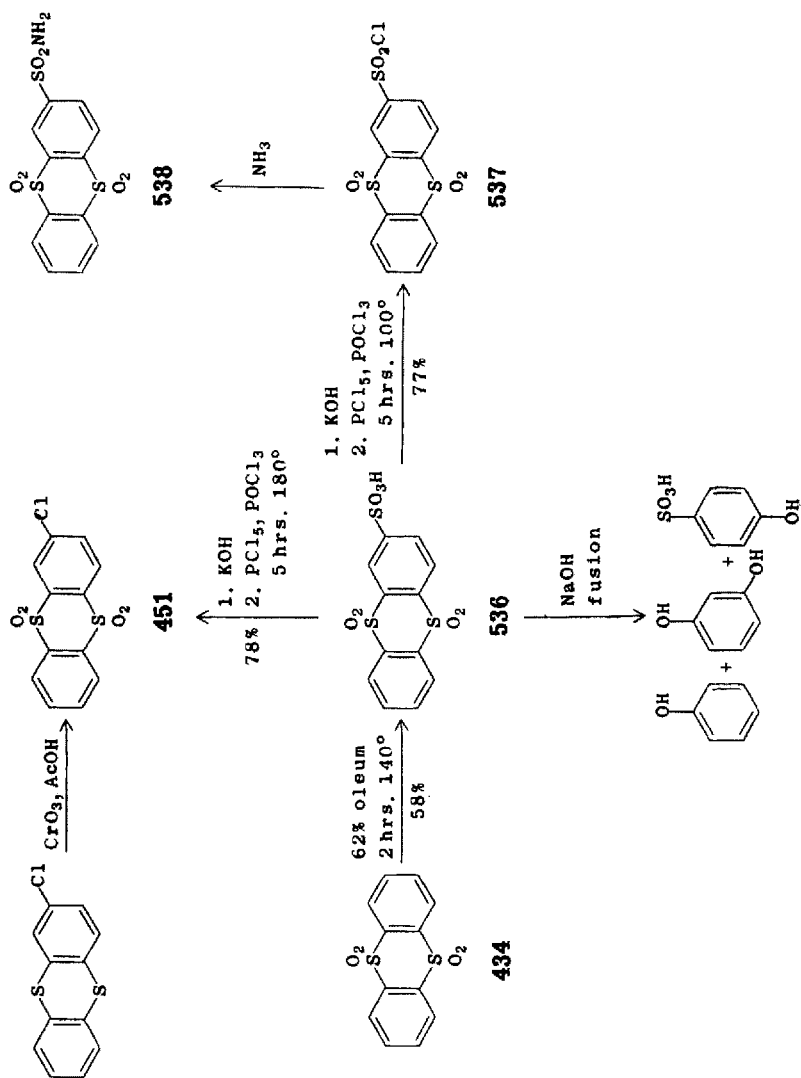
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8. Sulfonic Acids

Few thianthrenesulfonic acids have been prepared and adequately characterized, as shown in Table 28. Genvresse^{209,212} was the first to show that thianthrene reacted with fuming sulfuric acid to give a water-soluble compound with the empirical formula $C_6H_4S_2O_3$; this dyed wool, silk, and cotton reddish brown. Genvresse wrote an unreasonable formula for this compound, and it was Deuss¹⁵⁷ who formulated it as a thianthrenedisulfonic acid, $C_{12}H_8S_4O_6$.

The only reasonably well characterized compound in this class is thianthrene-2-sulfonic acid 5, 5, 10, 10-tetroxide (**536**), prepared by Kozlov, Fruktova, and Shemyakina.³¹¹ Thianthrene 5, 5, 10, 10-tetroxide (**434**) was found to be very inert to sulfonation, but reaction with a large excess of oleum in a sealed tube gave a monosulfonic acid. A variety of salts were prepared, as well as a sulfonyl chloride (**537**) and sulfonamide (**538**). The compound was shown to be the 2-sulfonic acid by reaction with phosphorus pentachloride; the chlorothianthrene 5, 5, 10, 10-tetroxide (**451**) isolated was identical with that prepared by the oxidation of an authentic sample of 2-chlorothianthrene. Further evidence for the structure was obtained from alkaline fusion; it would be difficult to explain the products as being formed from the 1-sulfonic acid.

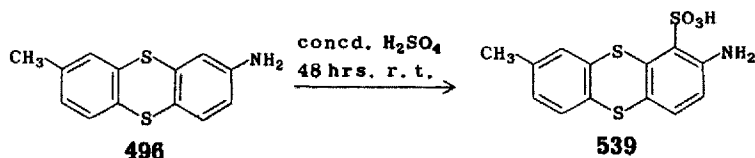


Kozlov and Stakhovskaya³¹² also converted the 2-sulfonic acid into thianthren-2-ol 5, 5, 10, 10-tetroxide and thianthrene-1, 2-diol 5, 5, 10, 10-tetroxide (see section III K-4).

TABLE 28. Thianthrenesulfonic Acids

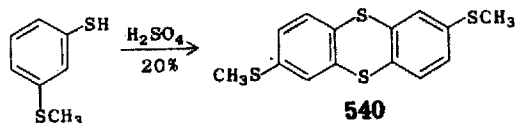
Substituents	Yield (%)	M.p. (°C)	Ref.
2-SO ₃ H 5, 5, 10, 10-tetroxide	58		311
2-SO ₂ Cl 5, 5, 10, 10-tetroxide	77	dec. 194	311
2-SO ₂ NH ₂ 5, 5, 10, 10-tetroxide		178	311
(SO ₃ H) ₂			157, 209, 212
1(?) -SO ₃ H-2-NH ₂ -8-CH ₃ -			196
2, 7-(CH ₃) ₂ - (?) -SO ₃ H			256

Herminghaus²⁵⁶ claimed that sulfonation of 2, 7-dimethylthianthrene with sulfuric acid at 100-160° yielded a monosulfonic acid, but the compound was not characterized. Fries, Koch, and Stukenbrock¹⁹⁶ claimed that 2-amino-8-methylthianthrene-1-sulfonic acid (**539**) was formed when a solution of 2-amino-8-methylthianthrene (**496**) in concentrated sulfuric acid was allowed to stand at room temperature. However, no evidence for the position of the sulfonic acid group was offered.



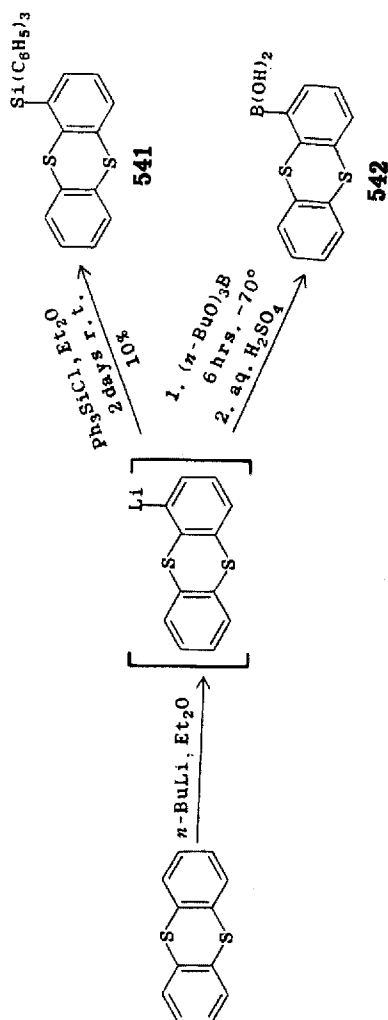
9. Miscellaneous Derivatives

Rumpf⁴²² applied the Fries sulfuric acid ring closure to methyl *m*-mercaptophenyl sulfide and obtained a compound formulated as 2, 7-bis(methylthio)thianthrene (**540**), m.p. 144, 5°, although no evidence for this assignment was offered.

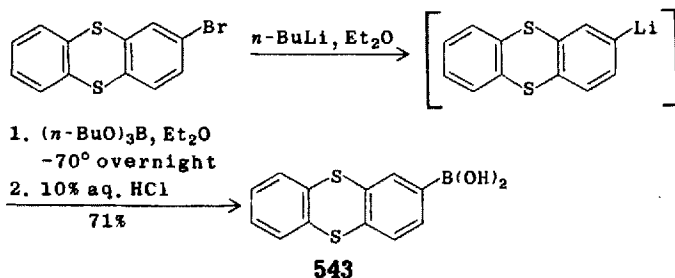


Gilman and Swayampati²²¹ reacted 1-thianthrenyllithium with triphenylchlorosilane and obtained 1-thianthrenyltriphenylsilane (**541**), m.p. 190-191, 5°. Similarly, tri-*n*-butyl borate gave thianthrene-1-boronic acid (**542**), m.p. 147-148°, after acid hydrolysis.

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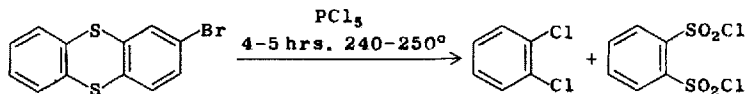


Santucci and Gilman⁴²⁵ carried out the same reaction with 2-thianthrenyllithium and tri-*n*-butyl borate to obtain thianthrene-2-boronic acid (**543**). Material recrystallized from aqueous acetone dehydrated at 170° and melted at 215–216°, whereas from ethylene dichloride it melted at 226° without prior dehydration; the latter sample analyzed as the anhydride, $C_{12}H_7BOS_2$.



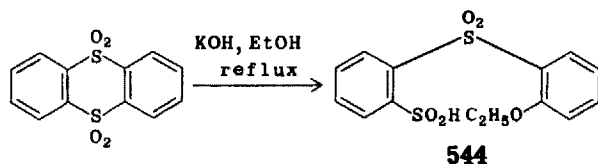
10. Ring Cleavage Reactions

Although the thianthrene ring system is quite stable, cleavage reactions have been known for some time. Thus, in 1908 Deuss¹⁵⁶ heated thianthrene with phosphorus pentachloride and isolated *o*-dichlorobenzene and *o*-benzenedisulfonyl chloride, the first real proof that thianthrene has the structure which had been assigned to it.



More recently, Tits-Skvortsova and co-workers⁴⁸⁸⁻⁴⁹⁰ decomposed thianthrene by passage over an aluminosilicate catalyst at 400°; benzene and thiophenol were isolated. 2, 7-Dimethylthianthrene yielded *p*-thiocresol. Obolentsev and Mashkina^{374c} have studied the kinetics of hydrogenolysis of thianthrene over an aluminum-cobalt-molybdenum oxide catalyst at 325–425°; the products are benzene and hydrogen sulfide.

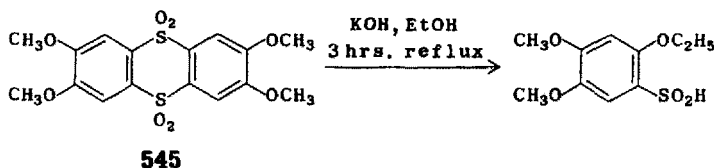
Oxides of thianthrene are considerably less stable to basic reagents than is thianthrene. Thus, Fries and Vogt¹⁹⁴ described the cleavage of thianthrene 5, 5, 10, 10-tetroxide with alcoholic potassium hydroxide to 2-(2-ethoxybenzenesulfonyl)benzenesulfinic acid (**544**). This could be considered to be a nucleophilic displacement of a sulfone by ethoxide.



Fries, Koch, and Stukenbrock¹⁹⁶ reported a similar reaction with 2, 3, 7,

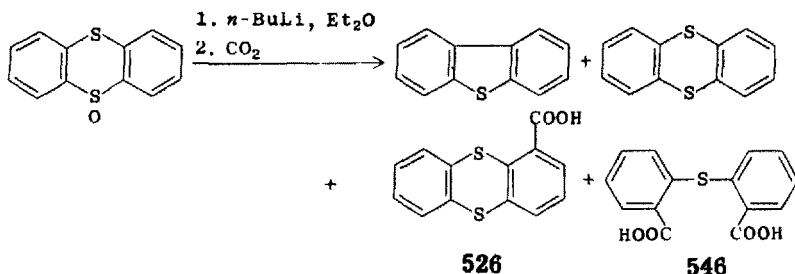
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8-tetramethoxythianthrene 5, 5, 10, 10-tetroxide (**545**) to give a compound formulated as 2-ethoxy-4, 5-dimethoxybenzenesulfinic acid; presumably the intermediate sulfone analogous to **544** was cleaved further.



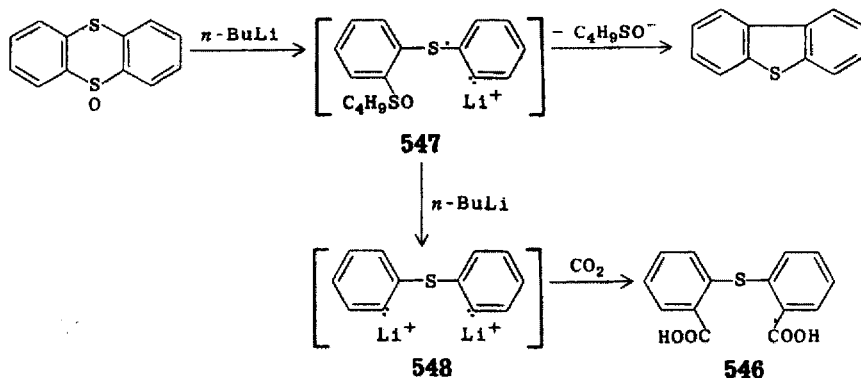
The caustic fusion of thianthrene-2-sulfonic acid 5, 5, 10, 10-tetroxide³¹¹ to give phenol, resorcinol, and *p*-hydroxybenzenesulfonic acid has already been described (see section III K-8).

Gilman and Swayampati,^{217,220} in the course of their investigation on the metalation of thianthrene, studied the reaction of thianthrene 5-oxide with *n*-butyllithium. The products isolated after carbonation were dibenzothiophene, thianthrene, thianthrene-1-carboxylic acid (**526**), and 2, 2'-dicarboxydiphenyl sulfide (**546**).

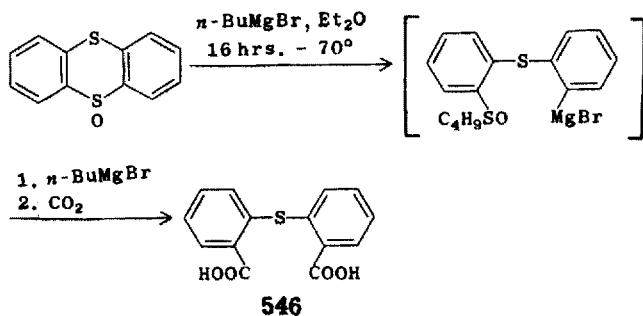


The reaction was very rapid, but the products formed depended on the reaction conditions. Thus, in three minutes at -70° , 1.1 equivalents of *n*-butyllithium yielded 27% dibenzothiophene and 9% thianthrene. After seven hours at -70° three equivalents of *n*-butyllithium yielded 52% dibenzothiophene, 3% thianthrene, and 1% **546**. In seven hours at $5-10^{\circ}$, two equivalents of *n*-butyllithium yielded 10% dibenzothiophene, 13% thianthrene, and 8% **526**. The authors formulated the reaction as involving first a ring cleavage and then a displacement of the sulfoxide group in the intermediate (**547**) to form dibenzothiophene. Alternatively, **547** can react with additional metalating agent to give the dilithio derivative (**548**), which yields the dicarboxylic acid (**546**) on carbonation. It is not surprising that the intramolecular reaction takes precedence, yielding dibenzothiophene as the major product of the reaction.

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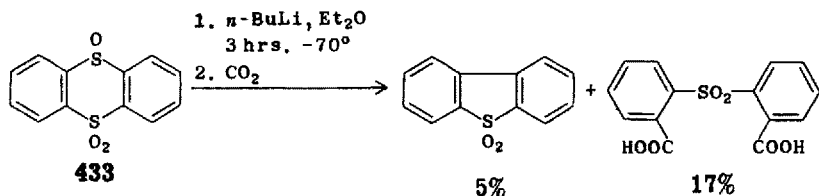


Evidence for this mechanism was found in the reaction of thianthrene 5-oxide with Grignard reagents. Here the reaction stopped at the intermediate stage, presumably because of the weaker carbanion formed with the Grignard reagent; *n*-butylmagnesium bromide gave a 50% yield of the dicarboxylic acid (**546**) after carbonation.



It is interesting that methyllithium gave only reduction and no cleavage.

Gilman and Swayampati²²¹ also investigated the reaction of thianthrene 5, 5, 10-trioxide (**433**) with *n*-butyllithium. Here the products were reversed, more 2, 2'-dicarboxydiphenyl sulfone than dibenzothio-
 phene 5, 5-dioxide being formed, although the yields of both products were low.



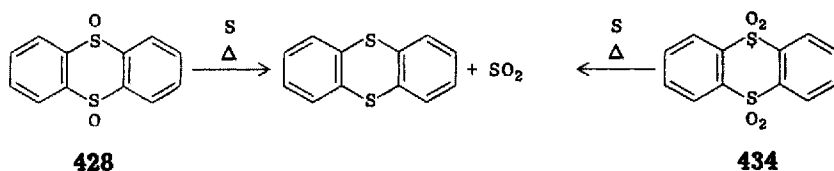
The mechanism would presumably be the same as for thianthrene 5-oxide. Gilman and Swayampati attributed the larger amount of dicarboxylic acid formed here to the electron-attracting sulfone group, which would assist elimination of sulfoxide by the alkyl lithium. This explana-

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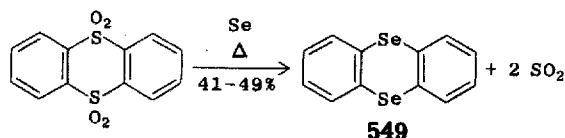
tion is unlikely, however, inasmuch as the formation of both products involves a nucleophilic displacement of sulfoxide. A more likely explanation is a decrease of the nucleophilic character of the aryl anion by the sulfone group, thus favoring the attack by more *n*-butyllithium. Thianthrene 5, 10-dioxide did not react with *n*-butyllithium, probably because of its insolubility in ether at -70° .

Gilman and Dietrich²²⁴ investigated the reaction of thianthrene with metallic lithium in tetrahydrofuran. The molecule was cleaved, but no identifiable products were isolated; carbonation of the reaction mixture yielded an acidic oil with an unpleasant odor. According to Tomita and Ujiie^{492a} both sodium and lithium in liquid ammonia cleave thianthrene to a mixture of thiophenol and diphenyl disulfide. The mechanism of this cleavage is obscure.

Thianthrene appears to be more stable than its oxides in thermal reactions as well. As early as 1896 Krafft and Lyons³¹³ reported that thianthrene 5, 10-dioxide (**428**) and 5, 5, 10, 10-tetroxide (**434**) yielded thianthrene and sulfur dioxide when heated with sulfur.

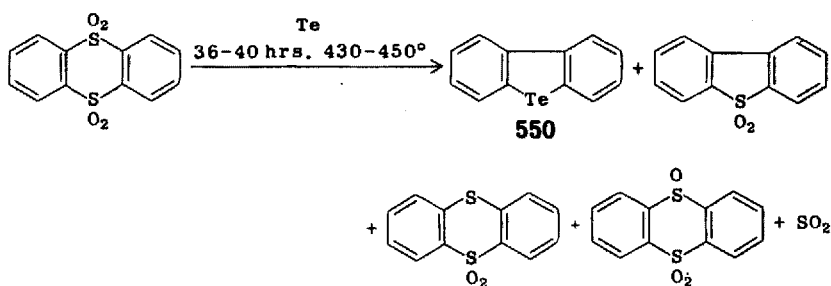


The reaction with the disulfone was confirmed by Böeseken and van der Meulen,⁵⁷ thianthrene being formed at $430-440^{\circ}$. It is quite likely that the reaction with the disulfoxide involves a reduction by sulfur rather than a ring cleavage, but the reduction of a sulfone by sulfur is much less reasonable, although it cannot be eliminated as a possibility under these drastic conditions. That the latter reaction probably did not involve a reduction of sulfone groups, however, was demonstrated by Krafft and Kaschau,³¹⁴ who found that replacement of sulfur by selenium gave selenanthrene (**549**) in good yield (see Chapter 13, section XIII B-2).

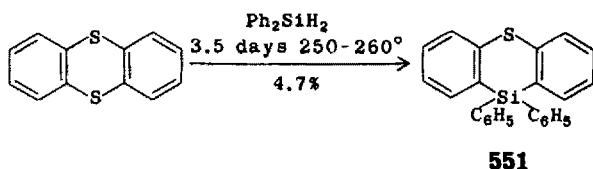


This was confirmed by Cullinane, Morgan, and Plummer.¹³⁸ These are probably free radical reactions, the driving force being the formation of the stable sulfur dioxide molecule. The reaction with tellurium followed a different course according to Passerini and Purrello,³⁹² the products being dibenzotelluophene (**550**), dibenzothiophene 5, 5-dioxide, thianthrene 5, 5-dioxide, and probably thianthrene 5, 5, 10-trioxide.

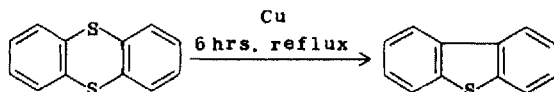
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Wittenberg, McNinch, and Gilman^{223, 510} prepared 10, 10-diphenylphenothiasilin (551) by heating thianthrene with diphenylsilane; the yield was low.



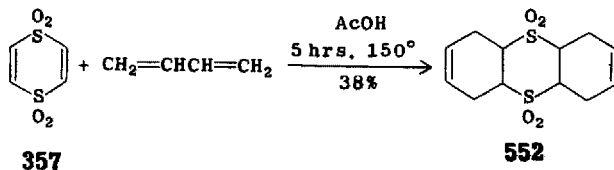
Cullinane, Morgan, and Plummer¹³⁸ found that heating thianthrene with copper gave dibenzothiophene.



This too is probably a free radical reaction, the formation of the aromatic compound being the driving force. Loudon, Sloan, and Summers³³¹ have discussed other examples of this sulfur extrusion reaction.

11. Hydrogenated Derivatives

Very few hydrogenated derivatives of thianthrene have been reported. Parham and co-workers³⁸¹ prepared 1, 4, 4a, 5a, 6, 9, 9a, 10a-octahydrothianthrene 5, 5, 10, 10-tetroxide (552) by a Diels-Alder reaction between butadiene and *p*-dithiin 1, 1, 4, 4-tetroxide (357) (see section III E-2).

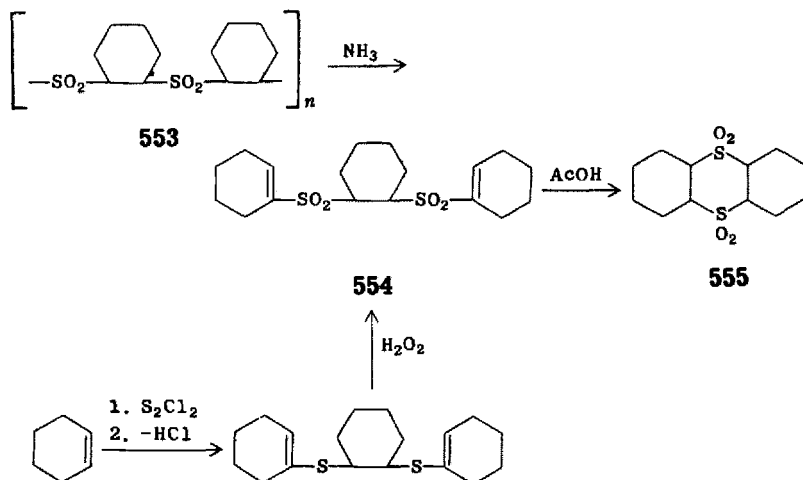


Dimethylbutadiene gave the 2, 3, 7, 8-tetramethyl analog.

By analogy with other examples (see section III A-1f) it would have been expected that treatment of a cyclohexene-sulfur dioxide copolymer (553) with liquid ammonia would have yielded the disulfone of perhy-

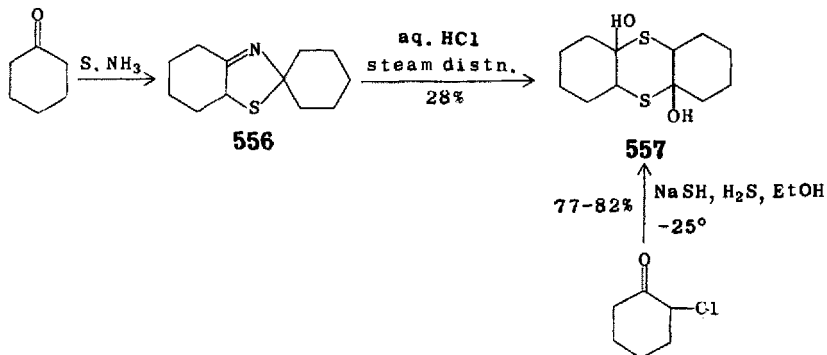
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drothianthrene (**555**). Marvel, Davis, and Glavis³⁴⁹ found, however, that the initial product of the reaction was a molecule containing three rings and two sulfur dioxides (**554**). Upon recrystallization from acetic acid it yielded the expected product, perhydrothianthrene 5, 5, 10, 10-tetroxide (**555**), presumably by elimination of cyclohexene. The structure of **554** was indicated by an independent synthesis.



Although there appears to be no reason to doubt the structure of the final compound, the unusual nature of the ring closure reaction warrants further study.

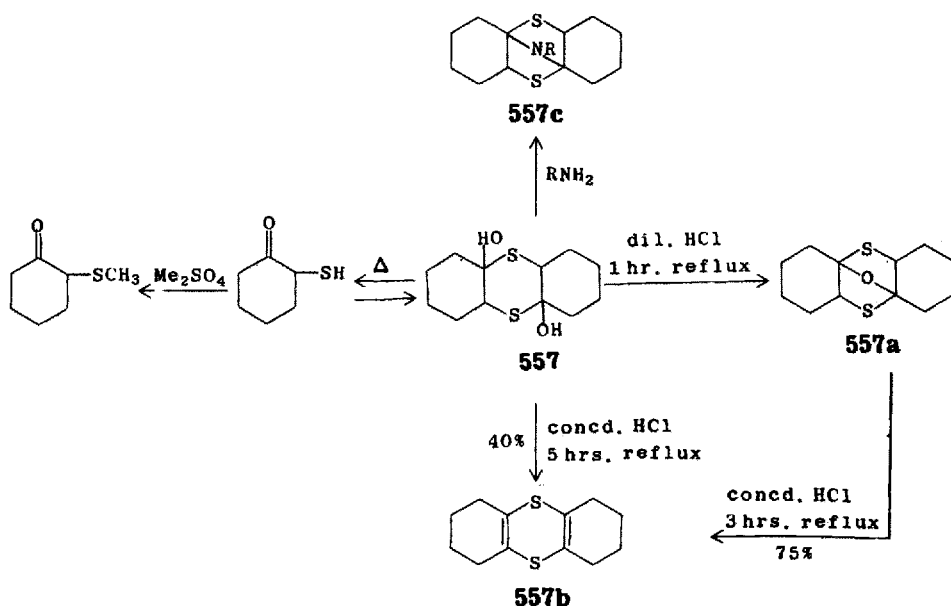
Octahydro-4a, 9a(2*H*, 5a*H*)-thianthrenediol (**557**) was prepared by Asinger and co-workers^{11, 15a} by two different routes. Treatment of cyclohexanone with sulfur and ammonia yielded 2,2-pentamethylene-4,5-tetramethylene-3-thiazoline (**556**). This, on acid hydrolysis, gave the dihydroxyperhydrothianthrene (**557**); presumably **556** hydrolyzes to 2-mercaptocyclohexanone, which then dimerizes to **557**. The same compound was obtained from 2-chlorocyclohexanone and sodium hydrosulfide, undoubtedly *via* the intermediate formation of 2-mercaptocyclohexanone.



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In 1941 Backer, Strating, and Huisman^{24a} had reacted sodium sulfide with 2-chlorocyclohexanone and had formulated the product as the disulfide of 2-mercaptocyclohexanone. Asinger and co-workers^{15a} showed it to be identical with **557**. Milligan and Swan^{360a} independently reached the same conclusion; they obtained two isomeric forms of **557**.

557 undergoes reactions similar to those of other *p*-dithiane-2,5-diols (see section III A-1j). Thus, it distills at 110° at 12 mm, undoubtedly as the monomer. Dilute hydrochloric acid yields the oxide (**557a**) (see Chapter 4, section II K), while concentrated acid forms 1,2,3,4,6,7,8,9-octahydrothianthrene (**557b**). A number of nitrogen compounds form bicyclo derivatives (**557c**, R = H, CH₃-, NH₂CONH-).



Hydrogenated thianthrenes are listed in Table 29.

12. Uses

The use of certain thianthrene derivatives as dyes has already been discussed. Crude 2,7-dimethylthianthrene has been known under a variety of names—Mitigal, Mesulphen, Odylen, Sudermo, Neosulfine. It was apparently used, prior to DDT, for the treatment of scabies and other skin infections caused by mites.²²⁹ Geigy²⁰⁶⁻²⁰⁸ patented it in conjunction with DDT, either because of improved insecticidal proper-

TABLE 29. Hydrogenated Thianthrenes

Substituents	Yield (%)	M.p. (°C)	Ref.
1, 2, 3, 4, 6, 7, 8, 9-H ₈	40	97	15a
	48	97	360a
1, 2, 3, 4, 6, 7, 8, 9-H ₈ 5, 5, 10, 10-tetroxide	83	249-258	15a
1, 4, 4a, 5a, 6, 9, 9a, 10a-H ₈ 5, 5, 10, 10-tetroxide		>350 (dec.)	381
2, 3, 7, 8-(CH ₃ -) ₄ -1, 4, 4a, 5a, 6, 9, 9a, 10a-H ₈ 5, 5, 10, 10-tetroxide		304-306	381
H ₁₂		291	349
4a, 9a-(OH) ₂ -H ₁₀	77-82	151-152	11, 15a
		150-151.5	24a
		143-144, 168-170	360a

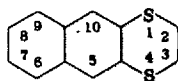
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ties or because it prevented the crystallization of DDT. Matsudo³⁵⁴ patented thianthrene as an ingredient of a salve active against skin infections. In the agricultural field thianthrene was found to be non-toxic to young screwworms⁴⁵⁹ and to have no fungicidal activity, at least in tests against *Fusarium* wilt of tomatoes.¹⁴⁹

Herminghaus²⁵⁶ claimed that sodium 2, 7-dimethylthianthrenesulfonate shows antiphlogistic action. A commercial protective preparation called "R", which is or was marketed in Germany, might be the same material. Carrié and Neuhaus⁹⁴ found that it does give skin protection against caustic and turpentine but not against sulfuric acid. Burtner and Brown⁸¹ claimed that γ -oxo- γ -2-thianthrenylbutyric acid shows choleric activity. This was confirmed by Gunter, Kim, and co-workers,²³⁹ but the activity is low, being only half that of the corresponding phenoxathiin derivative and one-third that of dehydrocholic acid. Thianthrene shows no anthelmintic activity.⁴¹⁹

2, 7-Dimethylthianthrene has been investigated as a solvent and plasticizer for poly(vinyl chloride).^{146, 176, 177, 177a, 180} It and 2, 3, 7, 8-tetramethylthianthrene have been patented as stabilizers for poly(vinyl acetals).²⁴³ Denison and Condit¹⁵⁴ found thianthrene to be a very poor antioxidant in lubricating oils, as did Murphy, Ravner, and Smith.³⁷¹ Hugen²⁸³ tested it as an ingredient in extreme pressure lubricants, and Lincoln and Byrkit³²⁸ patented it for that purpose. Thianthrene has been reported to be useful as a stabilizer in coolant-moderator fluids for nuclear reactors.^{57a, 507a} In the stereospecific polymerization of propylene with a titanium trichloride-triethylaluminum catalyst thianthrene is reported to increase the molecular weight of the polymer.^{410a}

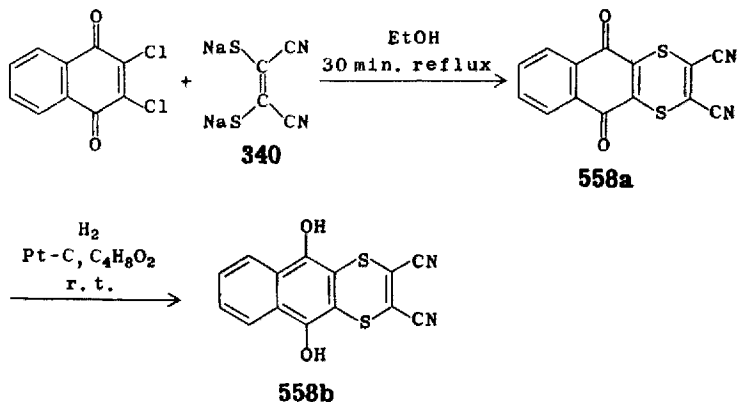
13. Naphtho[2, 3-*b*]-*p*-dithiin (558)



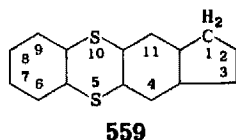
558

van Schoor, Jacobi, and co-workers,^{439a} reacted the disodium salt of dimercaptomaleonitrile (340) (see section III A-2a) with 2, 3-dichloro-1, 4-naphthoquinone and isolated 2, 3-dicyano-5*H*, 10*H*-naphtho[2, 3-*b*]-*p*-dithiin-5, 10-dione (558a), m.p. 220°, as gray-brown needles with a violet, metallic sheen. Catalytic reduction of 558a yielded 2, 3-dicyano-5, 10-dihydroxynaphtho-[2, 3-*b*]-*p*-dithiin (558b), m.p. 215°. Both compounds were reported to be highly active fungicides; E. Merck A.-G. is marketing the quinone as "Delan" in Germany.

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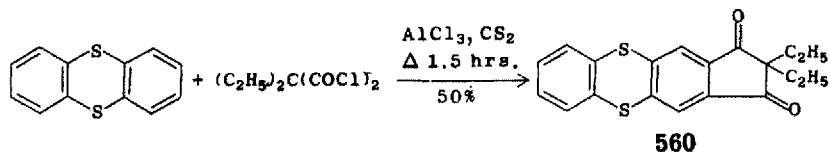
L. C₅-C₄S₂-C₆-C₆ 1*H*-CYCLOPENTA[*b*]THIANTHRENE (559)



(RRI 4722)

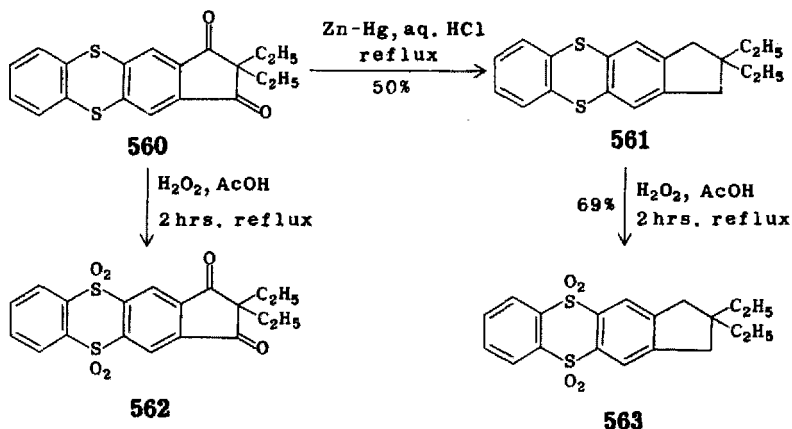
This ring system is known only in the form of the 2, 3-dihydro derivative. It was first prepared in 1921, at which time Chemical Abstracts indexed it as β -thianthrindan.

Fleischer and Stemmer¹⁸¹ carried out a Friedel-Crafts reaction between thianthrene and 2, 2-diethylmalonyl dichloride to yield a compound, obtained in the form of lemon-yellow prisms, m.p. 135-136°, which they formulated as 2, 2-diethyl-2, 3-dihydro-1*H*-cyclopenta[*b*]thianthrene-1, 3-dione (**560**).

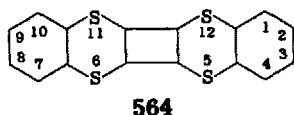


The alternative structure of a cyclopenta[*a*]thianthrene, which would involve reactions in the 1, 2-positions of the thianthrene ring, was also considered. The structure resulting from reaction in the 2, 3-positions appears more reasonable. As well as can be determined, thianthrene appears to acylate in the 2-position (see section III K-6). It seems likely, therefore, that the ring closure, involving a second acylation, would take place *para* to a sulfur atom rather than *ortho*, leading to **560**. Reduction yielded 2, 2-diethyl-2, 3-dihydro-1*H*-cyclopenta[*b*]thianthrene (**561**) as a viscous yellow oil, b.p. 277-278° at 16 mm. Oxidation of **560** yielded 2, 2-diethyl-2, 3-dihydro-1*H*-cyclopenta[*b*]-thianthrene-1, 3-

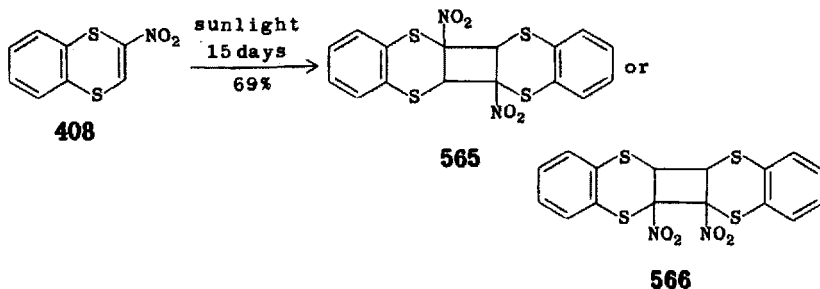
dione 5, 5, 10, 10-tetroxide (**562**) as pale yellow needles, m.p. 213-215°, while **561** yielded 2, 2-diethyl-2, 3-dihydro-1*H*-cyclopenta[*b*]thianthrene 5, 5, 10, 10-tetroxide (**563**), m.p. 191-192°.



M. $\text{C}_4\text{-C}_4\text{S}_2\text{-C}_4\text{S}_2\text{-C}_6\text{-C}_6$ CYCLOBUTA[1, 2-*b*: 3, 4-*b'*] BIS[1, 4]-BENZODITHIIN (**564**)

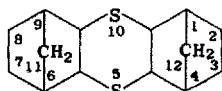


Parham, Stright, and Hasek³⁸⁹ exposed 2-nitro-1, 4-benzodithiin (**408**) to sunlight and isolated a yellow, crystalline solid, m.p. 170. 5-172°. Analysis showed the material to be a dimer of **408**. Oxidation yielded *o*-benzenedisulfonic acid, showing that the nitro groups had not rearranged to the benzene rings, and both infrared and ultraviolet spectra indicated that the nitro groups were no longer conjugated with the double bonds. The compound appears, therefore, to be either 5a, 11a-dinitro-5a, 5b, 11a, 11b-tetrahydrocyclobuta[1, 2-*b*: 3, 4-*b'*] bis[1, 4]-benzodithiin (**565**) or the 5a, 5b-dinitro derivative (**566**). The symmetrical structure (**565**) was preferred by Parham and co-workers by analogy with the photochemical dimerization of β -nitrostyrene.



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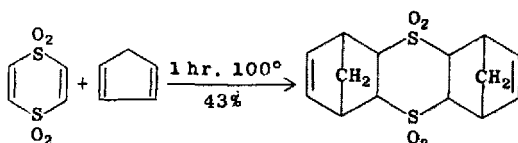
N. C₅-C₅-C₅-C₅-C₄S₂ 1, 4, 6, 9-DIMETHANTHIANTHRENE (567)



567

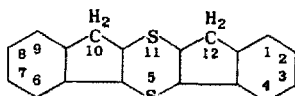
(RRI 5467)

1, 4, 4a, 5a, 6, 9, 9a, 10a-Octahydro-1, 4, 6, 9-dimethanthianthrene 5, 5, 10, 10-tetroxide (568), melting above 370°, was prepared by Parham, Wynberg, and co-workers,³⁸¹ by a Diels-Alder reaction between *p*-dithiin 1, 1, 4, 4-tetroxide and cyclopentadiene. No 1:1 adduct was isolated.



568

O. C₅-C₅-C₄S₂-C₆-C₆ 10*H*, 12*H*-DIINDENO[1, 2-*b*;2', 1'-*e*]-*p*-DITHIIN (569)

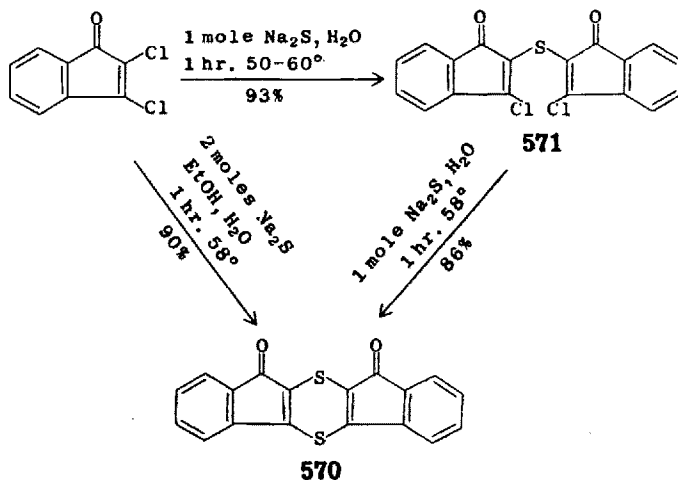


569

(RRI 5728)

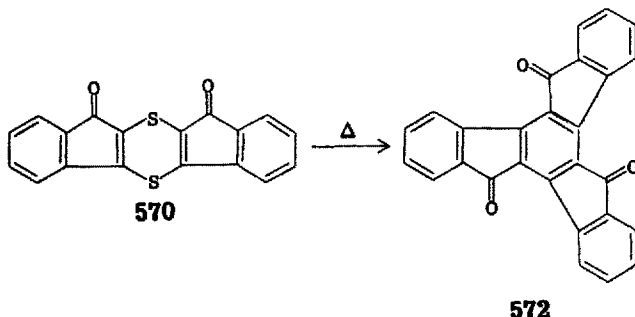
Chemical Abstracts indexed this ring system, at the time of its preparation, as [2, 3, 3', 2'-*p*]-diindenodithiin.

Brass and Mosl⁶⁶ prepared 10*H*, 12*H*-diindeno[1, 2-*b*;2', 1'-*e*]-*p*-dithiin-10, 12-dione (570) both directly and in two steps from 2, 3-dichloroindenone.



The synthesis was confirmed by DeFazi and Pirrone.¹⁵⁰ The assigned structure is based on the assumption, verified in other work, that the chlorine atom adjacent to the carbonyl group is more reactive than the β -chlorine. It would be expected, therefore, that the intermediate sulfide would be bis(3-chloro-1-oxinden-2-yl) sulfide (571), and the subsequent reaction with sodium sulfide would give the unsymmetrical p -dithiin derivative.

570, recrystallized from xylene or pyridine, was obtained as dark blue-violet needles. Its solution in concentrated sulfuric acid was black by reflected light and deep olive-green by transmitted light. The pure compound readily lost two sulfur atoms on heating and yielded a compound called diindonylene by Brass and Mosl. Stobbe and Zschoch⁴⁶⁸ showed, however, that this compound is not a dimer of indenone but a trimer, benzo[1,2-*a*,3,4-*a'*;5,6-*a''*]triindene-5,10,15-trione (572), also known as tribenzoylenebenzene or truxenetrione.

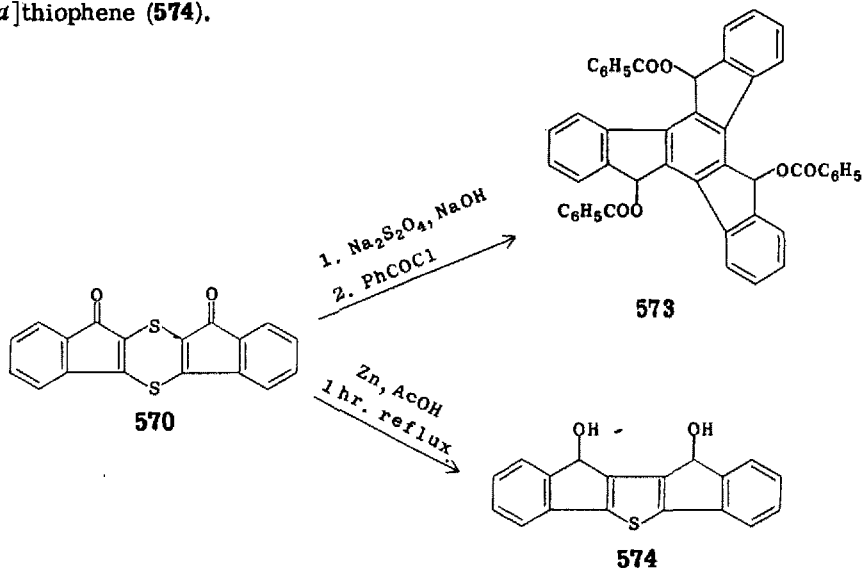


Whereas the elimination of one sulfur atom from p -dithiin derivatives to yield a derivative of thiophene is fairly common,³³¹ the loss of two sulfur atoms is rather unusual. If, however, the driving force in the sulfur extrusion is considered to be the formation of an aromatic sys-

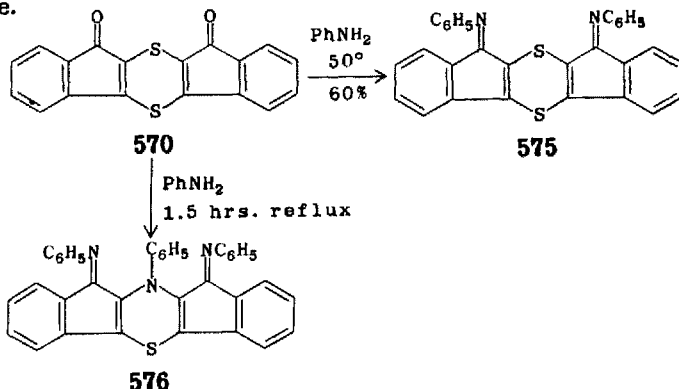
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tem, the reaction is understandable in this case, the truxene derivative (572) being highly aromatic. The same compound was formed by treatment of 570 with nitric or sulfuric acids.

570 yielded a deep blue solution with sodium sulfide or alkaline hydrosulfite; treatment with benzoyl chloride gave the tribenzoate of truxene-triol (573). Reduction under acidic conditions, however, eliminated only one sulfur atom to give 10, 11-dihydroxy-10*H*, 11*H*-diideno[1, 2-*b*:2' 1'-*a*]thiophene (574).

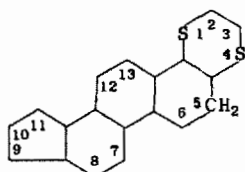


Although evidence indicated a greater lability for the sulfur adjacent to the carbonyl groups, it is possible that the β -sulfur was eliminated to give the isomeric thiophene derivative. Under mild conditions 570 reacted with aniline to give 10, 12-dianilino-10*H*, 12*H*-diideno[1, 2-*b*:2' 1'-*e*]-*p*-dithiin (575), while under more vigorous conditions a thiazine derivative (576) was formed; under both conditions some truxene-trione (572) was also isolated. 570 would not form an oxime or a hydrazone.

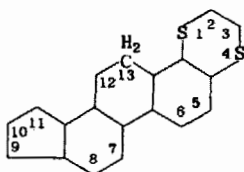


[For references, see pp. 1252-1271.]

P. $C_5-C_4S_2-C_6-C_6-C_6$ 5*H*-CYCLOPENTA[7,8]PHENANTHRO[1,2-*b*]-
p-DITHIIN (576a) AND 13*H* CYCLOPENTA [7,8]PHENANTHRO
 [1,2-*b*]-*p*-DITHIIN (576b)

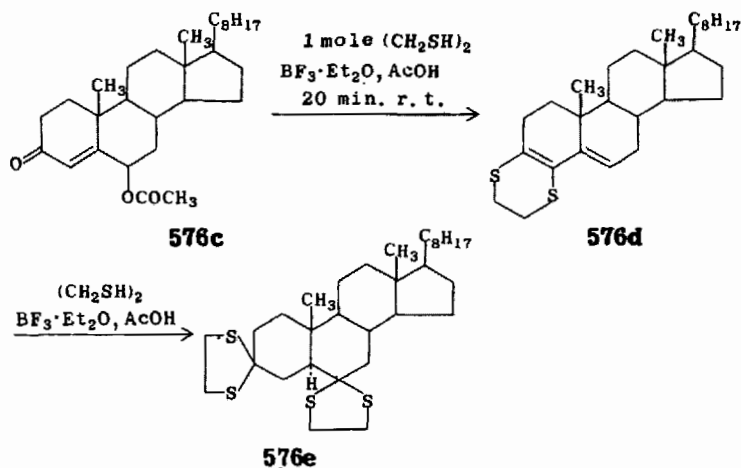


576a



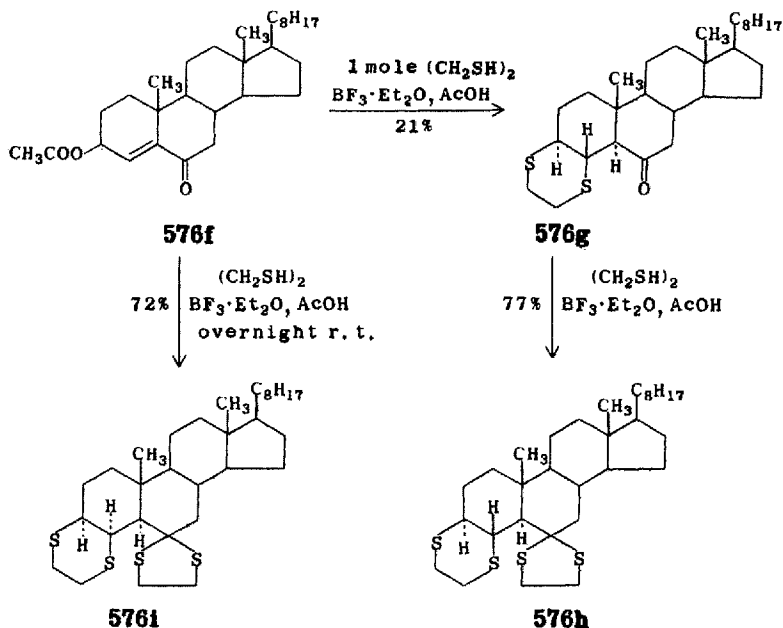
576b

Fieser, Yuan, and Goto^{177b} reacted 6 β -acetoxy-4-cholesten-3-one (576c) with one equivalent of 1,2-dimercaptoethane and isolated 9-(1,5-dimethylhexyl)-2,3,6,6a,6b,7,8,8a,9,10,11,11a,11b,12-tetradecahydro-6a,8a-dimethyl-5*H*-cyclopenta[7,8]phenanthro[1,2-*b*]-*p*-dithiin (576d), m.p. 165°, $[\alpha]_D - 121^\circ$. Treatment with additional 1,2-dimercaptoethane converted it into the 3,6-bis(cyclic ethylene mercaptole) (576e).



3 β -Acetoxy-4-cholesten-6-one (576f) reacted with one equivalent of 1,2-dimercaptoethane to form 9-(1,5-dimethylhexyl)octadecahydro-6a,8a-dimethyl-13*H*-cyclopenta[7,8]phenanthro[1,2-*b*]-*p*-dithiin-13-one (576g), m.p. 185–186°, $[\alpha]_D - 76^\circ$. 576g formed a disulfoxide with hydrogen peroxide, m.p. 270–275° (dec.), $[\alpha]_D - 188^\circ$, and reacted with additional 1,2-dimercaptoethane to yield the corresponding cyclic ethylene mercaptole (576h), m.p. 234°, $[\alpha]_D - 20^\circ$. Treatment of the acetoxycholestenone directly with excess 1,2-dimercaptoethane yielded an isomer of 576h (576i), m.p. 280–281°.

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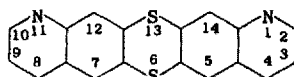


Structures were assigned by comparison of the ultraviolet and proton magnetic resonance spectra with those of known compounds. The postulated mode of formation of these unusual derivatives has already been discussed (see Chapter 5, section IIA-4b).

Q. C₄S₂-C₅N-C₅N-C₆-C₆

These ring systems were described in a series of papers by Edinger and co-workers¹⁶⁷⁻¹⁷³ who called the compounds thioquinanthrene and isomeric thioquinanthrene.

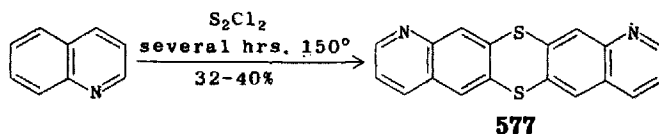
1. *p*-Dithiino[2, 3-*g*, 6, 5-*g'*]diquinoline (577)



577

(RRI 6248)

Edinger found that heating quinoline with sulfur monochloride yielded a sharp-melting, sublimable solid, C₁₈H₁₀N₂S₂.



[For references, see pp. 1252-1271.]

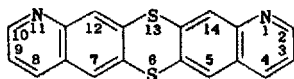
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Sulfur dichloride gave the same compound, although in lower yield, as did sulfur at 180°. The structure was assigned on the following grounds. The compound was exceedingly resistant to oxidation and reduction and liberated no sulfur with hot metallic copper. Drastic nitric acid oxidation gave a small amount of nicotinic acid, showing that the nitrogen-containing ring was unsubstituted. In agreement with this latter conclusion, a comparable compound could not be prepared from pyridine and sulfur monochloride. The compound yielded a crystalline dimethiodide and a crystalline trinitrobenzene complex.

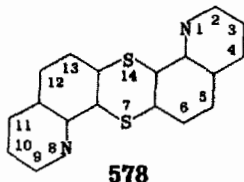
Edinger gave no reason for assigning the unsymmetrical structure (577) to this compound, and the structure is open to question on several grounds. Electrophilic substitution on quinoline is difficult and, when it does take place, substitution is generally in the 5- and 8-positions. Thus, this compound could be any one of a number of possible *p*-dithi-inodiquinolines. Secondly, it is quite surprising that no sulfoxides or sulfones could be prepared from a compound with this thianthrene-like structure, and both this compound and its isomers consistently gave analyses too high in hydrogen. These last two points make any thianthrene-like structure questionable, and the structure of this and related compounds needs further investigation.

A number of salts of this compound were prepared. Sulfuric acid gave a mono-salt and a salt with two sulfuric acid molecules, nitric acid gave a salt with four acid groups, while hydrochloric and hydrobromic acids gave the expected di-salts. The compounds reported are listed in Table 30.

TABLE 30. *p*-Dithiino[2, 3-*g*: 6, 5-*g'*]diquinoline Derivatives

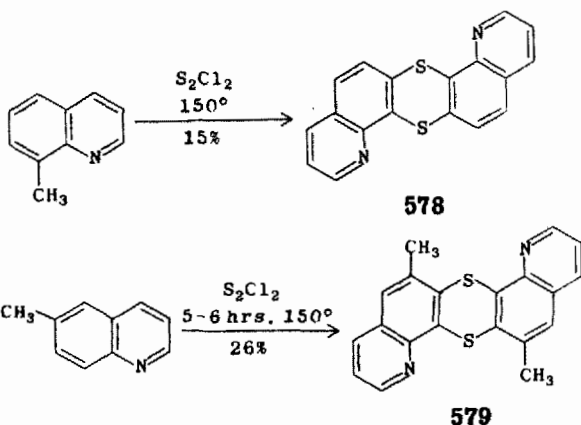


Substituents	Physical properties	Ref.
None	long needles, m.p. 306°, sublimes 170° at 28 mm.	167, 168, 171
2CH ₃ I · 2H ₂ O	dark red crystals, m.p. >360°	167, 168
2CH ₃ Cl	long red needles, m.p. 284-285° (dec.)	168
C ₆ H ₃ (NO ₂) ₃	golden yellow crystals, m.p. 281°	168
2H ₂ SO ₄ · 2H ₂ O	small yellow crystals	167, 168
2H ₂ SO ₄	red-brown anhydrous needles	172, 173
4HNO ₃ · 2H ₂ O	yellow needles	172, 173
2HCl	yellow needles	173
2HBr	yellow needles	173

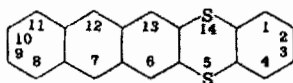
2. *p*-Dithiino[2, 3-*h*: 5, 6-*h'*]diquinoline (578)

(RRI 6249)

Treatment of 8-methylquinoline with sulfur monochloride under the same conditions as used with quinoline gave an isomeric thioquinanthrene (578) with loss of the methyl groups. Edinger claimed that sulfur dichloride gave 6, 8-dichloroquinoline, also with methyl group elimination. 6-Methylquinoline gave a dimethyl derivative, formulated as 6, 13-dimethyl-*p*-dithiino[2, 3-*h*: 5, 6-*h'*]diquinoline (579).



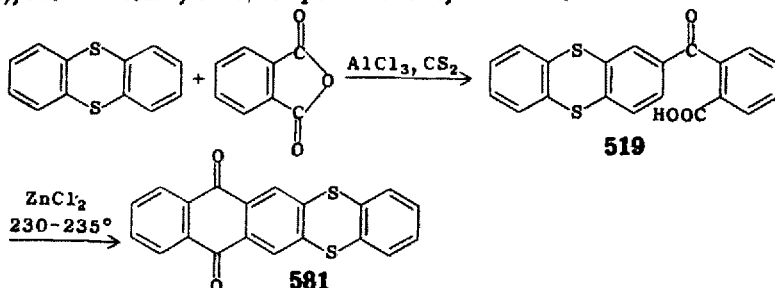
The objections to these assignments are the same as those listed for the product from quinoline. The unmethylated compound gave no methiodide, while the 6, 13-dimethyl derivative gave a dimethiodide, an indication in itself that the basic ring systems are different in the two compounds. The derivatives reported are listed in Table 31.

R. C₄S₂-C₆-C₆-C₆-C₆1. Naphtho[2, 3-*b*]thianthrene (580)

580
(RRI 6250)

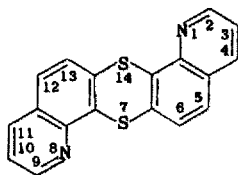
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Scholl and Seer⁴³⁹ reacted thianthrene with phthalic anhydride to give 2-(*o*-carboxybenzoyl)thianthrene (519) (see section III K-6). Ring closure with zinc chloride yielded naphtho[2,3-*b*]thianthrene-7,12-dione (581), also called 5,14-dithiapentacene-7,12-dione.



The compound was obtained as dark red, star-shaped crystals, melting at about 253° and giving a wine-red solution in sulfuric acid. The postulated structure seems reasonable, in view of the demonstrated acyla-

TABLE 31. *p*-Dithiino[2,3-*h*:5,6-*h'*]diquinoline Derivatives

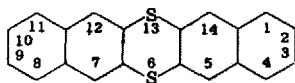


Substituents	Physical properties	Ref.
None	gleaming white leaflets, m.p. $>360^\circ$, sublimes 150° at 16 mm.	169, 170
$4\text{HNO}_3 \cdot 2\text{H}_2\text{O}$	stout yellow prisms	172, 173
$2\text{H}_2\text{SO}_4$	red-brown needles	172, 173
2HCl	scarlet-red needles	173
$2\text{HCl} \cdot 2\text{H}_2\text{O}$	yellow	173
2HBr	dark red	173
$6,13-(\text{CH}_3)_2$	small white needles, m.p. 316°	173.
$2\text{CH}_3\text{I}$	red needles	173
Dipicrate	yellow needles	173
4HNO_3	golden yellow needles	172, 173
$2\text{H}_2\text{SO}_4 \cdot 2\text{H}_2\text{O}$	red crystals	172, 173
$2\text{H}_2\text{SO}_4$	yellow crystals	172, 173
2HCl	yellow needles	173
2HBr	yellow needles	173

C₄S₂ Ring Systems

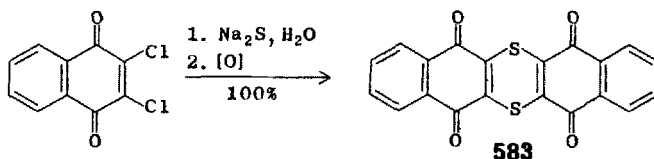
tion of thianthrene in the 2-position, plus the expectation that ring closure would take place by reaction *para* to a sulfur atom. **581** gave a soluble vat with alkaline hydrosulfite, but this was useless for dyeing.

2. Dibenzo[*b, i*]thianthrene (**582**)



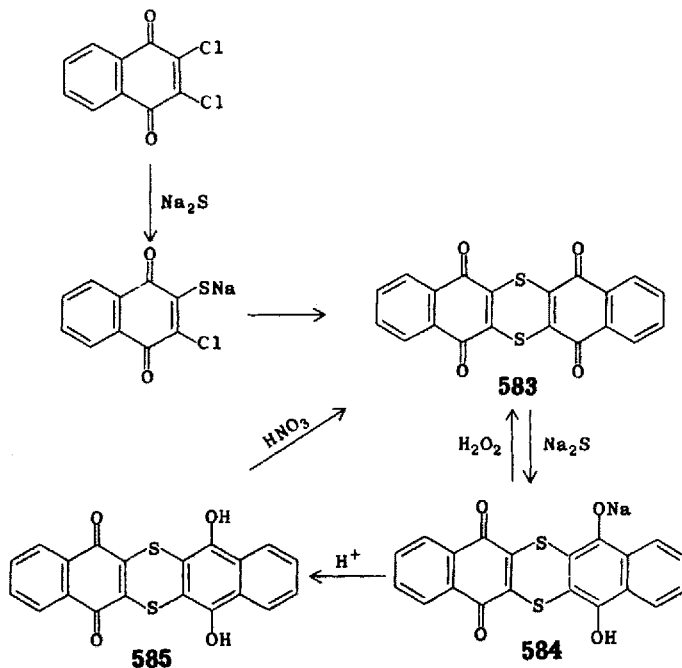
582
(RRI 6251)

This ring system, also called β, β' -dibenzothianthrene and 6, 13-dithiapentacene, was first prepared by Brass and Köhler.^{62,63} These authors treated 2, 3-dichloro-1, 4-naphthoquinone with an excess of aqueous sodium sulfide; the solution turned red, then blue, and a green solid precipitated. Oxidation with dilute nitric acid or chromic anhydride gave a quantitative yield of dibenzo[*b, i*]thianthrene-5, 7, 12, 14-tetrone (**583**) as violet-red needles melting at 302° with decomposition.



If the reaction was interrupted before oxidation and acidified, a blue compound, dibenzo[*b, i*]thianthrene-5, 14-diol-7, 12-dione (**585**), could be isolated. Thus, part of the sodium sulfide was acting as a reducing agent, and the reaction was considered to follow the course shown:

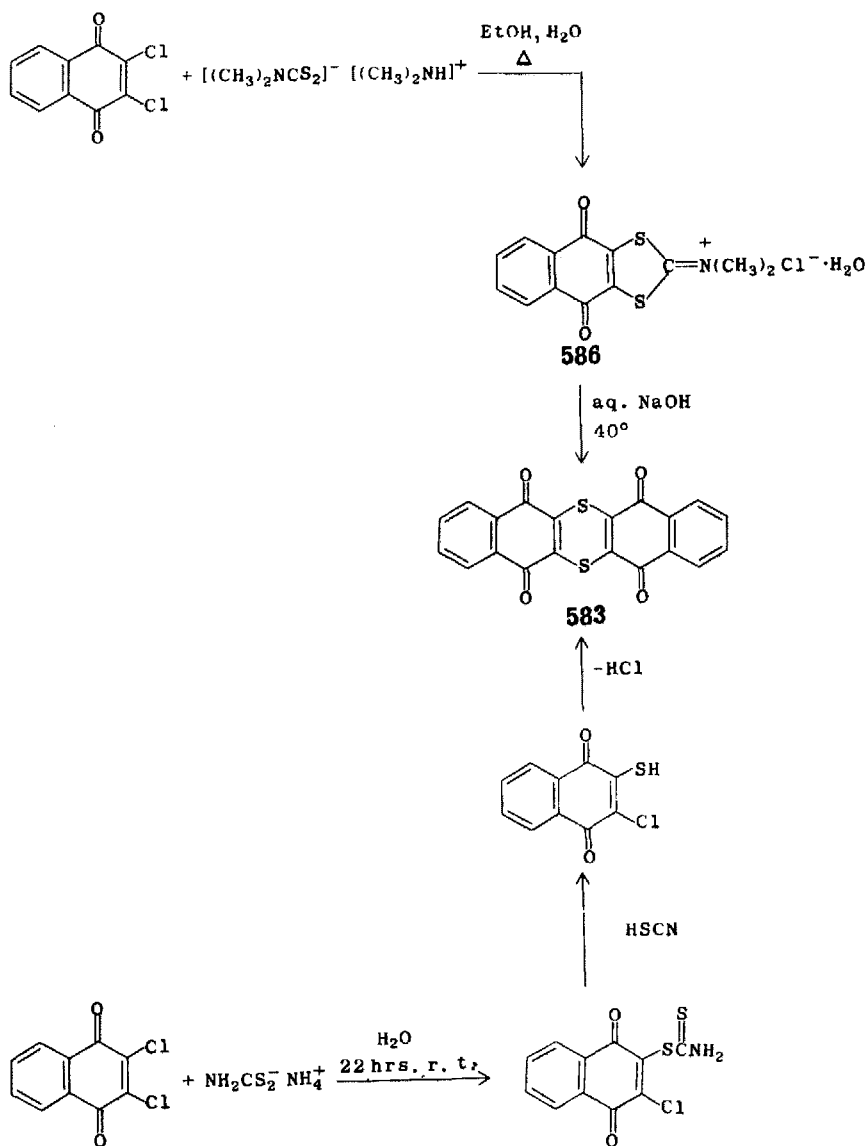
Chapter 12



As proof of this, oxidation of the monosodium salt (**584**) with alkaline peroxide or of the dihydroxy compound (**585**) with dilute nitric acid gave the tetrone (**583**).

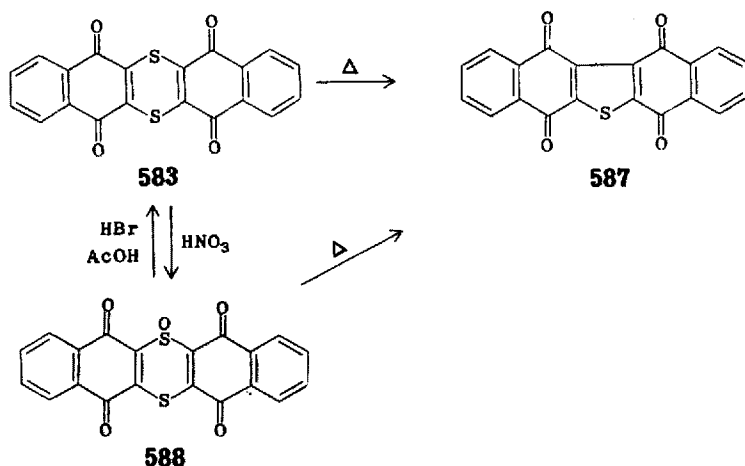
Sundholm and Smith⁴⁷⁴ used a somewhat related route to prepare **583**. 2,3-Dichloro-1,4-naphthoquinone reacted with dimethylammonium *N,N*-dimethyldithiocarbamate to form 4,9-dioxonaphtho[2,3-*d*]-1,3-dithiole-2-dimethylimmonium chloride hydrate (**586**) (see Chapter 5, section II F). This on hydrolysis yielded the tetrone (**583**). Similarly, reaction of 2,3-dichloro-1,4-naphthoquinone with ammonium dithiocarbamate at a lower temperature gave a compound which, on recrystallization from refluxing chlorobenzene, gave **583**, presumably *via* the following path:

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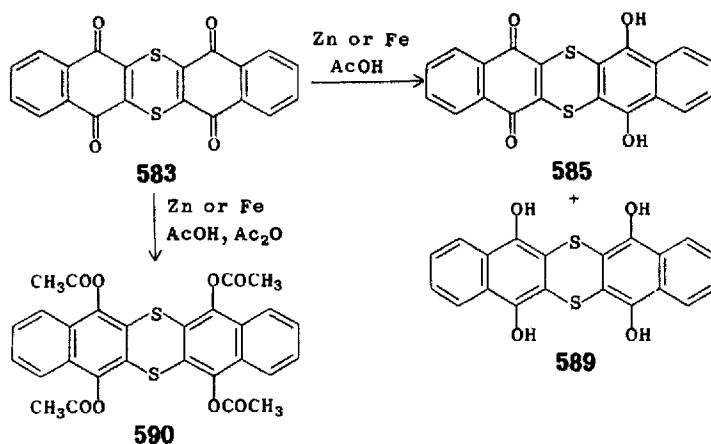


Brass and Köhler⁶³ investigated the properties of **583**. The compound was insoluble in the common organic solvents, dissolving only in hot nitrobenzene, aniline, and quinoline. In concentrated sulfuric acid it gave a red solution, the tetrone being recovered on dilution. On long heating in nitrobenzene or in sulfuric acid, sulfur was eliminated and dinaphtho[2, 3 : 2', 3']thiophene-5, 7, 12, 13-tetrone (**587**) was formed.

Concentrated nitric acid yielded a yellow monosulfoxide (**588**), which eliminated sulfur more readily than **583** to give the same thiophene derivative.



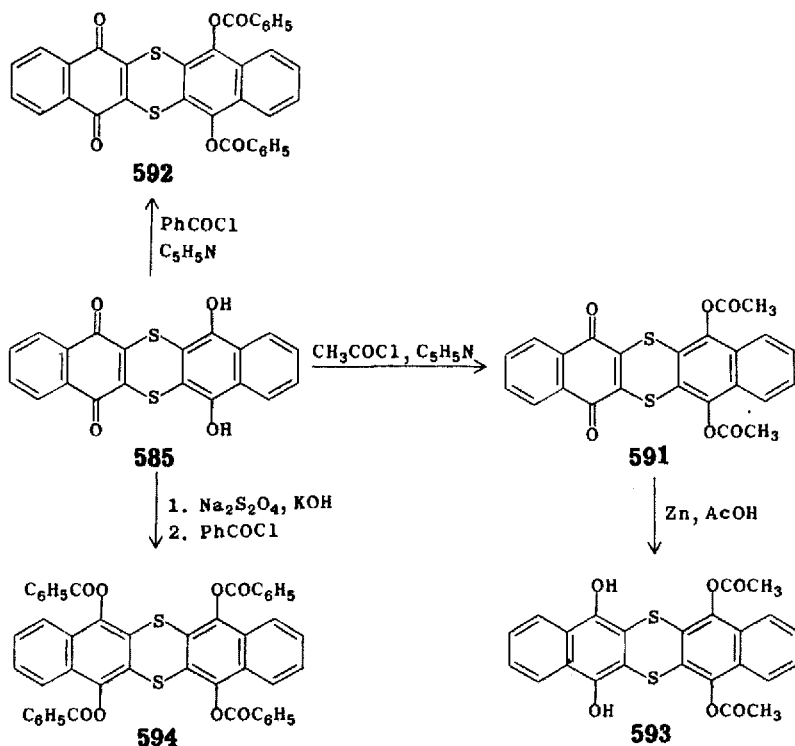
The dibenzothianthrenetetrone was reduced to a soluble vat dye with alkaline hydrosulfite, but this was only a faint dye for unmordanted cellulose. With zinc or iron and acetic acid it was reduced to a mixture of dihydroxydione (**585**) and tetrahydroxy compound (**589**); hydrogen iodide effected complete reduction. Reduction in the presence of acetic anhydride gave the colorless tetraacetate (**590**).



The dihydroxydione (**585**) could be recrystallized from aniline, in the absence of oxygen, to yield deep blue needles. Although stable to air when dry, a variety of oxidizing agents converted it back to the tetrone. Esterification gave a green diacetate (**591**), melting unsharply at 265–268°, and a red dibenzoate (**592**), which appeared green under the microscope, melting at about 290°. Both esters hydrolyzed to **585** when

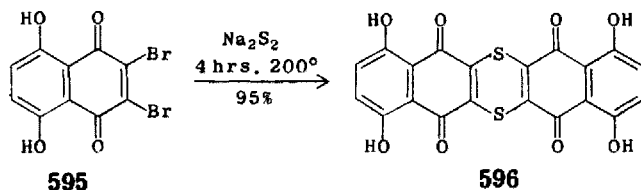
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dissolved in sulfuric acid. Reduction of the diacetate (**591**) gave the dihydroxydiacetate (**593**), which was sensitive to oxidation and melted at 262° with decomposition, while reduction of the tetrone (**583**) or the dihydroxydione (**585**) with alkaline hydrosulfite followed by treatment with benzoyl chloride yielded the colorless tetrabenzoate (**594**), melting at about 360°.



Several of these compounds were patented by Brass.⁶⁴

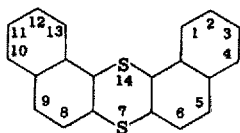
In order to improve the dyeing properties of this type of vat dye, Brass, Pfluger, and Honsberg⁶⁷ carried out the same synthesis with di-bromonaphthazarin (**595**) to form 1,4,8,11-tetrahydroxydibenzo[*b,i*]thianthrene-5,7,12,14-tetrone (**596**). In this case excess sodium sulfide gave a mixture of sodium salts, and best yields were obtained with equimolar amounts of the two reagents.



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The compound was isolated as a brown-black, amorphous solid, which would not melt below 320°. It was slightly soluble in dichlorobenzene, nitrobenzene, and pyridine to give violet solutions. It gave a blue solution in dilute alkali and in concentrated sulfuric acid. Treatment with alkali and hydrosulfite gave a red-yellow vat, turning blue in air, which dyed cotton a deep violet; the dye was not fast, however. Treatment of the hydrosulfite vat with benzoyl chloride yielded a colorless, amorphous octabenzoate melting at 283°.

3. Dibenzo[*a, j*]thianthrene (597)

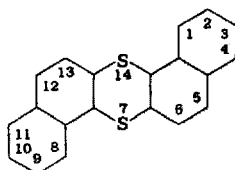


597

(RRI 6252)

This structure was assigned to the compound prepared by Fries and Volk¹⁹² from 2, 2'-dinaphthyl disulfide and sulfuric acid. The preponderance of evidence indicates that the compound is dibenzo[*a, h*]thianthrene (see next section). The [a, *j*] isomer has probably never been prepared.

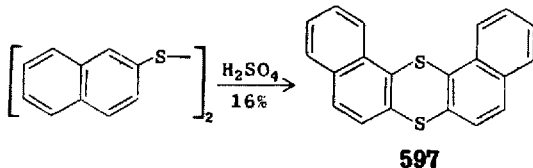
4. Dibenzo[*a, h*]thianthrene (598)



598

(RRI 6253)

Fries and Volk¹⁹² reacted 2, 2'-dinaphthyl disulfide with sulfuric acid and isolated a compound in the form of colorless needles, m.p. 184°, to which they assigned the structure dibenzo[*a, j*]thianthrene (597).

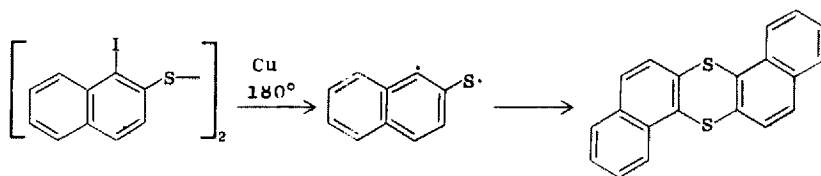


597

Hinsberg²⁶³ prepared the same compound by irradiating the disulfide dissolved in a mixture of acetic acid and benzene containing a trace of

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iodine. Neither synthesis gives an unequivocal proof of structure. However, Barber and Smiles³² prepared the same compound from bis(1-iodonaphthyl-2) disulfide and copper. Inasmuch as bis(4-iodotolyl-3) disulfide yielded 2, 7-dimethylthianthrene and not the 2, 8-isomer, it follows that the sulfur-sulfur bond must cleave and react in the positions occupied by the iodine atoms, presumably by a free radical mechanism. In the naphthalene case this would lead to dibenzo[*a, h*]thianthrene (598), and there remains little doubt that the structure assigned by Fries and Vogt is incorrect.

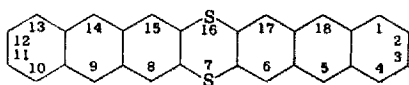


598

It is rather surprising that Barber and Smiles did not point out the improbability of obtaining the [*a, j*] isomer from their compound.

S. C₄S₂-C₆-C₆-C₆-C₆-C₆-C₆

1. Dinaphtho[2, 3-*b* : 2', 3'-*i*]thianthrene (599)

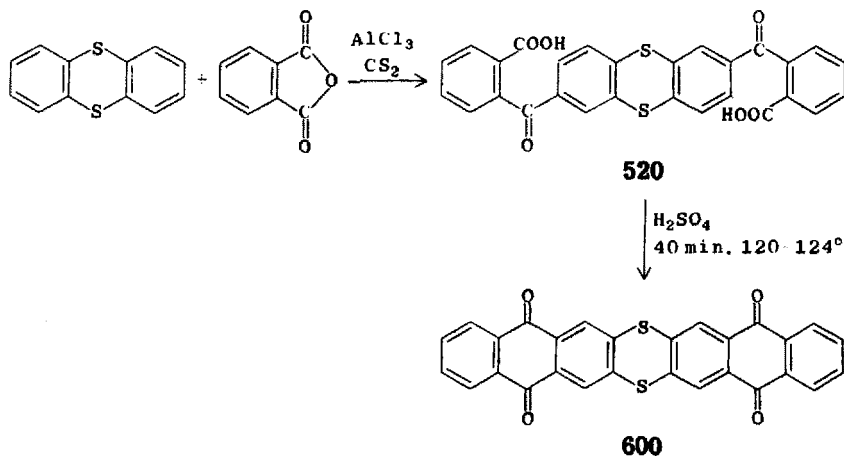


599

(RRI 7291)

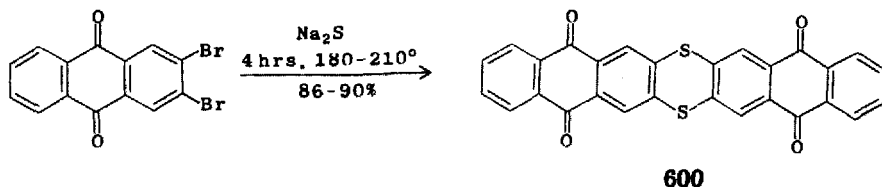
This ring system, indexed in Chemical Abstracts as β, β' -dinaphtho-thianthrene, was first prepared by Schöll and Seer.⁴³⁹ 2, 7-Bis(*o*-carboxybenzoyl)thianthrene (520) was prepared from thianthrene and two moles of phthalic anhydride (see section III K-6). Ring closure with sulfuric acid yielded dinaphtho[2, 3-*b* : 2', 3'-*i*]thianthrene-5, 9, 14, 18-tetrone (600) as a brown-red microcrystalline powder, which did not melt below 325°. It gave a grass-green solution in sulfuric acid.

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The soluble vat formed with alkaline hydrosulfite was useless for dyeing.

Although the properties of the compound did not agree too well with those of the same compound prepared by Brass and Heide⁶⁵ by a more unequivocal synthesis, the latter authors considered the two to be identical. Reaction of 2,3-dibromoanthraquinone with sodium sulfide gave the same compound, isolated as small brown needles, after recrystallization from nitrobenzene, which did not melt below 360° . However, the compound prepared by Brass and Heide gave a brown solution in sulfuric acid, the compound being recovered unchanged on dilution.



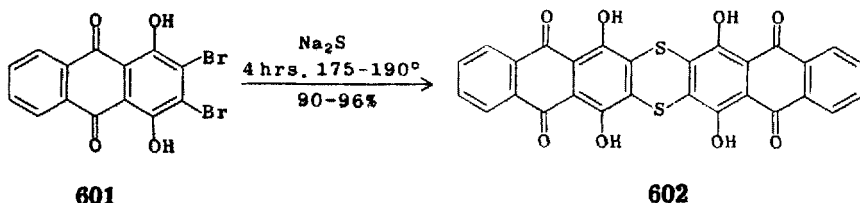
Reduction with alkaline hydrosulfite or with zinc and alkali gave a blood-red vat which dyed cotton a yellow-olive shade. Acidification of the vat gave dinaphtho[2,3-*b*:2',3'-*i*]thianthrene-5,9,14,18-tetrol, isolated as greenish yellow needles from ethanol, while treatment of the alkaline solution with benzoyl chloride gave the corresponding tetrabenzoate as golden yellow needles, which decomposed at 320° . Both the tetrahydroxy compound and the tetrabenzoate gave the tetrone on solution in sulfuric acid, benzoic acid being recovered quantitatively in the latter case.

It is rather surprising that 600, according to Brass and Heide, is stable to hot concentrated nitric acid. The tetrone was unchanged in boiling nitrobenzene, no sulfur being lost, in contrast to those compounds with the carbonyl groups adjacent to the sulfur atoms.

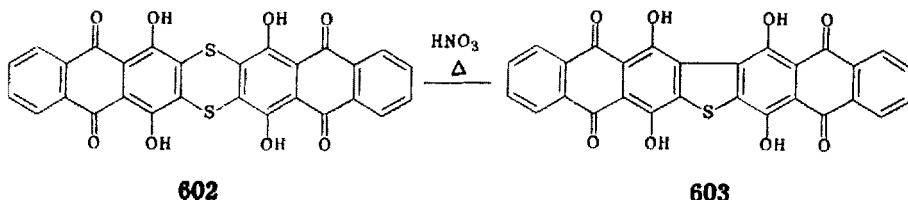
Brass and Heide also prepared 6,8,15,17-tetrahydroxydinaphtho[2,3-

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b:2',3'-*i*thianthrene-5,9,14,18-tetrone (**602**) from 2,3-dibromoquinizarin (**601**) and sodium sulfide.

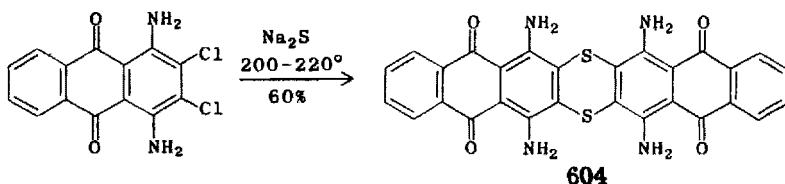


The compound was isolated as dark green needles with a metallic luster, and did not melt below 360°. Like similar compounds of this type, it dissolved in hot aniline, nitrobenzene, and pyridine with a violet color. It gave a blue solution in sulfuric acid and was recovered unchanged on dilution. No sulfur was eliminated in hot nitrobenzene, but the compound dissolved in concentrated nitric acid and, on heating, yielded a compound formulated as 6,8,15,16-tetrahydroxydinaphthra[2,3-*b*:2',3'-*d*]thiophene-5,9,14,17-tetrone (**603**); the formation of the compound in the presence of a strong oxidizing agent is questionable.



602 gave a tetraacetate with acetic anhydride, isolated as brown leaflets, and a greenish-yellow tetrabenzoate with benzoyl chloride. Both compounds were readily hydrolyzed with sulfuric acid. **602** gave a clear red vat dye with alkaline hydrosulfite which dyed cotton a dark blue, the color of the sodium salt, turning violet-red with acid. Wool was dyed a brown-violet, and both colors were very fast. Zinc and alkali gave the same vat dye, acidification of which gave dinaphtho[2,3-*b*:2',3'-*i*]thianthrene-5,6,8,9,14,15,17,18-octaol as an orange solid, m. p. 238-244°, which was readily oxidized back to **602**. The hydrosulfite vat dye with benzoyl chloride yielded the corresponding octabenzoate as pale yellow needles, m. p. 240-244°.

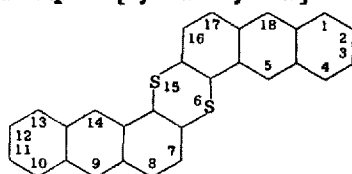
In an analogous synthesis 1,4-diamino-2,3-dichloroanthraquinone with sodium sulfide yielded 6,8,15,17-tetraaminodinaphtho[2,3-*b*:2',3'-*i*]thianthrene-5,9,14,18-tetrone (**604**).



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The compound was isolated as deep blue, coppery needles, with properties quite similar to those of **602**. Thus, it gave a red vat dye which dyed cotton and wool blue, the color being fast to washing on cotton but not on wool. Benzoyl chloride gave a tetrabenzoyl derivative, isolated as greenish-yellow needles, which dyed cotton a fast light brown from a red vat dye. Treatment of the hydrosulfite vat from **604** with benzoyl chloride yielded the corresponding octabenzoyl derivative, isolated as pale yellow, prismatic needles melting at 302° with decomposition.

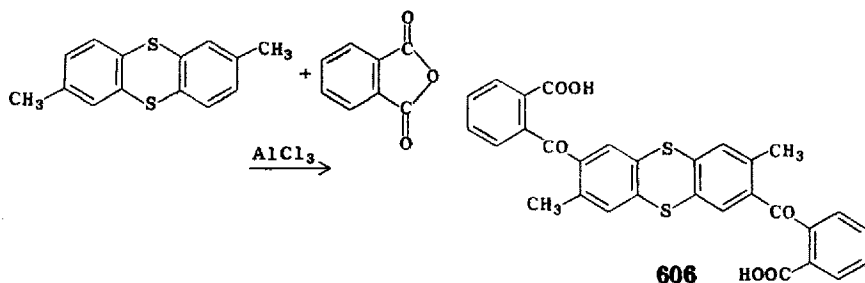
2. Dinaphtho[2, 3- α : 2', 3'-*h*]thianthrene (**605**)



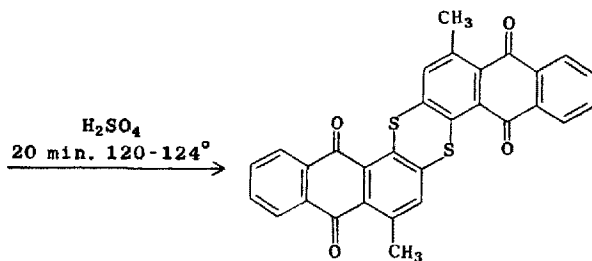
605

(RRI 7292)

This ring system, indexed as α, γ' -dinaphthothianthrene in early volumes of Chemical Abstracts, was first prepared by Scholl and Seer.⁴³⁹ Treatment of 2, 7-dimethylthianthrene with phthalic anhydride yielded 2, 7-dimethyl-3, 8-bis(*o*-carboxybenzoyl)thianthrene (**606**), ring closure of which with sulfuric acid gave 8, 17-dimethyldinaphtho[2, 3- α : 2', 3'-*h*]thianthrene-5, 9, 14, 18-tetrone (**607**) as red-brown needles, m.p. 380-385° (dec.).



606

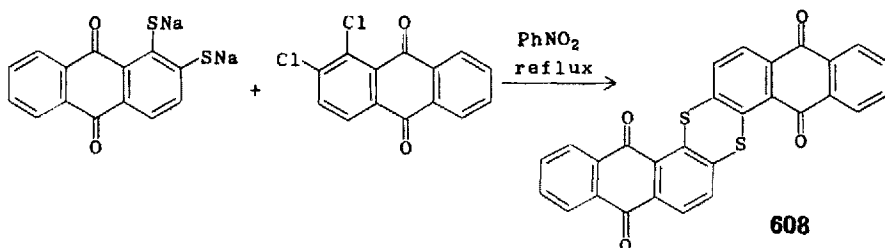


607

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The compound gave a green solution in sulfuric acid and dyed cotton pale yellow.

A German patent²⁷ described the demethylated compound (**608**), prepared from the disodium salt of 1,2-dimercaptoanthraquinone and 1,2-dichloroanthraquinone.



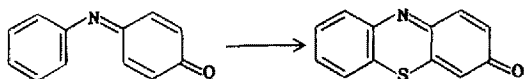
608 was isolated from nitrobenzene as metallic red crystals. It gave a green-blue solution in sulfuric acid and vat dyed wool a brick-red. Brass and Heide⁶⁵ prepared it from 1,2-dibromoanthraquinone and sodium sulfide, and the properties of the two products agree reasonably well. These latter authors described a red hydrosulfite vat dye, which dyed cotton fast red. Treatment of the vat solution with benzoyl chloride gave the tetrabenzoate of dinaphtho[2,3-*a*:2',3'-*h*]thianthrene-5,9,14,18-tetrol as yellow leaflets, while acidification of the vat dye gave the readily oxidizable tetrol itself.

More recently Hiyama, Ito, and Noguchi²⁶⁵ described the preparation of **608** by the procedure of the German patent in 18% yield and claimed that treatment with zinc and ammonium hydroxide removed the carbonyl groups and yielded the parent compound, dinaphtho[2,3-*a*:2',3'-*h*]thianthrene (**605**); however, the compound was not described.

T. SULFUR DYES

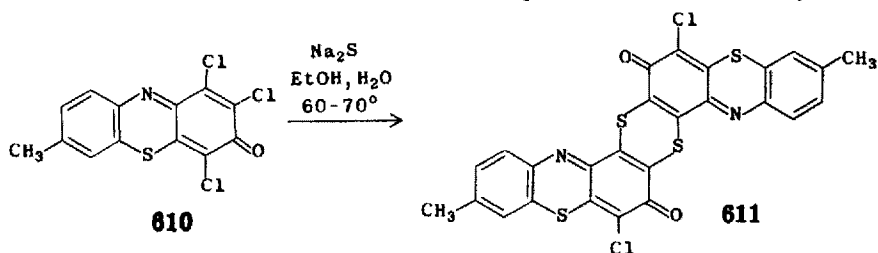
A variety of aromatic hydroxy, amino, or nitro compounds, when heated with sulfur or with sodium polysulfide, yield amorphous, high molecular weight, colored materials. These are reducible with aqueous sodium sulfide to water-soluble derivatives, which are substantive to cellulose and which become insoluble upon oxidation. The materials are known as sulfur dyes and have been used commercially for about eighty years.^{332,500}

With few or no exceptions the sulfur dyes are amorphous and of variable composition, and no pure compounds have been isolated. Zerweck, Ritter, and Schubert⁵²¹ were among the first to postulate that some sulfur dyes contain thianthrene rings as part of their chromophore. In view of the fact that it has rarely been possible to isolate a simple, known species from a sulfur dye, their evidence was necessarily indirect. These authors believed that the first step in the reaction of quinone imines with polysulfide leads to the formation of phenothiazones (**609**).



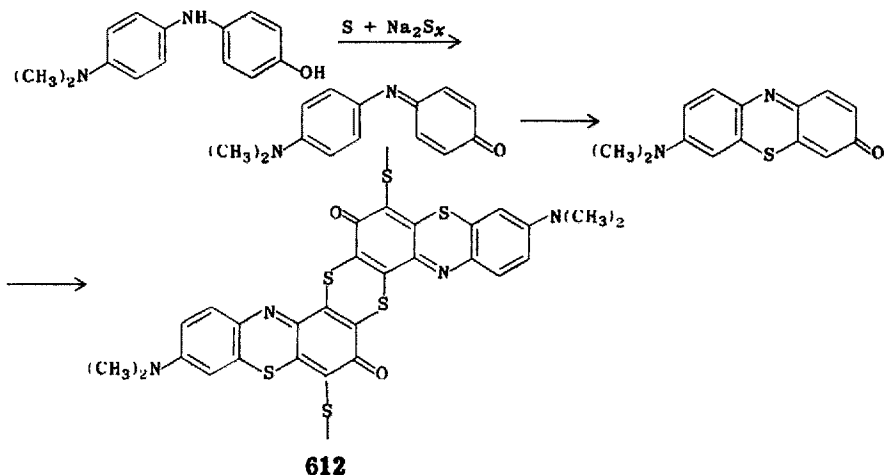
609

Subsequent reaction with polysulfide then yields the sulfur dye containing a thianthrene ring. As evidence for this they reacted 1, 2, 4-trichloro-7-methylphenothiazone (610) with one mole of sodium sulfide and isolated a crystalline product formulated as 611, whose properties were not described. The structure was assigned on the basis of analysis



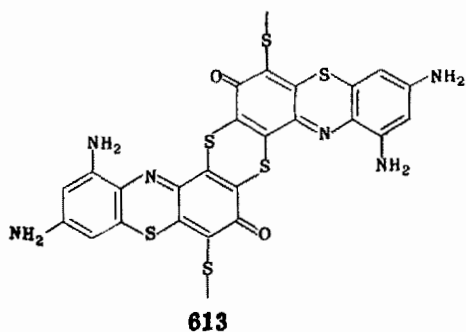
and by analogy with the reaction of 2, 3-dichloronaphthoquinone with sodium sulfide to yield a thianthrene derivative as described by Brass and Köhler⁶³ (see section III R-2). Solution in sodium sulfide yielded a dye very similar in properties to that prepared from *p*-hydroxydiphenylamine, the precursor of the quinone imine.

From evidence such as this, Zerweck and his co-workers⁵²¹ reached the conclusion that dyes formed by thionation of quinone imines, phenothiazones, phenoxazones, etc., contain thianthrene rings in their structure. Thus, *p*-dimethylamino-*p*'-hydroxydiphenylamine yields Immedial Pure Blue (612).

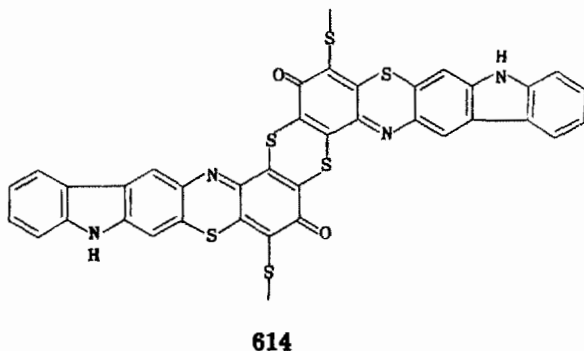


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Immedial Black V has been similarly postulated to be **613**.



Hydron Blue R, an important sulfur dye derived from carbazole, has been formulated as **614**.



However, other structures have been proposed for these dyes,^{332,500} and additional evidence would be desirable.

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C_4S_2 Ring Systems

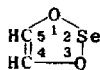
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RING SYSTEMS CONTAINING SELENIUM AND TELLURIUM

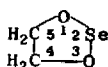
I. C_2O_2Se AND C_2O_2Te RING SYSTEMS

In contrast to the C_2O_2S ring system (Chapter 1), the C_2O_2Se and C_2O_2Te ring systems have been barely scratched. Through 1960, there have been only three papers on these two ring systems.^{1,11,72}

Five-membered rings containing two oxygens and a selenium or tellurium are known with only one arrangement of the hetero atoms, 1, 3-dioxo-2-selenium or -2-tellurium. In this arrangement they are selenite or tellurite esters of glycols and phenols.

A. C_2O_2Se 1, 3, 2-DIOXASELENOLE (1) AND 1, 3, 2-DIOXASELENO-LANE (2)

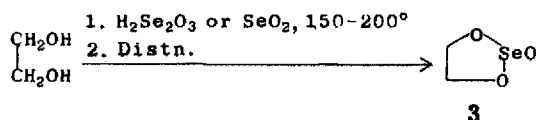
1



2

The parent compound and its 2-oxide, the cyclic selenite of an enediol, are unknown. The only reported member of this ring system is 1, 3, 2-dioxaselenolane 2-oxide, the cyclic selenite of ethylene glycol.

Simon and Heintz⁷² prepared 1, 3, 2-dioxaselenolane 2-oxide (3) by dissolving selenic acid or selenium dioxide in ethylene glycol at 150-200° and rapidly distilling off the water of reaction.

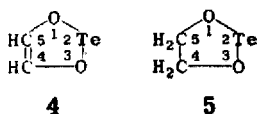


3

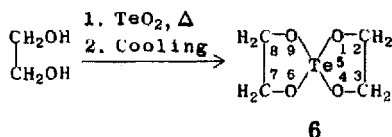
No yield or property of 3 was reported, except that heating it with disodium glycolate, alkali alcoholates, alkali metals, or toluenesulfonic acid results in no polymerization. The structure of 3 was verified by infrared and Raman spectra, which were similar to those of succinic anhydride and of 1, 3, 2-dioxathiolane 2-oxide.

Ring Systems containing Selenium and Tellurium

B. C_2O_2Te 1, 3, 2-DIOXATELLUROLE (4) AND 1, 3, 2-DIOXATELLUR- OLANE (5)

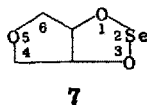


Only one member of this ring system has been reported, 1, 4, 6, 9-tetroxa-5-tellurasp[4.4]nonane (6). Tellurium dioxide is more difficultly soluble in ethylene glycol than is selenium dioxide. Simon and Heintz,⁷² on dissolving tellurium dioxide in boiling ethylene glycol and cooling the mixture, obtained 1, 4, 6, 9-tetroxa-5-tellurasp[4.4]nonane (6) as a white precipitate which, after purification by sublimation, melted at 201-202°. Elemental analysis and molecular weight determination confirmed the assigned structure.

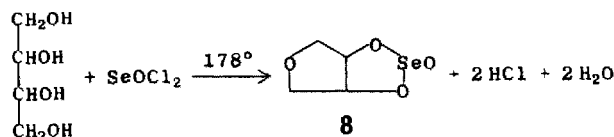


6 showed no tendency to polymerize. It is colorless in water-free organic solvents; addition of water, however, causes tellurium oxide to separate. This sensitivity of 6 makes it useful for the detection of water.

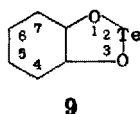
C. $C_2O_2Se-C_4O$ Furo[3, 4-*d*]-1, 3, 2-DIOXASELENOLE (7)



Chabrie and Jacob¹¹ reported the only member of this ring system, tetrahydrofuro[3, 4-*d*]-1, 3, 2-dioxaselenole 2-oxide (8), colorless needles, softening at 150° and melting at 155°, by the reaction of erythrite with selenium oxychloride. The structure was not confirmed.

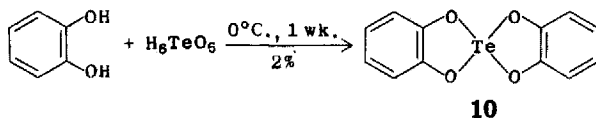


D. $C_2O_2Te-C_6$ 1, 3, 2-BENZODIOXATELLUROLE (9)

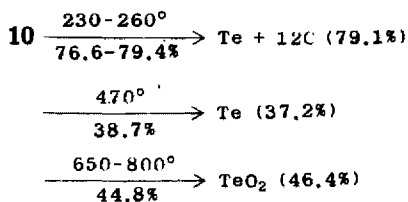


Chapter 13

Only one member of this ring system has been reported, 2, 2'-spirobi-1, 3, 2-benzodioxatellurole (**10**), which was prepared by Antikainen and Mälkönen¹ from the reaction of telluric acid with pyrocatechol in aqueous solution and partially in the fused state.



Carrying out the reaction at room temperature for 20 hours resulted in a 0.5% yield. **10**, which is difficultly soluble, was obtained as yellow to yellow-green crystals, melting at about 230° with decomposition. Its structure was confirmed by infrared spectrum and thermogravimetric analysis. Its thermal decomposition yielded the following residues (theoretical yields are given in parentheses after the products):



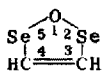
Antikainen and Lundgren,^{1a} in a crystal structure study of **10**, reported that the crystals are monoclinic with $a = 22.6$, $b = 6.93$, and $c = 16.5 \text{ \AA}$, $\beta = 123.3^\circ$, and $V = 2.17 \times 10^3 \text{ \AA}^3$, and that the crystals contain eight formula units per unit cell giving a calculated density of 2.10 g/ml.

Antikainen and co-workers called **10** tellurium(IV) pyrocatecolate; Chemical Abstracts indexed it under *o*-phenylene tellurate(IV).

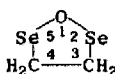
II. C₂OSe₂ RING SYSTEMS

As expected from the C₂OS₂ ring system (Chapter 2), which has a small literature, the C₂OSe₂ ring system is represented by only two members: 1, 2, 5-oxadiselenolane and the bicyclic derivative, [1, 2, 3]oxadiselenolo[3, 2-*b*][1, 2, 3]oxadiselenole. The tellurium analogs are unknown.

A. C₂OSe₂ 1, 2, 5-OXADISELENOLE (**11**) AND 1, 2, 5-OXADISELENO-LANE (**12**)



11



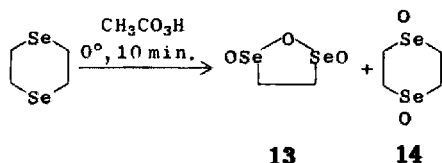
12

The parent ring (**11**) is unknown and its dihydro class is represented by only one derivative, 1, 2, 5-oxadiselenolane 2, 5-dioxide (**13**), which

Ring Systems containing Selenium and Tellurium

Chemical Abstracts indexed under 1, 2-ethanediseleninic anhydride.

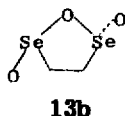
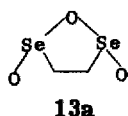
1, 2, 5-Oxadiselenolane 2, 5-dioxide was first reported by Gould and Post,³⁴ who prepared it in 14% yield by treating 1, 4-diselenane in glacial acetic acid with peracetic acid.



The expected product in this reaction was **14**, which was obtained in 30% yield. **13**, isolated in low yield as a dense white solid, presumably arose through the oxidative degradation of the diselenane ring system. **13**, an alkane seleninic anhydride, surprisingly could be recovered unchanged by crystallization from aqueous methanol.

13 darkens at 95°, taking on a yellow color, and melts at 100-102°. It decomposes slightly on standing in warm humid air for one week. Its density was reported as 2.92 g/ml.

Gould and Post pointed out that if the configuration of the three bonds about the selenium atoms is pyramidal, **13** should be capable of existence in *cis* (**13a**) and *trans* (**13b**) forms.



X-ray diffraction confirmed the structure to be *trans* and allowed the bond distances and angles given in Table 1 to be calculated.

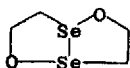
TABLE 1. Bond Distances and Angles in **13b**

Distances (Å)		Angles	
Se-C	1.99 ± 0.04	C-C-Se	107 ± 2°
Se-O _e (exocyclic)	1.61 ± 0.03	C-Se-O _e	107 ± 3°
Se-O _c (cyclic)	1.82 ± 0.02	O _e -Se-O _c	106 ± 2°
C-C	1.59 ± 0.07	C-Se-O _c	91 ± 1°
Se-Se	3.19 ± 0.01	Se-O _c -Se	123 ± 3°

A major structural feature of interest pointed out by Gould and Post is the tight packing of molecules within the crystal of **13b** resulting in the very high density of 2.92, which is the highest density which has been reported for an organoselenium compound containing no other heavy atoms.

Chapter 13

B. $C_2OSe_2-C_2OSe_2[1, 2, 3]$ OXADISELENOLO[3, 2-*b*] [1, 2, 3]-OXADISELENOLE (15)

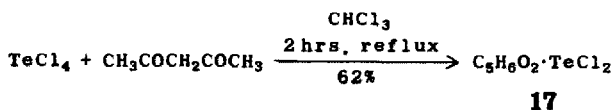
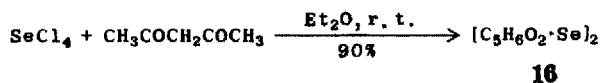


15

(RRI 867)

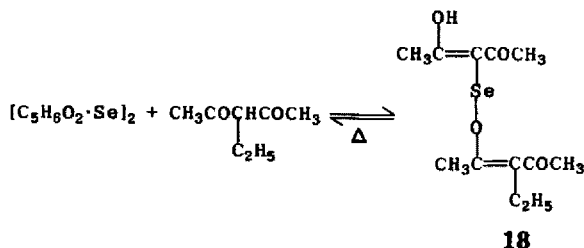
This ring system was studied by Morgan and co-workers^{55-57,59,60,62} between 1920 and 1924. Chemical Abstracts indexed the few compounds in this ring system under selenium, such as selenium acetylpropionylmethane. The parent compound (15) has not been reported. Members of this ring system have been prepared by the reaction of selenium tetrachloride with a 1, 3-diketone or its copper derivative.

Morgan and Drew in 1920,⁵⁵ on reacting $SeCl_4$ and $TeCl_4$ with acetylacetone, or copper acetylacetone, observed two different kinds of products, 16 and 17 (see section XA).



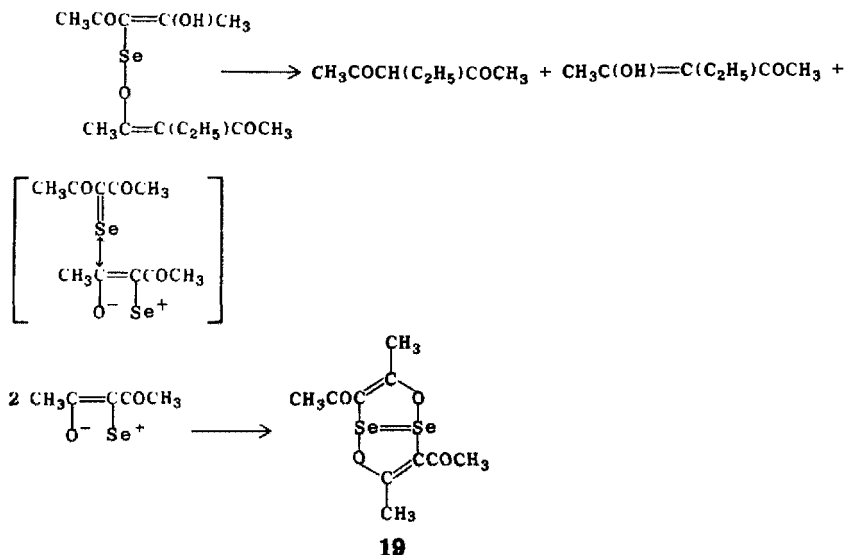
It was not until 1922, however, that Morgan and co-workers elucidated the structure⁵⁹ and extended the reaction to other β -diketones.^{59,60,62}

16 is a well defined pale yellow, crystalline, dimeric compound, melting at 185° (sealed tube),⁵⁵ and without enolic properties. It reacts with 3-ethylacetylacetone to form 18 which on heating or treatment with alkali is converted to 16.

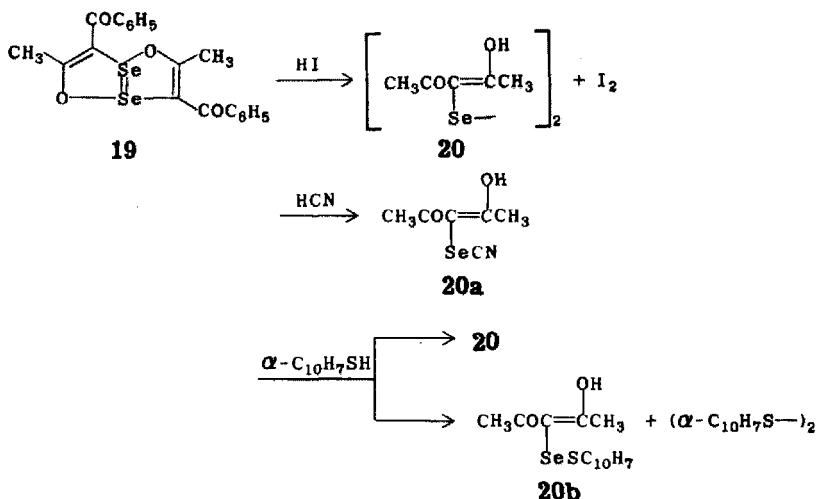


These facts indicate the following reaction course and lead to the assignment of structure 19 for 16.

Ring Systems containing Selenium and Tellurium



19 on treatment with hydriodic acid is converted to bis(2, 4-pentanedione)-3, 3'-diselenenide (**20**), which is also a minor product in the condensation of copper acetylacetonate with selenium tetrachloride. **19** reacts with hydrogen cyanide to give 2, 4-pentanedione-3-selenocyanate (**20a**) and with α -naphthyl mercaptan to give 3-(α -naphthylthioseleno)-2, 4-pentanedione (**20b**) in competition with **20** and α, α' -dinaphthyl disulfide.

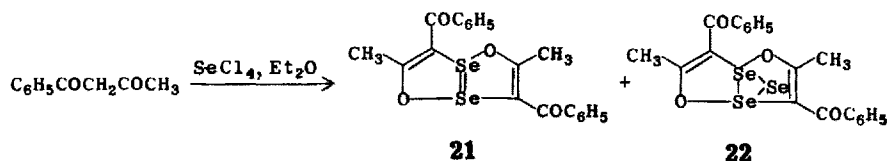


The preferred procedure for the preparation of **19** is the reaction of equimolar quantities of copper acetylacetonate and selenium tetrachloride suspended in chloroform in a salt-ice bath; a yield of 69% was obtained. Using a slight excess of selenium tetrachloride gave a 78%

yield. An excess of copper acetylacetonone caused an increase in by-product formation, bis(2, 4-pentanedione)-3, 3'-diselenide in particular.

19 is not affected by methyl or ethyl iodide or acetone. Acetonitrile is an excellent solvent for its recrystallization. Hydrogen chloride in dry ether dissolves **19** without reaction, whereas hydrochloric acid decomposes **19** into selenium and chloroacetylacetone. **19** is decomposed by ammonia in a sealed tube to give selenium, acetamide, and hydrocyanic acid. It is reduced by potassium bisulfite to acetylacetone and potassium selenodithionate.⁵⁷

The reaction between selenium tetrachloride and benzoylacetone in ether resulted in two products,⁵⁹ **21** and **22**, which were separated by extraction with benzene; **22** remained in the benzene.



Similarly, the reaction between selenium tetrachloride and a slight excess of copper benzoylacetone in chloroform gave a 5% yield of **21** and a 6% yield of **22**. On using silver benzoylacetone, **21** was obtained without **22**.

21, obtained as small, yellow needles, exists in two forms, one becoming discolored at 175° and decomposing to a reddish-brown tar at 200°, the other beginning to change color at 207° and melting sharply at 210-212°. **21**, separated from toluene, had a faint elderberry odor. It is insoluble in water, ether, and alcohol; sparingly soluble in boiling chloroform, benzene, and ethyl acetate; and somewhat soluble in toluene and acetic acid. The reaction of **21** with HI and with HCN is similar to that of **19**.

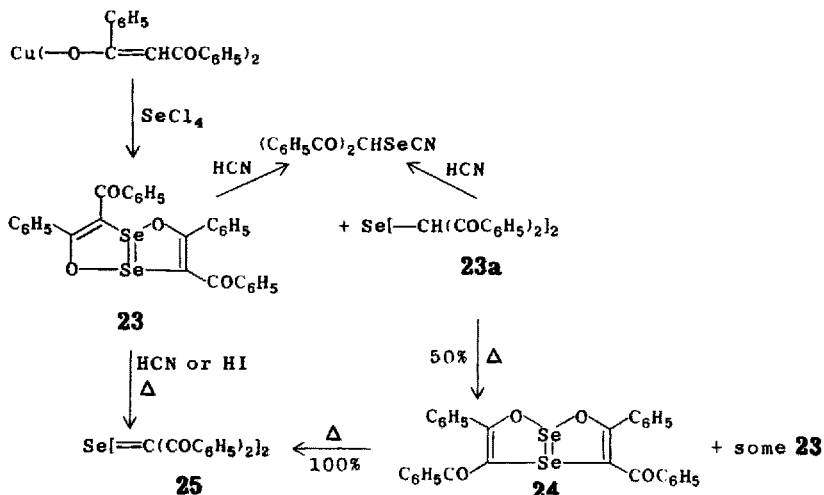
It is unlikely that **22** has the structure assigned by Morgan, Drew, and Barker.⁵⁹ **22** was obtained as bright yellow crystals; it had no odor, was insoluble in alcohol, ether, and water, somewhat soluble in cold benzene and chloroform, and was best crystallized from boiling ethyl acetate. It sintered and darkened at 190-195°, liberating selenium and changing to a dark tar at 196-200°. Its analysis corresponded to $\text{C}_{20}\text{H}_{16}\text{O}_4\text{Se}_3$; its molecular weight, however, was about 5% high for this formula. Its structure remains to be elucidated. Indeed, the assignment of many structures in this heterocyclic series is open to question.

Failure to obtain a product analogous to **19** from the reaction of copper 3-ethylpenta-2, 4-dione with selenium tetrachloride indicated that the selenium reacts on the middle carbon atom of the diketone.⁵⁹

23 was obtained in a 10% yield by reacting copper dibenzoylmethane with selenium tetrachloride in chloroform at room temperature and separating from selenium bisbenzoylmethane (**23a**) by fractional crystallization from ethyl acetate.⁵⁹

Ring Systems containing Selenium and Tellurium

23 undergoes the usual reaction with HCN and HI. On heating **23a** at 135–150° for one-half hour, about 50% underwent reaction to yield **24**. On heating **23a** above 150°, half of the selenium present was set free with the formation of **25**, slowly at 155° and rapidly at 180°.

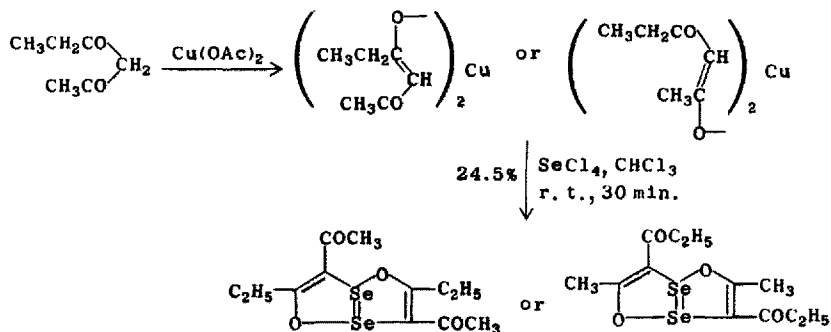


23 was crystallized from benzene as lustrous, pale golden-yellow plates containing two molecules of benzene of crystallization. When freed from benzene, it was obtained as a pale primrose-yellow powder melting at 211° to a deep yellow liquid with liberation of selenium. It is sparingly soluble in boiling ethyl acetate, moderately soluble in benzene, and readily soluble in chloroform.

24, recrystallized from ethyl acetate in rosettes of pale golden-yellow needles or flakes, melted at 175–176°. A mixed melting point with **23** was markedly depressed. **24** was sparingly soluble in ethyl acetate, insoluble in ether, and readily soluble in benzene or chloroform. Its behavior with HCN and HI was characteristic but different from that of **23**, as selenium was set free with production of **25**.

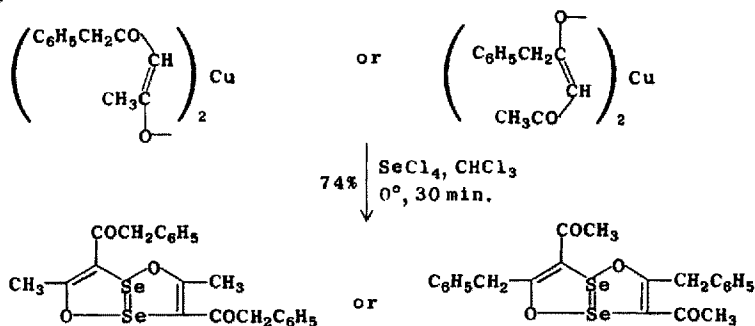
The reaction of copper acetylpropionylmethane with selenium tetrachloride in CHCl_3 gave a **24**, 5% yield of **26** as pale-yellow glistening plates melting at 137° (from ethyl alcohol). **26** yielded selenium on warming with alcoholic aniline and became superficially coated with red selenium on exposure to light. It underwent the expected reactions with HCN and HI. The two possible structures of **26** were not elucidated.⁶⁰

Chapter 13

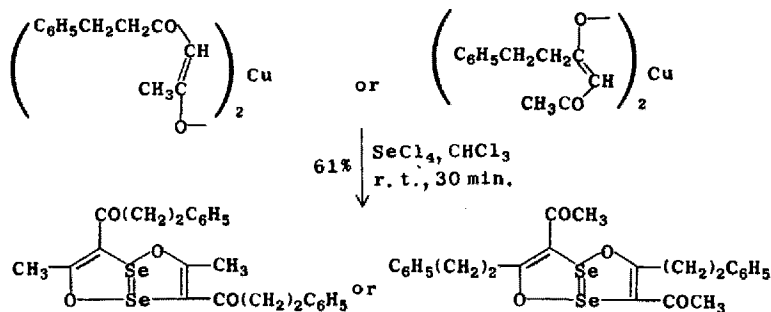


26

Similarly, the structures of **27** and **28** could not be assigned to either of the two possibilities from the reaction of the unsymmetrical diketone copper enolate and selenium tetrachloride.⁶²



27



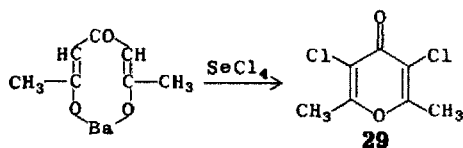
28

27, recrystallized from chloroform and benzene, sintered at 161° and melted at 164-165°. Red selenium separated on warming **27** with 3 *N* sodium hydroxide or with mineral acid; it underwent the expected reaction with HCN and HI.

Ring Systems containing Selenium and Tellurium

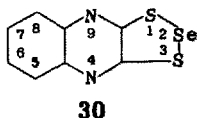
28, recrystallized from benzene as pale yellow leaflets, sintered at 128° and melted at 141-142°. It was more soluble than **27** in organic solvents.

Diacetylacetone, as the barium enolate, reacted with selenium tetrachloride to give 3, 5-dichloro-2, 6-dimethyl- γ -pyrone (**29**) rather than the expected product.⁶² The selenium tetrachloride, in this reaction, behaved as a dehydrating and chlorinating agent.

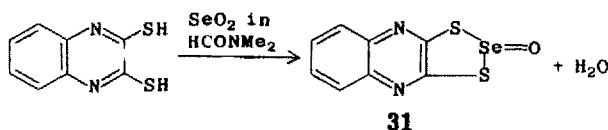


III. $\text{C}_2\text{S}_2\text{Se}$ RING SYSTEMS

$\text{C}_2\text{S}_2\text{Se}-\text{C}_4\text{N}_2-\text{C}_6$ 1, 3, 2-Dithiaselenolo[4, 5-*b*]quinoxaline (**30**)



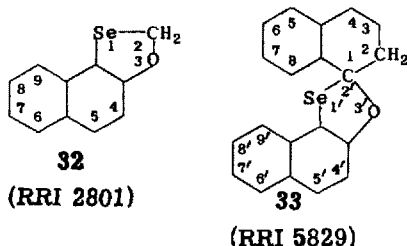
Only one member of the dithiaselenole ring system has been reported, 1, 3, 2-dithiaselenolo[4, 5-*b*]quinoxaline 2-oxide (**31**). This was prepared by Sasse, Wegler, Unterstenhöfer, and Grewe⁶⁸ in 1960 by the reaction of 2, 3-dimercaptoquinoxaline in dimethylformamide with selenium dioxide. This compound was prepared among many others in an exhaustive study of acaricides and fungicides derived from quinoxalines. **31** exhibited only a weak effect; no physical property or yield was cited.



IV. C_3OSe RING SYSTEMS

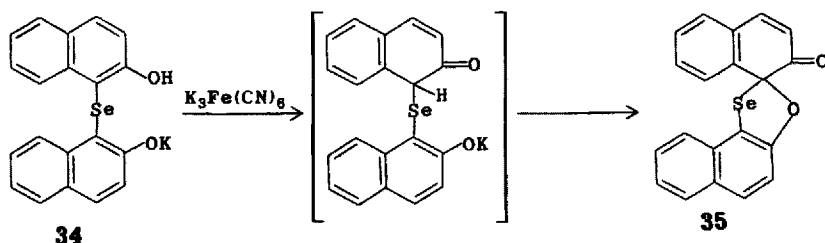
In contrast to the C_3OS ring systems (Chapter 4), the C_3OSe ring systems are represented by only three defined members and the C_3OTe ring system is not known.

A. $\text{C}_3\text{OSe}-\text{C}_6-\text{C}_6$ NAPHTH[1, 2-*d*] [1, 3]OXASELENOLE (**32**)



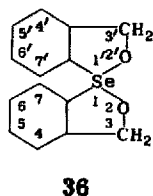
[For references, see pp. 1344-1346.]

Only one member of this ring system has been reported, spiro[naphthalene-1(2*H*), 2'-naphth[1, 2-*d*] [1, 3]oxaselenol-2-one (**35**), which Dvorkowitz and Smiles²² prepared in 1938 by treating bis(2-hydroxy-1-naphthyl)selenide (**34**) in aqueous potassium hydroxide with potassium ferricyanide and extracting the product with chloroform.

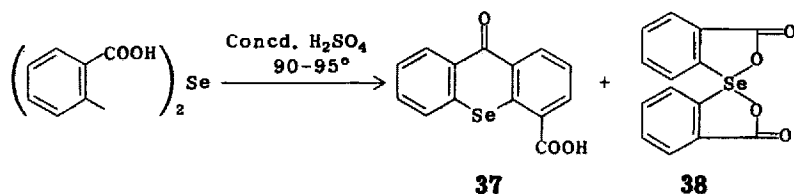


The 2-one derivative (**35**), crystallized from ethyl alcohol as a red-brown crystalline powder, melts at 145°. The compound was not characterized beyond carbon and hydrogen analyses.

B. $C_3OSe-C_3OSe-C_6-C_6$ 1, 1'-SPIROBI-(3*H*-2, 1-BENZOXASELENOLE) (36**)**



Lesser and Weiss⁴⁶ in 1913, on treating diphenylselenide-2, 2'-dicarboxylic acid with concentrated sulfuric acid, obtained two compounds, one being acid and the other neutral. The acid compound was apparently selenoxanthen-10-one-4-carboxylic acid (**37**) and the neutral compound was later⁴⁷ postulated to be 1, 1'-spirobi-(3*H*-2, 1-benzoxaselenol-3-one) (**38**).



38 was obtained from the reaction mixture as the alkali-insoluble part in long, colorless needles, melting at 323-325° with decomposition. When the reaction temperature was 90-95°, the yield of **38** was 60-70%; at a temperature of 45-50°, the yield was 10-20%, **37** being the main product.

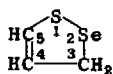
Ring Systems containing Selenium and Tellurium

Schoeller⁷⁰ obtained **38** by treating diphenylselenide-2, 2'-dicarboxylic acid with dilute nitric acid or in alkali solution with hydrogen peroxide.

38 dissolves in sodium, potassium, and ammonium hydroxide, and sodium carbonate solutions. Treating a sodium hydroxide or glacial acetic acid solution of **38** with zinc dust yielded diphenylselenide-2, 2'-dicarboxylic acid.⁴⁷

V. C₃SSe RING SYSTEMS

A. C₃SSe 3H-1, 2-THIASELENOLE (**38a**) AND 1, 2-THIASELENOLANE (**38b**)

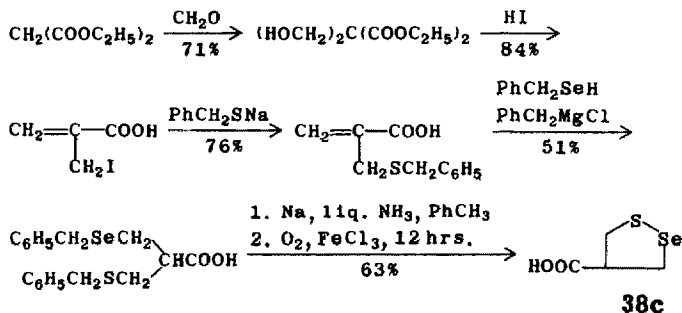


38a



38b

The only known member of this heterocyclic ring system is 1, 2-thiaselenolane-4-carboxylic acid (**38c**), which was reported by Bergson and Biezais^{7c} in 1961 as resulting from the following series of reactions:

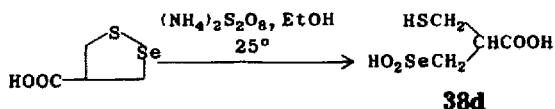


38c

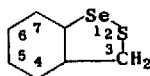
1, 2-Thiaselenolane-4-carboxylic acid was obtained as reddish-yellow crystals, melting at 105.5-107.5°, from chloroform-cyclohexane. Above the melting point, it polymerizes rapidly to a semi-solid mass, and at higher temperatures depolymerization occurs. Its ultraviolet spectrum shows a characteristic peak at 386 mμ. Its spectrum has the same shape as that of 1, 2-dithiolane-4-carboxylic acid and that of 1, 2-diselenolane-4-carboxylic acid but with maxima occurring at 386, 330, and 440 mμ, respectively.

Bergson^{7b} studied the oxidation of 1, 2-thiaselenolane-4-carboxylic acid with ammonium persulfate in aqueous ethanol and observed that it followed a path similar to that of 1, 2-diselenolane-4-carboxylic acid, the speed of the thiaselenolane-4-carboxylic acid being less than that for the diselenolane but faster than that for α-lipoic acid. Bergson postulated that in the oxidation the primary oxidation product is the thiol-seleninate (**38d**).

Chapter 13



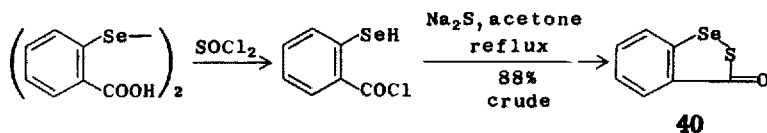
B. $\text{C}_3\text{SSe}-\text{C}_6$ 3H-2, 1-BENZOTHIASELENOLE (39)



39

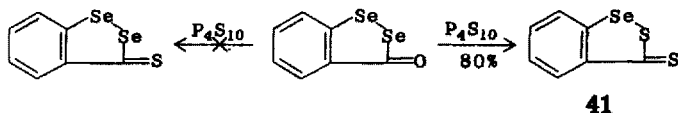
(RRI 1239)

The 3-one (**40**) was prepared by Lesser and Weiss⁴⁸ in 1924 from the reaction of sodium sulfide with an acetone solution of *o*-selenobenzoyl chloride, which they obtained on treating diphenyldiselenide-2, 2'-dicarboxylic acid with thionyl chloride.



40, recrystallized from benzene as glossy, orange prisms, melted at 83-84°. It was insoluble in hot sodium hydroxide or sodium carbonate solutions and dissolved in concentrated sulfuric acid, the solution having a yellow color.

The 3-thione, **41**, gleaming, green-red crystals, m.p. 129°, was obtained by Schmidt⁶⁹ on reacting **1**, 2-benzodiselenol-3-one with P_4S_{10} with the intention of preparing 1, 2-benzodiselenol-3-thione.



41 also has been prepared⁶⁹ by the treatment of **40** with P_4S_{10} and by heating diphenyldiselenide-2, 2'-dicarboxylic acid and P_4S_{10} in carbon disulfide at 130° for 1 hour.

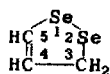
VI. C_3Se_2 RING SYSTEMS

The C_3Se_2 ring system parallels the C_3S_2 ring system. It has not been the subject, however, of numerous investigations as has the C_3S_2 ring system. Relatively little is reported on diselenole; its dihydro form, diselenolane, has been more thoroughly investigated, particularly 6-selenoctic acid, the selenium analog of 6-thioctic acid or α -lipoic acid. There have been several studies reported on benzodiselenoles and one on naphthaceno-bisdiselenole. Most of the investigators of this ring system have also been active in studies on the C_3S_2 ring system.

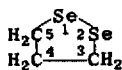
Ring Systems containing Selenium and Tellurium

All members of the C_3Se_2 ring system have the seleniums in the 1, 2-arrangement.

A. C_3Se_2 3*H*-1, 2-DISELENOLE (42) AND 1, 2-DISELENOLANE (43)



42



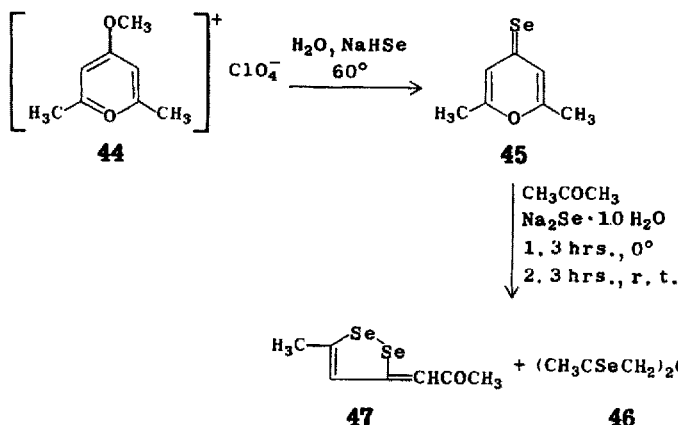
43

(RRI 139)

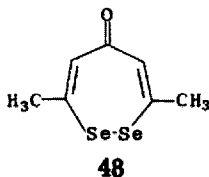
Chemical Abstracts indexes these compounds and their derivatives under 1, 2-diselenole and 1, 2-diselenolane, crossing 6-selenoctic acid to 1, 2-diselenolane-3-valeric acid. Other names for diselenolane used in the literature have been 1, 2-diselenacyclopentane² and cyclotrimethylene diselenide.⁶⁴ Sanesi and Traverso⁶⁷ employed the epidiseleno nomenclature for 1, 2-diselenole derivatives.

1. 3*H*-1, 2-Diselenole

The parent compound, 3*H*-1, 2-diselenole (42), has not been reported. The only members of this class which have been reported are 3-acetyliden-5-methyl-3*H*-1, 2-diselenole (47) (which Chemical Abstracts indexed under 2-propanone, 5-methyl-1, 2-diselenol-3-ylidene), its thione, and 2, 4-dinitrophenylhydrazone derivatives. 47 was prepared by Traverso⁷⁹ in 1957 from the reaction of 2, 6-dimethyl-4-methoxy-pyrylium salts (44) with NaHSe and Na₂Se. Whereas a pyrylium salt itself does not react with NaHSe or Na₂Se, a 2, 6-dimethylpyrylium salt, *e.g.*, 44, reacts to give supposedly 2, 6-dimethyl-4-selenopyrone (45), which reacts with Na₂Se to give 25% bis(selenoacetyl)acetone (46) and 12% diselenole (47).

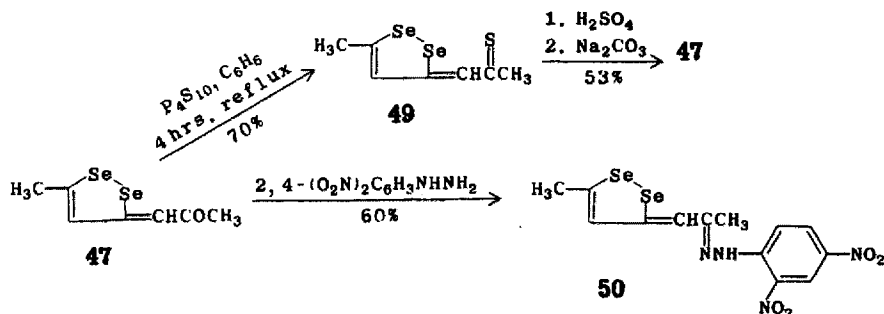


Traverso believed that he had isolated 3, 7-dimethyl-5*H*-1, 2-diselenepin-5-one (48).

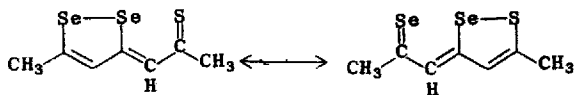


In a later study,⁶⁷ however, in which he purified his product by distilling twice at 0.3 mm and recrystallizing twice from petroleum ether, the dipole moment of 3, 30 at 20° led him to postulate a planar structure for **47** with aromatic character. This structure is in harmony with the dithiole analog which he studied at the same time.

47 was obtained as shiny, yellow needles melting at 86.1-86.8°. The thione derivative (**49**), obtained by refluxing **47** and P_4S_{10} in benzene, melted at 215-216° (from toluene) and was converted back to **47** by treatment with concentrated sulfuric acid. The 2, 4-dinitrophenylhydrazone of **47** (**50**), obtained as metallic blue crystals, melted at 280°.



This preparation of 3-acetyl-5-methyl-3H-1, 2-diselenolane and its reactions are analogous to the corresponding 1, 2-dithiole as discussed in Chapter 5, section IA-2c. The mechanism for the conversion of **45** to **47** is probably that proposed for the similar conversion to dithiole in Chapter 5. There is no evidence that **49** exists as a resonance hybrid, nor has the possibility been excluded.



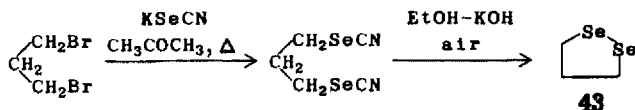
2. 1, 2-Diselenolane

a. Preparation

Table 2 lists the 1, 2-diselenolanes reported in the literature by Hagelberg³⁷ in 1890 from the reaction of 1, 3-propylene diselenocyanate with alcoholic potassium hydroxide. Hagelberg believed that his product might also be the dimer. Morgan and Burstall⁶⁴ in 1930 obtained 1, 2-diselenolane as a yellow amorphous precipitate on aspirating air

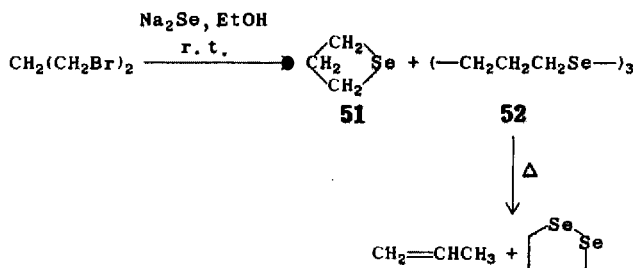
Ring Systems containing Selenium and Tellurium

through an alcoholic potassium hydroxide solution. This product, melting at 59°, showed a molecular weight of 225 in boiling benzene and not the expected 200; therefore a polymer was present.

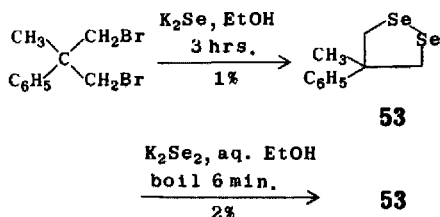


Bergson and Claeson⁴ repeated the Hagelburg and the Morgan and Burstall preparations and obtained an insoluble yellow powder which was undoubtedly the polymer. Heating this in a solvent at 60° gave a dark yellow solution containing the monomer which precipitated out as polymer on standing for several days. This difficulty in obtaining the monomer is parallel to that for dithiolane (Chapter 5, section IA-1a), with the selenium polymer showing a remarkably greater ease of depolymerization.

In contrast to the preparation of dithiolane by the reaction of 1, 3-dibromopropane with a sodium sulfide, Morgan and Burstall⁶⁴ could not prepare diselenolane by the analogous reaction using a sodium selenide. They obtained instead selenetane (51) and its trimer (52). The trimer, on gentle heating, however, yielded propylene and 1, 2-diselenolane.



On the other hand, Backer and Winter² prepared 4-methyl-4-phenyl-1, 2-diselenolane (53), although in poor yield, from the reaction of 1, 3-dibromo-2-methyl-2-phenylpropane with potassium selenide or diselenide.



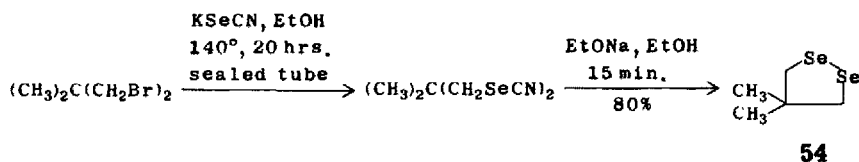
They obtained an 80% yield of 4, 4-dimethyl-1, 2-diselenolane (54), however, on treating 2, 2-dimethyl-1, 3-propylene diselenocyanate with sodium ethoxide.

TABLE 2. 1, 2-Diselenolanes

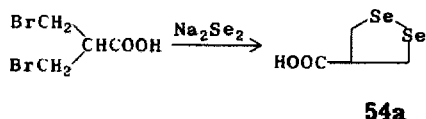


Substituent	Yield (%)	M.p. (°C)	Color	Form	Ref.
None					37
3-[HO ₂ C(CH ₂) ₃ CH ₂ -]	>50	88-90.5	yellow	amorphous	64
	56	84-86	dark brown-red	crystalline	5, 7a
4-COOH		148.5-149.5		needles	14a
4, 4-(CH ₃ -) ₂	80	34	brown	flakes	7b
4-CH ₃ -4-C ₆ H ₅ -	2	114-114.5	brown	needles	2
4, 4-(HOCH ₂ -) ₂	8	133-135	dark red	needles	6

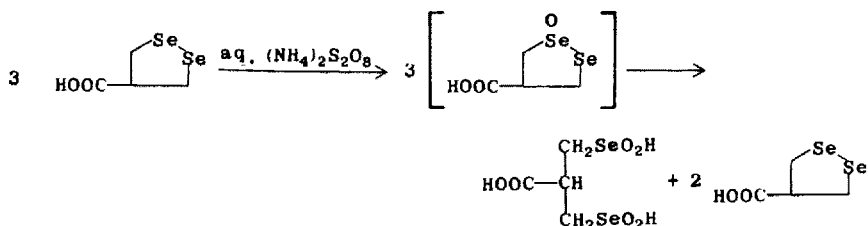
Ring Systems containing Selenium and Tellurium



Bergson^{7b} prepared 1, 2-diselenolane-4-carboxylic acid (**54a**) from the reaction of β, β' -dibromoisobutyric acid and sodium diselenide.



Oxidation of the 4-carboxylic acid (**54a**) with ammonium persulfate in aqueous ethanol was followed spectrophotometrically; the characteristic peak of the 1, 2-diselenolane ring at 440 μ reached a minimum after about 16 minutes, then increased to approximately two-thirds of the original value, which corresponds to the oxidation of one-third of the 1, 2-diselenane to seleninic acid. The initial oxidation product, presumably the monoxide, could not be isolated.

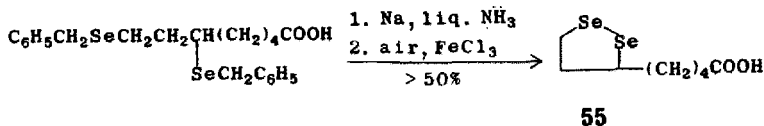


Bergson,^{5,7a} in connection with his studies on organic disulfides and diselenides, considered several ways of preparing the selenium analog of 6-thioctic acid, more commonly known as α -lipoic acid (see Chapter 5, section 1A-1b). He was interested in the selenium analog, which he called 6-selenoctic acid (**55**), because of its expected greater stability over 1, 2-diselenolane through stabilization of the ring with substituents and because 6-selenoctic acid might have interesting biological properties in comparison with α -lipoic acid. Employing a method used for the preparation of α -lipoic acid, Bergson reacted ethyl 6, 8-dichlorooctanoate with the sodium salt of benzylselenol, treated the resulting 6, 8-dibenzylselenooctanoic acid with sodium in liquid ammonia, and oxidized the reaction mixture with air in the presence of a trace of ferric chloride to give 6-selenoctic acid.

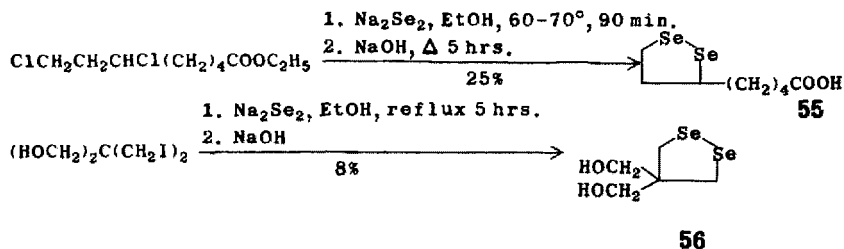
Chapter 13



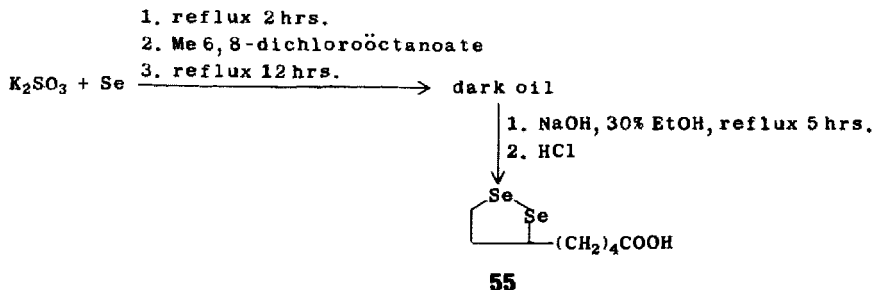
1. EtONa, EtOH, 5hrs. reflux
2. KOH, 20hrs. r. t.



On treating ethyl 6, 8-dichlorooctanoate with sodium diselenide, Bergson⁶ surprisingly obtained 6-selenoctic acid in 25% yield. This was unexpected, as Fredga²⁸ obtained only the five-membered selenophane derivative on reacting α, α' -dibromoadipic acid with potassium diselenide. It is difficult to explain why ring closure to give a five-membered ring occurs with deposition of selenium in the latter case. This synthesis also allowed Bergson to prepare 4, 4-bis(hydroxymethyl)-1, 2-diselenolane (56) in 8% yield.



Deguchi^{14a} prepared selenoctic acid in 56% yield by the following series of reactions:



b. Properties and Reactions

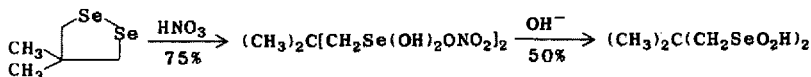
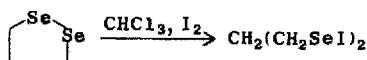
1, 2-Diselenolanes are solid compounds with melting points higher than the corresponding dithiolanes. For example, α -lipoic acid melts at 47.5-48.5° and 6-selenoctic acid melts at 88-90.5°C. Whereas the dithiolanes are yellow, diselenolanes are yellow, brown, or red. Diselenolane dimer can be distilled under reduced pressure without

Ring Systems containing Selenium and Tellurium

decomposition.⁶⁴ It is insoluble in ethyl ether, soluble in benzene, acetic acid, hot ethyl alcohol, and easily soluble in methyl iodide and ethylene bromide.³⁷

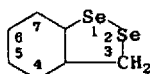
Bergson⁷ studied the electronic and steric effects on the ultraviolet and infrared spectra of several organic selenium compounds from which it is evident that diselenides behave analogously to the disulfides. The steric effect is the largest of the effects studied and was most pronounced for -Se-Se- in a five-membered ring when compared to a six-membered ring or to a dialkyl diselenide. 1,2-Diselenolane has an absorption maximum in the ultraviolet at 444 μ , 4,4-bis(hydroxymethyl)-1,2-diselenolane at 443, and 6-selenoctic acid at 442; 1,2-diselenane at 365; and diethyl diselenide at 311.5. This corresponds to a change of the dihedral angle of the two selenium atoms from 90° in diethyl diselenide to a much smaller one in 1,2-diselenolane and an intermediate one in 1,2-diselenane. Bergson's studies of these compounds was somewhat complicated in the infrared region as the absorption bands associated with selenium groups come at long wavelengths, such as 15-20 μ for the C-Se stretching and about 40 μ for Se-Se. The spectrum of 6-selenoctic acid and of diethyl diselenide due to C-Se occurred at 18.7 μ . 6-Selenoctic acid showed some relatively strong bands at 35-38 μ which might be associated with Se-Se stretching.

On treating a chloroform solution of 1,2-diselenolane with iodine, Morgan and Burstall⁶⁴ obtained a red precipitate of 1,3-propylene diselenodiiodide. Backer and Winter² obtained diselenic acids as white precipitates on treating 4,4-disubstituted-1,2-diselenolanes with nitric acid.



According to Schwarz, Foltz, and Bergson⁷¹ 6-selenoctic acid is not identical with or related to Factor 3; it has only one-fifth the potency of Factor 3 against dietary liver necrosis in the rat and pig, multiple necrotic degeneration in the mouse, and exudative diathesis in the chick and turkey.

B. $\text{C}_3\text{Se}_2\text{-C}_6$ 3H-1,2-BENZODISELENOLE (57)



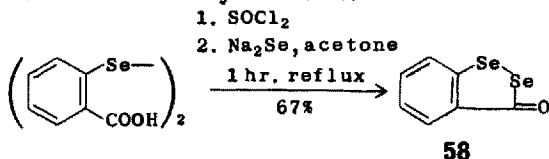
57

(RRI 1248)

[For references, see pp. 1344-1346.]

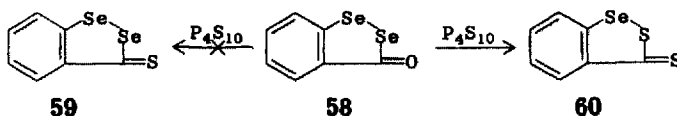
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The 3-one is the only compound of this ring system which has been reported. Lesser and Weiss⁴⁸ prepared the 3-one (**58**) in 1924 from the reaction of sodium selenide with an acetone solution of *o*-selenobenzoyl chloride which they obtained on treating diphenyldiselenide-2,2'-dicarboxylic acid with thionyl chloride.

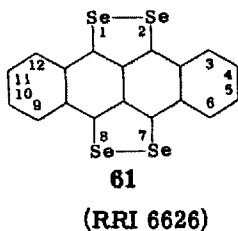


58, recrystallized from benzene as red crystals, melted at 91-92°. Lesser and Weiss called **58** diselenobenzoyl.

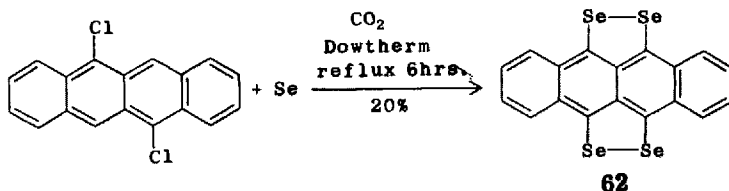
Schmidt,⁶⁹ on reacting **58** with P_4S_{10} unexpectedly obtained 3*H*-2,1-benzothiaselenol-3-thione (**60**) and no 3*H*-1,2-benzodiselenol-3-thione (**59**) (see section V B).



C. $\text{C}_3\text{Se}_2\text{-C}_3\text{Se}_2\text{-C}_6\text{-C}_6\text{-C}_6\text{-C}_6$ NAPHTHACENO[5,6*cd*: 11,12-*c'd'*] BIS[1,2]DISELENOLE (**61**)

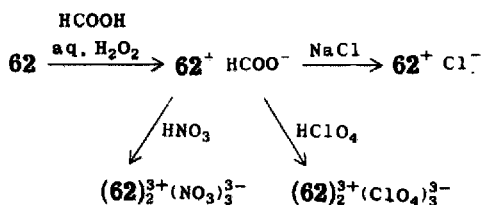


Marschalk⁴⁹ prepared naphthaceno[5,6-*cd*: 11,12-*c'd'*]bis[1,2]-diselenole (**62**) in 1952 by the action of selenium on 5,11- or 6,11-dichlorotetracene. He named the product tetraselenotetracene; Chemical Abstracts used the above nomenclature.



62, recrystallized from trichlorobenzene (green solution) was obtained as black needles. The dithiole analog (see Chapter 5, section IN), was prepared in excellent yield by treating tetracene with sulfur in refluxing trichlorobenzene. The solubilities of the two compounds are similar, poorly soluble in ordinary solvents. The elemental analysis of **62** corresponded to $C_{18}H_8Se_4$. Its ultraviolet absorption spectrum, closely related to the sulfur analog, showed a maximum at 471 m μ and was displaced towards the violet.

Treatment of **62** with formic acid and dilute hydrogen peroxide yields a blue monoformate; an excess of peroxide and air agitation transforms the blue solution to an orange. The acetate, whose solution is blue, is obtained similarly. Addition of sodium chloride to the monoformate solution yields a blue microcrystalline monochloride. The monoformate solution is used to prepare salts of other acids, such as a red perchlorate, a red nitrate, and a blue sulfate.

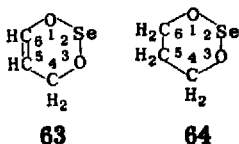


Reduction with titanium trichloride reconverts the salts to **62**.

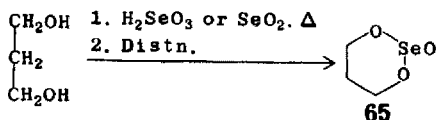
VII. C_3O_2Se AND C_3O_2Te RING SYSTEMS

The only study of these two ring systems is that of Simon and Heintz.⁷² This is in striking contrast to the many studies reported in the C_3O_2S ring system (Chapter 8).

A. C_3O_2Se 4H-1, 3, 2-DIOXASELENIN (**63**) AND 1, 3, 2-DIOXASELENANE (**64**)

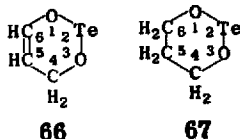


The parent compounds (**63** and **64**) are unknown. 1, 3, 2-Dioxaselenane 2-monoxide (**65**) was prepared by Simon and Heintz⁷² in 1960 by dissolving selenic acid or selenium dioxide in trimethylene glycol at 150-200° and rapidly distilling off the water of reaction.



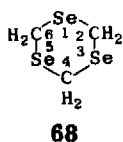
No yield or properties of **65** were given except that it does not polymerize on heating with disodium glycolate, alcoholates, alkali metals, or toluenesulfonic acid.

B. C_3O_2Te 4H-1, 3, 2-DIOXATELLURIN (66**) AND 1, 3, 2-DIOXATELLURANE (**67**)**



Simon and Heinta⁷² attempted to prepare **67** or a derivative but the solubility of tellurium oxide in 1, 3-propanediol was so low that they were unable to isolate a definable compound.

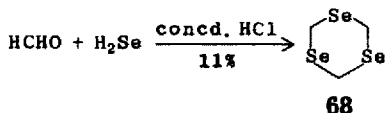
VIII. C_3Se_3 s-TRISELENANE (68**)**



(RRI 227)

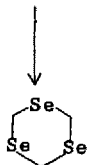
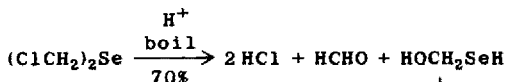
The Ring Index and Chemical Abstracts use the above name as well as 1, 3, 5-triselenacyclohexane. Bridger and Pittman⁹ who prepared **68** called it selenoformaldehyde and trimethylene triselenide.

It is one of three products obtained on passing hydrogen selenide over or into a solution of 36% formaldehyde and hydrochloric acid. A yield of 11% **68** was obtained on passing hydrogen selenide over the surface of a well-stirred mixture of 36% formaldehyde and concentrated hydrochloric acid. The white needles, recrystallized from xylene, melted at 210°; selenium analysis fitted **68** but the molecular weight determination was low.



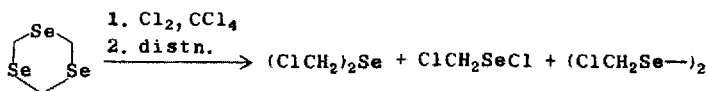
Bridger and Pittman also prepared s-triselenane in 70% yield by hydrolyzing bis(chloromethyl) selenide, a chlorination product of s-triselenane, with boiling aqueous solutions of sodium bicarbonate or boric acid.

Ring Systems containing Selenium and Tellurium



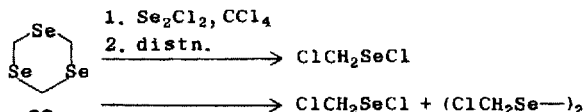
68

Treatment of *s*-triselenane in cold anhydrous carbon tetrachloride with dry chlorine induces several color changes, the color of the carbon tetrachloride layer being a good index of the extent of chlorination, going from white to yellow and finally to a deep red; it gives on distillation bis(chloromethyl) selenide, a pale yellow liquid; chloromethylselenenyl chloride, a dark red, heavy oil; and bis(chloromethyl) diselenide, a golden-yellow, heavy oil.



68

The products from the reaction of *s*-triselenane with selenium monochloride depend on the relative proportions of the reactants, as in the above chlorination reaction, being bis(chloromethyl) selenide for 15 g 68 and 34 g Se_2Cl_2 and a mixture of chloromethylselenenyl chloride and bis(chloromethyl) diselenide for 60 g 68 and 70 g Se_2Cl_2 .



68

These two chlorination reactions, however, offer little support for the ring structure of the product called *s*-triselenane. The structure as formulated, however, is reasonable in analogy with the sulfur analog (Chapter 10).

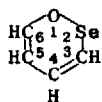
IX. C_4OSe RING SYSTEMS

Relatively little work has been done in this ring system compared to the sulfur analog, C_4OS , described in Chapter 11. Of the three possible isomers, *ortho*, *meta*, and *para*, only the *para* has a sizable literature. There is no reported study of the *meta* isomer and only one of the *ortho* isomer, that of *o*-oxaselenin.

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A. *o*-OXASELENO COMPOUNDS

1. C_4OSe 1,2-Oxaselenin (69)

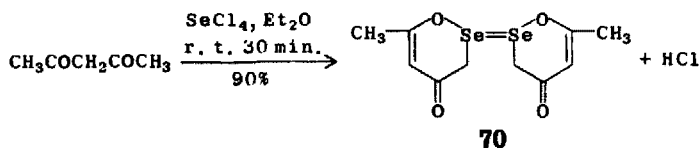


69

(RRI 256)

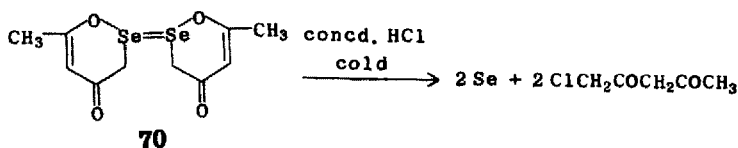
The parent compound (69) is not known. Only one member of this ring system has been described, 2,2-bis(6-methyl-3,4-dihydro-1,2-oxaselenin-4-one) (70), which Chemical Abstracts called 6-methyl- Δ^5 -1,2-selenoxen-4-one dimer and which Morgan and Drew,⁵⁵ who prepared it, called selenium acetylacetone.

Morgan and Drew,⁵⁵ on treating a suspension of one mole of selenium tetrachloride in dry ether with two moles of acetylacetone in dry ether, letting the mixture stand for about thirty minutes, evaporating off the ether and unreacted acetylacetone at room temperature, obtained 2,2-bis(6-methyl-3,4-dihydro-1,2-oxaselenin-4-one) (70) in 90% yield. 70 recrystallized from benzene in pale primrose-yellow, glistening plates or lath-like needles. Its organic solutions were yellow. On exposure to light for prolonged periods its surface became thinly coated with pink selenium; in this decomposition traces of hydrogen selenide also evolved as detected by its faintly nauseating odor. 70 reddened at about 140° and melted at 175° with decomposition; it melted to an orange-red liquid at 185° in a sealed capillary tube. It had a faintly acidic, sweetish taste, dissolved slightly in hot water, was sparingly soluble in boiling ether, ethanol, acetone, or chloroform, and more soluble in hot acetic acid or benzene.



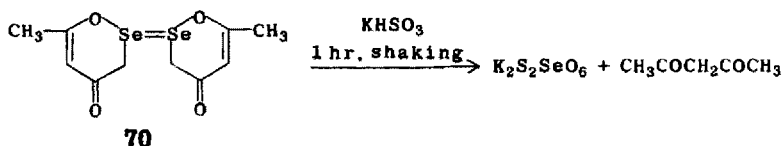
Elemental analysis was in agreement with that required; molecular weight determination gave a value of 314, somewhat low for the required 354.

70 was readily decomposed by concentrated hydrochloric acid into selenium and chloroacetylacetone.



Ring Systems containing Selenium and Tellurium

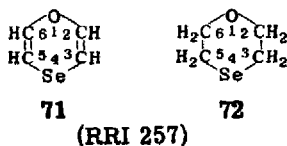
70 dissolved readily in cold aqueous alkali hydroxides or ammonia to give bright yellow solutions and was regenerated when neutralized. If the alkaline solutions were not neutralized at once, **70** began to decompose with precipitation of selenium. When distilled with zinc dust, **70** lost selenium. Iodine in chloroform solution had no action on **70**, but chlorine in chloroform decomposed it to selenium tetrachloride and chloroacetylacetone. Aqueous hydrogen sulfide decomposed **70** with liberation of sulfur and selenium. Hydroxylamine, phenylhydrazine, *p*-bromophenylhydrazine, *p*-nitrophenylhydrazine, and 6-chloro-3, 4-toluenediamine induced elimination of selenium. Addition of **70** to aqueous potassium bisulfite with shaking for one hour gave a precipitate of potassium selenodithionate, $K_2S_2SeO_6$, and a 97% yield of acetylacetone. A similar reaction occurred with aqueous sulfur dioxide.



As will be seen in the next section, tellurium tetrachloride with a β -diketone is a more general reaction, yielding the monomeric heterocycle C_4OTe . Selenium tetrachloride with other β -diketones yields the C_2OSe_2 ring system as discussed in section II of this Chapter.

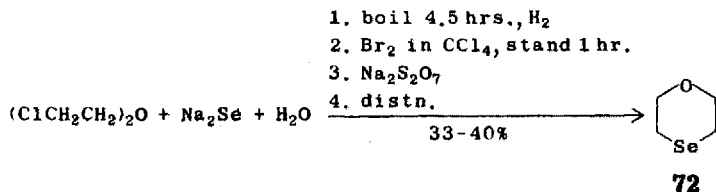
B. β -OXASELENO COMPOUNDS

1. C_4OSe 1, 4-Oxaselenin (**71**) and 1, 4-Oxaselenane (**72**)



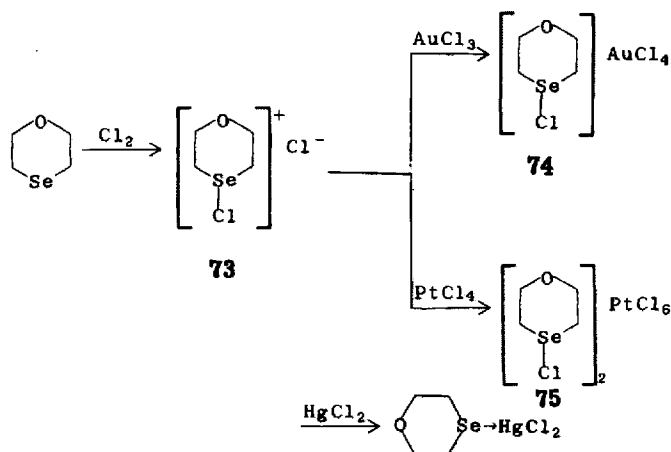
The parent compound (**71**) is unknown. Its tetrahydro derivative (**72**) was first reported in 1930 by Gibson and Johnson³¹ who named it 1, 4-selenoxane, the name also used by Chemical Abstracts.

Gibson and Johnson^{31, 31a} prepared 1, 4-oxaselenane in 33-40% yield by reacting bis(2-chlorethyl) ether or bis(2-iodoethyl) ether with sodium selenide and water at 100° for 4.5 hours with hydrogen passing through the mixture, treating the reaction mixture with bromine, and treating the resulting dibromide with sodium pyrosulfate or bisulfite.



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1, 4-Oxaselenane is a colorless liquid with a characteristic, but not unpleasant, odor. It melts at -21.5° ^{31a} and boils at $66^{\circ}/22, 69.5^{\circ}/26, 73^{\circ}/35, 79.5^{\circ}/37, 100.8^{\circ}/95, 119.7^{\circ}/183, 138.7^{\circ}/330, 148.9^{\circ}/440, 156.6^{\circ}/548, \text{ and } 167.5-168.5^{\circ}/763 \text{ mm.}$ ^{31, 31a, 39} Other physical properties are: $n_D^{20} 1.5480, d_4^{16} 1.575, d_4^{23.5} 1.565, d_4^{25} 1.549, d_4^{23} 1.539$, and parachor 245.2 (244.6, calculated). It is soluble in moderately concentrated mineral acids without salt formation by direct addition. It readily yields a methiodide, which behaves as a salt, a mercurichloride (76), a chloroaurate 74, and a chloroplatinate (75), the last two compounds being formed, however, from 1, 4-oxaselenane dichloride and auric or platinic chloride. Treatment of 1, 4-oxaselenane with chlorine, bromine, or iodine yields a colorless dichloride (73), melting at $127-129^{\circ}$ with decomposition, a yellow dibromide, melting at 132° with decomposition, and a deep violet diiodide, melting at $106-107^{\circ}$.

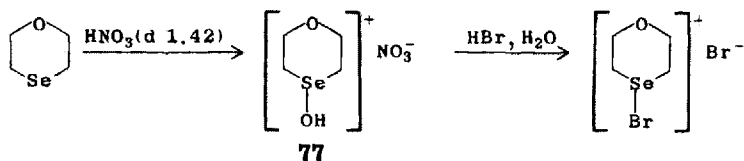


The diiodide showed a normal molecular weight in nitrobenzene. It was sparingly soluble in water whereas the dichloride and dibromide were moderately easily soluble, the solutions containing halogen ions. The halogen ions, however, may have arisen from hydrolysis, as the solutions also were acidic. The two halogen atoms attached to selenium in these halides were easily replaceable by hydroxyl. Passing ammonia through a benzene solution of the dibromide yielded a compound of the composition $\text{C}_4\text{H}_8\text{OCl}_2\text{Se} \cdot 2\text{NH}_3$ which was colorless, insoluble in ordinary solvents, and decomposed on treatment with water. Similar compounds were formed between 1, 4-oxaselenane dibromide and pyridine, piperidine, and aniline, and when ammonia was passed into a benzene solution of 1, 4-oxaselenane dichloride. The addition product of 1, 4-oxaselenane dibromide and ethylenediamine yielded ethylenediamine dihydrobromide on treatment with aqueous ethyl alcohol.

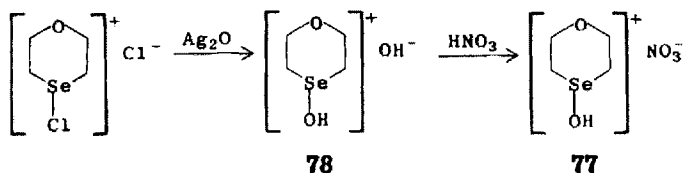
Treatment of 1, 4-oxaselenane with nitric acid under conditions which lead to the formation of a sulfoxide from a sulfide yielded instead of

Ring Systems containing Selenium and Tellurium

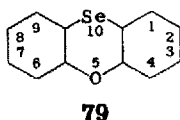
the oxide a hydroxynitrate (**77**). There was no apparent tendency for



the formation of a dinitrate. The hydroxynitrate, obtained as colorless, massive prisms, decomposed at 140-141° and detonated on heating in a sealed tube. The reaction of 1,4-oxaselenane and nitric acid took place with explosive violence. Treatment of an aqueous solution of **77** with hydrobromic acid in the cold precipitated the dibromide. The hydroxynitrate was also prepared by adding cold nitric acid and a little water to the dihydroxide (**78**); this reaction also was exothermic. The dihydroxide was prepared from the reaction of the dibromide with moist silver oxide.



2. C₄OSe-C₆-C₆ Phenoxaselenin (**79**)



(RRI 3412)

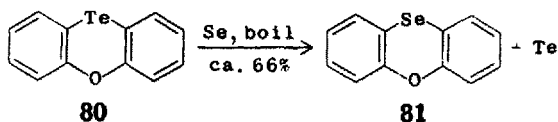
Phenoxaselenin, first prepared by Drew in 1928, is represented by a relatively small number of derivatives which are listed in Table 3. Drew used the name phenoxaselenine; Chemical Abstracts indexed this ring system under phenoxaselenin.

a. Preparation

Drew's method for the preparation of phenoxatellurin by the reaction of diphenyl ether with tellurium tetrachloride could not be applied to the preparation of phenoxaselenin because of the chlorinating action of selenium tetrachloride.²⁰ On heating phenoxatellurin with an atomic proportion of selenium, Drew obtained a mixture containing two moles phenoxaselenin and one mole phenoxatellurin. The mixture could not be separated by crystallization, but pure phenoxaselenin was obtained quantitatively from it by transformation to the dibromide and extract-

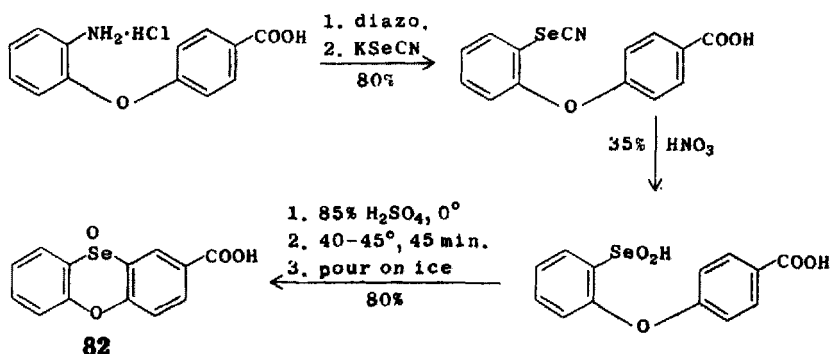
Chapter 13

ing the dibromide with ether, in which the phenoxatellurin dibromide is insoluble and the phenoxaselenin is soluble.

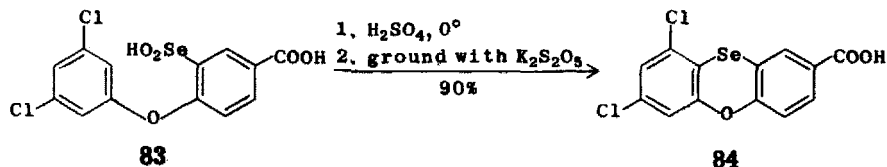


Phenoxathiin was prepared similarly (see Chapter 11, section III I-1a-(1)).

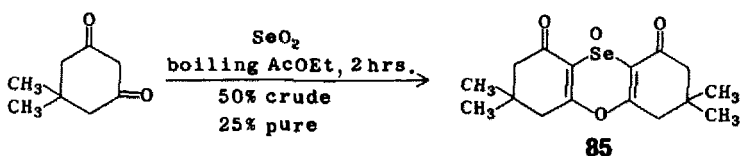
Thompson and Turner⁷⁸ prepared phenoxaselenin-2-carboxylic acid 10-monoxide (**82**) in 80% yield by the following series of reactions:



Thompson and Turner were unable to effect ring closure of 2',4'-dichloro-4-carboxydiphenyl ether 2-seleninic acid (**83**) with 85% sulfuric acid at 40°, but addition of **83** to concentrated sulfuric acid at 0° resulted in a 90% ring closure to 6,8-dichlorophenoxaselenin-2-carboxylic acid (**84**) (the 10-monoxide was eliminated during the purification step with potassium metabisulfite).



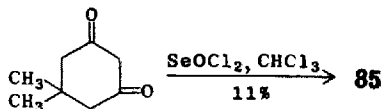
In attempting to oxidize dimethyl dihydroresorcinol (dimedone) to 1,1-dimethyl-2,4,5-trioxocyclohexane with selenium dioxide, Borsche and Hartmann⁸ obtained 3,3,7,7-tetramethyl-1,2,3,4,6,7,8,9-octa-hydro-1,9-phenoxaselenindione 10-monoxide (**85**).



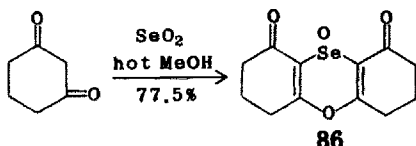
85 had been obtained earlier by Stamm and Gossrau⁷³ in 90% yield by treatment of dimedone in methanol with selenium dioxide. The free

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phenoxaselenin of **85** was obtained by reduction with hydrogen selenide, but the product was not isolated.⁷³ Stamm and Gossrau also obtained **85** in low yield on treating dimedone in chloroform with selenoxychloride.



King and Felton⁴³ obtained a 77% yield of 1,2,3,4,6,7,8,9-octahydro-1,9-phenoxaseleninindione 10-monoxide (**86**) by the treatment of 1,3-cyclohexanedione with selenium dioxide. They also obtained the diphenyl and tetraphenyl and dimethyl derivatives by the treatment of 5-phenyl- or 4,5-diphenyl- or 5-methyl-1,3-cyclohexanedione, respectively, with selenium dioxide.



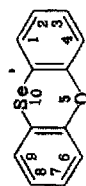
b. Properties and Structure

Phenoxaselenin was obtained by Drew²⁰ as colorless prisms from ethanol or acetic acid. It was described as having a faint odor of rose leaves. Its sulfuric acid solution had an intense olive-green color which became violet on heating or diluting. Moir⁵⁴ examined sulfuric acid solutions of phenoxaselenin and its 10-monoxide as part of a halochromic color study of doubly-linked diphenylene compounds. It formed mixed crystals with phenoxathiin and with phenoxatellurin which were inseparable by solvents. The crystal structure of phenoxaselenin was studied by Wood, McCale, and Williams⁸¹ by crystallographic, optical, and X-ray methods; X-ray observations showed that phenoxaselenin and phenoxathiin are isomorphous; each unit cell of phenoxaselenin, phenoxatellurin, phenoxathiin, and phenothiazine contain four molecules folded about the line joining the hetero atoms.

Phenoxaselenin 10-monoxide was obtained by Drew²⁰ as a colorless, crystalline powder which readily added water to form the dihydroxide, slender, colorless needles, readily soluble in water, and which lost a molecule of water when dried at 100° in a vacuum over phosphorus pentoxide. Above its melting point, phenoxaselenin 10-monoxide is quantitatively transformed to phenoxaselenin. Both the 10-monoxide and dihydroxide vigorously decomposed hydrogen peroxide in glacial acetic acid. The dihydroxide showed no bactericidal activity. The 10-monoxide is soluble in organic solvents. Its sulfuric acid solution has a deep violet color which becomes blue on warming.

Phenoxaselenin dichloride crystallized in light yellow, glistening plates from acetic acid; the dibromide formed orange-red spangles from acetic acid.²⁰

TABLE 3. Phenoxaselenins



Substituent	Yield (%)	M.p. (°C)	Ref.
None		87-88	20
		87	78
10-Monoxide		171-172	20
10, 10-Cl ₂		127 (dec.)	20
10, 10-Br ₂		147-148 (dec.)	20
2-COOH		251	78
2-COOH cinchonidine salt		207	78
2-COOH <i>α</i> - and <i>l</i> -C ₆ H ₅ CHNH ₂ CH ₃ salt		207	78
2-COOH brucine trihydrate salt			78
2-COOH 10-monoxide	80	217-218	78
2-COOH 10-monoxide nor- <i>α</i> - <i>ψ</i> -ephedrine salt		180	78
2-COOH-10, 10-Br ₂		214 (dec.)	78
6, 8-Cl ₂ -2-COOH	90	309	78
6, 8-Cl ₂ -2-COOH <i>d</i> - <i>α</i> -C ₆ H ₅ CHNH ₂ CH ₃ salt		250-265	78
1, 2, 3, 4, 6, 7, 8, 9-Hg-1, 9(=O) ₂ 10 monoxide	77	180 (dec.)	43

1, 2, 3, 4, 6, 7, 8, 9-Hg-3, 7-(CH ₃ -) ₂ -1, 9-(=O) ₂ 10 monoxide	185 (dec.)	43
1, 2, 3, 4, 6, 7, 8, 9-Hg-3, 7-(C ₆ H ₅ -) ₂ -1, 9-(=O) ₂ 10 monoxide	187-188	43
1, 2, 3, 4, 6, 7, 8, 9-Hg-2, 8-(or 4, 6-) (C ₆ H ₅ -) ₂ -1, 9-(=O) ₂ 10 monoxide	133	43
1, 2, 3, 4, 6, 7, 8, 9-Hg-2, 3, 7, 8-(or 3, 4, 6, 7-) (C ₆ H ₅ -) ₄ -1, 9-(=O) ₂ 10-monoxide	164 (dec.)	43
1, 2, 3, 4, 6, 7, 8, 9-Hg-3, 3, 7, 7-(CH ₃ -) ₄ -1, 9-(=O) ₂ 10-monoxide	50 crude	8
	25 pure	8
	90	73
	167 (dec.)	
	281-282	8
Bis(dinitrophenylhydrazone)		
1, 2, 3, 4, 6, 7, 8, 9-Hg-3, 3, 7, 7-(CH ₃ -) ₄ -1, 9-(=O) ₂ 10, 10-dioxide	86	73

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Drew,¹⁸ who studied phenoxaselenin, phenoxatellurin, and phenoxathiin, their 10-monoxides, and 10, 10-dichlorides, dibromides, and diacetates, found that the phenoxaselenins were the least stable (except that phenoxaselenin 10-monoxide is more stable than phenoxatellurin 10-monoxide). The gradation in stability he observed suggested to him that the linking between selenium and halides or oxygen is probably coordinate-covalent rather than covalent.

Phenoxaselenin-2-carboxylic acid crystallized from ethanol or benzene as pale yellow needles.⁷⁸ The sodium salt of the acid was sparingly soluble in cold, but readily soluble in hot water. When bromine was added to a solution of the acid in glacial acetic acid, orange-red plates of the unstable 10, 10-dibromide precipitated. Cold water at once converted the dibromide into the 10-monoxide acid. The 2-carboxylic acid was unaffected by heating with 75% sulfuric acid at 100° for 15 minutes.

Thompson and Turner⁷⁸ attempted to resolve phenoxaselenin-2-carboxylic acids, but were unsuccessful. 6, 8-Dichlorophenoxaselenin-2-carboxylic acid crystallized from glacial acetic acid or from dioxane in slender needles. Its sodium and ammonium salts were soluble in hot water, the solutions becoming gels when cooled. It formed very unstable salts with strychnine, brucine, quinine, cinchonine, cinchonidine, and nor-*d-ψ*-ephedrine. Its *d-α*-phenylethylamine salt was stable but showed no signs of resolving on repeated crystallizations; it softened at 186° and melted indefinitely at 250-265°.

Phenoxaselenin-2-carboxylic acid 10-monoxide crystallized from glacial acetic acid as a bright yellow compound which was apparently the diacetate, as water converted it to the 2-carboxylic acid 10-monoxide, which is sparingly soluble in methanol and ethanol and soluble in acetic acid. On attempting to resolve phenoxaselenin-2-carboxylic acid 10-monoxide with *l-α*-phenylethylamine, strychnine, and brucine, Thompson and Turner obtained reduction to phenoxaselenin-2-carboxylic acid. The nor-*d-ψ*-ephedrine salt crystallized satisfactorily from water, but its specific rotation was unaffected by repeated crystallizations.

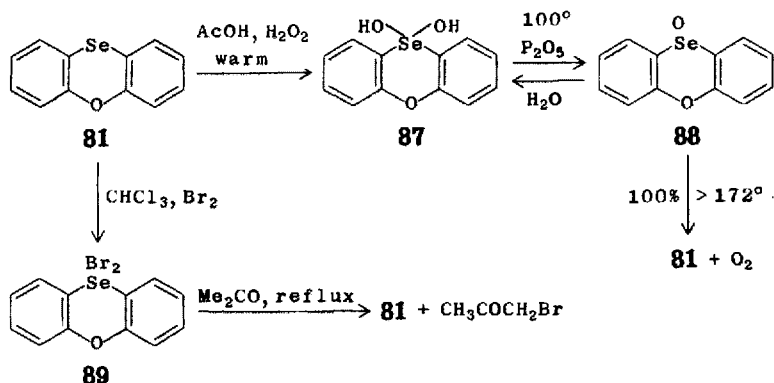
Octahydrophenoxaselenin-1, 9-dione 10-monoxide decomposed on prolonged exposure to daylight or on warming with dilute mineral acid; it also decomposed on melting as also did its 3, 7-dimethyl derivative; the 2, 3, 7, 8-(or 3, 4, 6, 7-) tetraphenyl derivative could not be dehydrated without decomposition and liberation of selenium.⁴³ The 3, 4, 7, 8-tetrahydroderivatives also tended to decompose on heating at their melting points with liberation of selenium.⁷³

c. Reactions

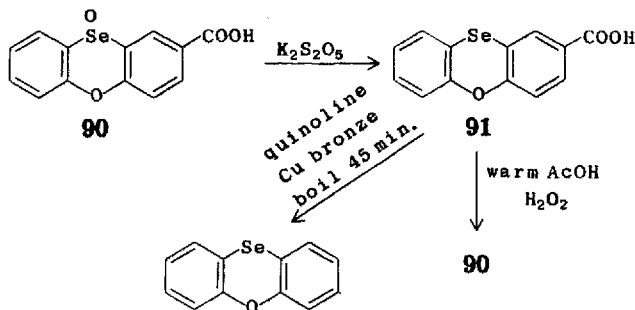
Phenoxaselenin in warm acetic acid is readily oxidized with a slight excess of hydrogen peroxide to the 10-monoxide (88), first forming the

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unstable diacetate then the dihydroxide (**87**) which loses a molecule of water when dried at 100° in a vacuum over phosphorus pentoxide.²⁰ Treatment with water converts the 10-monoxide to the dihydroxide. The 10-monoxide is quantitatively transformed to phenoxaselenin above its melting point, $171-172^\circ$; phenoxathiin 10-monoxide, on the other hand, is stable above its melting point. Both the 10-monoxide and the dihydroxide vigorously decompose hydrogen peroxide in glacial acetic acid solution. Treatment of phenoxaselenin with bromine in cold chloroform yields the 10,10-dibromide (**89**); the dichloride is prepared similarly. The two dihalides differ from the corresponding halides of phenoxatellurin in that they halogenate acetone, a reaction which permits the separation of phenoxatellurin dibromide from phenoxaselenin dibromide.

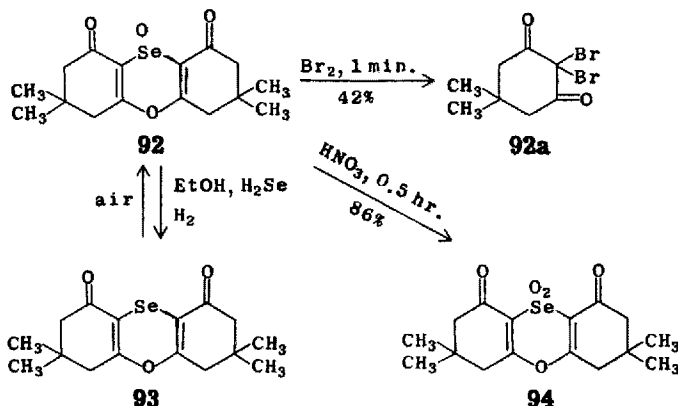


Thompson and Turner⁷⁸ in preparing phenoxaselenin-2-carboxylic acid (**91**) and the 6,8-dichloro derivative actually obtained the 10-monoxides, which on purification by grinding with potassium metabisulfite and a little water were reduced. Phenoxaselenin-2-carboxylic acid is readily converted to its 10-monoxide by heating or by treating in warm acetic acid with hydrogen peroxide. It decarboxylates on boiling with quinoline containing a little copper bronze.

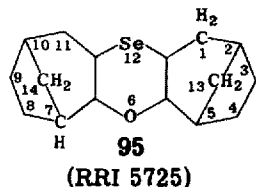


Stamm and Gossrau,⁷³ on treating 3,3,7,7-tetramethyl-1,2,3,4,6,7,8,9-octahydro-1,9-phenoxaselenindione 10 monoxide (**92**) in methanol

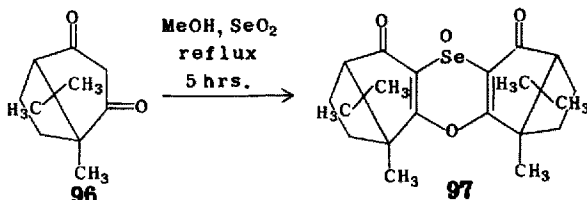
with bromine obtained 2, 2-dibromo-5, 5-dimethylcyclohexane-1, 3-dione (**92a**). The 10-monoxide (**92**) underwent no change with hydrogen sulfide, but in ethanol with hydrogen selenide and hydrogen it was reduced to **93**, which oxidized so easily in air to the 10-monoxide that it could not be isolated. Oxidation of a chloroform solution of **92** with nitric acid yielded the 10, 10-dioxide (**94**) as a snow-white compound which, however, could not be purified because of the ease with which selenium split out. **94** was very sensitive; irradiation in quartz caused decomposition; selenium deposited on heating in methanol, ethanol, chloroform, and acetic acid; it decomposed on heating at 150° without melting; on treatment with sulfur dioxide, **94** was reduced to the 10-monoxide (**92**).



3. $\text{C}_5\text{-C}_5\text{-C}_4\text{OSe-C}_6\text{-C}_6$ 2, 5 : 7, 10-Dimethano-1*H*, 7*H*-dicyclohept[1, 4]oxaselenin (**95**)



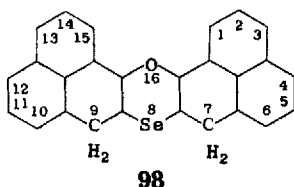
Takeda and co-workers,^{75,76} using Stamm and Gossrau's⁷³ condensation method, reacted 4-oxohomocamphor (**96**) in refluxing methanol with selenium dioxide and obtained 5, 7, 13, 13, 14, 14-hexamethyl-2, 3, 4, 5, 9, 10-hexahydro-2, 5 : 7, 10-dimethano-1*H*, 7*H*-dicyclohepta[1, 4]oxaselenin-1, 11(8*H*)-dione 12-monoxide (**97**), melting at 217–218°.



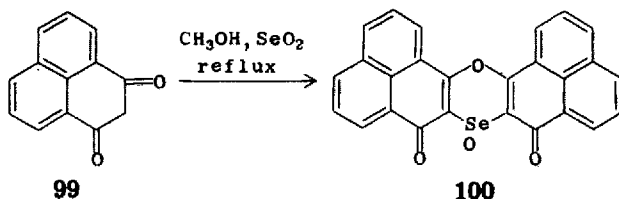
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97 was tested as an anti-tumor substance, but showed no apparent effect.⁷⁷ It was also evaluated on intestinal pathogenic and acid-fast bacteria, particularly on *M. tuberculosis* and *M. phlei* on which it was more effective than on other bacteria.

4. $C_4OSe-C_6-C_6-C_6-C_6-C_6-C_6$ 7*H*, 9*H*-Dinaphtho[1, 8-*bc*:1', 8'-*hi*] phenoxaselenin (**98**)



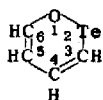
Takeda and co-workers,⁷⁶ on extending the Stamm and Gossrau⁷³ condensation method to ketones other than dimedone, reacted *peri*-naphthindan-1, 3-dione (**99**) in methanol with selenium dioxide and obtained 7*H*, 9*H*-dinaphtho[1, 8-*bc*:1', 8'-*hi*]-7, 9-phenoxaselenindione 8-monoxide (**100**), melting at 286°.



X. C_4OTe RING SYSTEMS

A. *o*-OXATELLURO COMPOUNDS

1. 1, 2-Oxatellurin (**101**)

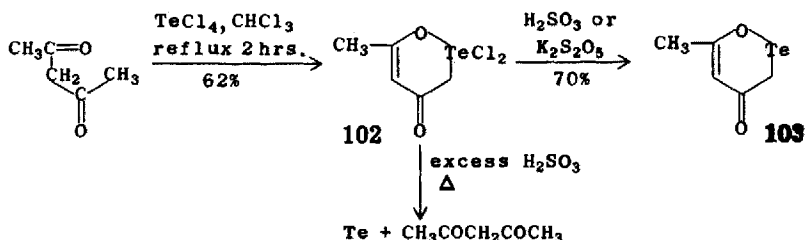


(RRI 259)

The parent compound (**101**) is unknown. The only derivatives of this system which have been reported are the 3, 4-dihydro derivatives listed in Table 4, and for which Chemical Abstracts used the 1, 2-telluroxene nomenclature. All of these compounds have been prepared by reaction of tellurium tetrachloride with a 1, 3-diketone in refluxing chloroform by Morgan and co-workers.^{55, 58-61, 61a, 62b}

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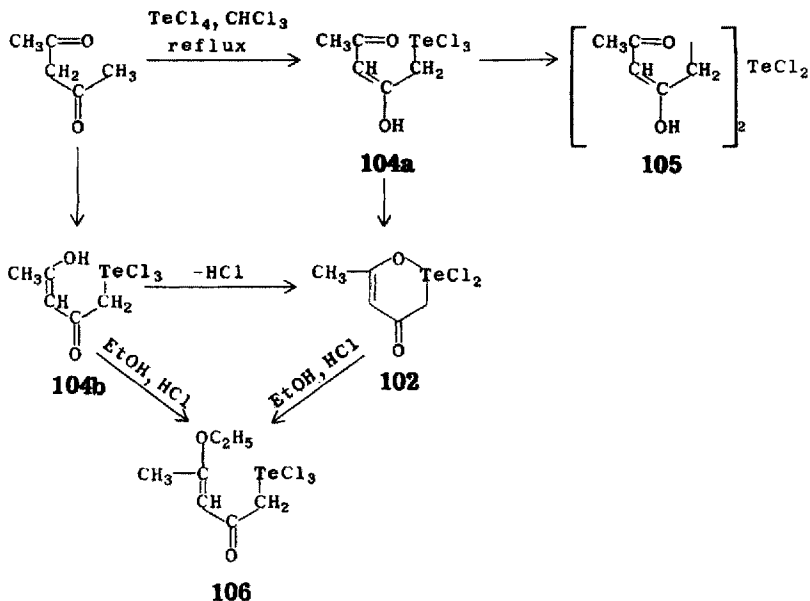
In a study of the reaction of metal chlorides with acetylacetone, Morgan and Drew⁵⁵ in 1922 observed that selenium and tellurium led to products different from other metals. The reaction with selenium tetrachloride is discussed in section II B. The reaction of tellurium tetrachloride and acetylacetone in refluxing chloroform gave a 62% yield of 2, 2-dichloro-6-methyl-3, 4-dihydro-1, 2-oxatellurin-4-one (**102**) as colorless hexagonal prisms from acetone. It was sparingly soluble in ether, benzene, and chloroform, soluble in hot alcohol, and readily soluble in cold acetone. On melting, tellurium was liberated and hydrogen chloride evolved. It was stable to light. It readily lost chlorine with hot water or aqueous acids or alkalis. Boiling aqueous potassium hydroxide did not liberate tellurium. When warmed in excess aqueous sulfurous acid, it decomposed to tellurium and acetylacetone. On trituration with potassium metabisulfite and water, Morgan and Drew⁵⁵ obtained a 60-70% yield of 6-methyl-3, 4-dihydro-1, 2-oxatellurin-4-one (**103**) along with a small amount of tellurium; less tellurium was liberated in the preparation of **103** by boiling **102** with a slight excess of sulfur dioxide.



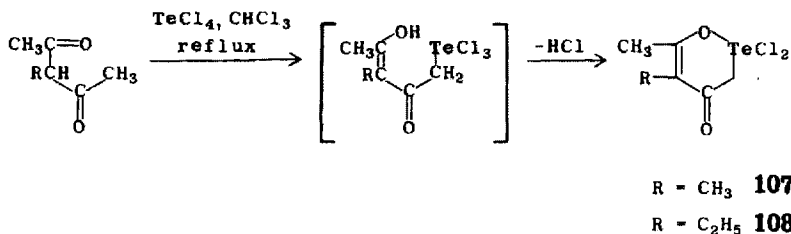
6-Methyl-3, 4-dihydro-1, 2-oxatellurin-4-one (**103**) was obtained as golden-yellow needles sparingly soluble in water, ether, chloroform, or alcohol and decomposing at 145-180°. It melted in a sealed tube to a yellow liquid, but on further heating decomposed to tellurium and acetylacetone. It sublimed under reduced pressure at 160° in glistening, yellow needles. It dissolved in aqueous potassium hydroxide from which it could be immediately recovered on neutralization but on standing tellurium deposited from the alkaline solution. Cold concentrated hydrochloric acid decomposed it with liberation of tellurium; warm sulfurous acid reduced it with liberation of tellurium. It was reduced quantitatively into tellurium and acetylacetone by Al-Hg couple or alkali hydrogen sulfites. **103** had a phenol coefficient of 1000.

In a detailed examination of the reaction of tellurium tetrachloride with acetylacetone, Morgan and Drew⁵⁸ found that three products are obtained: **102**, tellurium bisacetylacetone dichloride (**105**), and tellurium O-ethylacetylacetone trichloride (**106**), the product arising from the reaction of ethyl alcohol present in the chloroform. According to Morgan and Drew,⁵⁸ the initial reaction between tellurium tetrachloride and acetylacetone proceeds with elimination of hydrogen chloride to give **104a** which, although not isolated, was regarded as leading to the above three products (**102**, **105**, and **106**) in the following manner:

Ring Systems containing Selenium and Tellurium

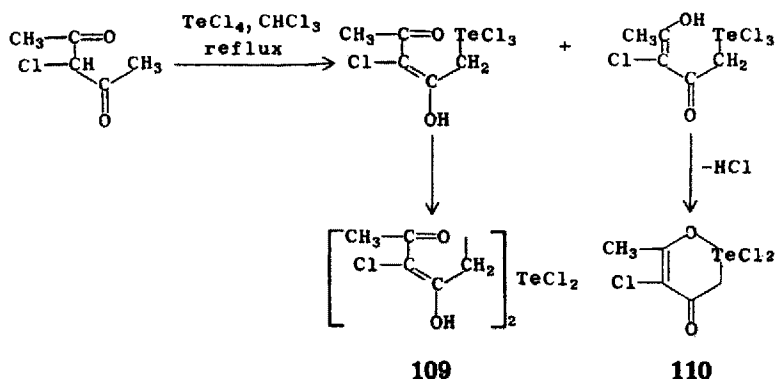


The condensation of tellurium tetrachloride with 3-methyl- or 3-ethyl-acetylacetone resulted in only one product, 5, 6-dimethyl-2, 2-dichloro-3, 4-dihydro-1, 2-oxatellurin-4-one (**107**) or 2, 2-dichloro-5-ethyl-6-methyl-3, 4-dihydro-1, 2-oxatellurin-4-one (**108**), as the methyl or ethyl group on C-3 of the diketone leads to only one enol form. The product had no enolic property towards ferric and cupric salts and had little residual acidity, thus ruling out a product such as **104b**.

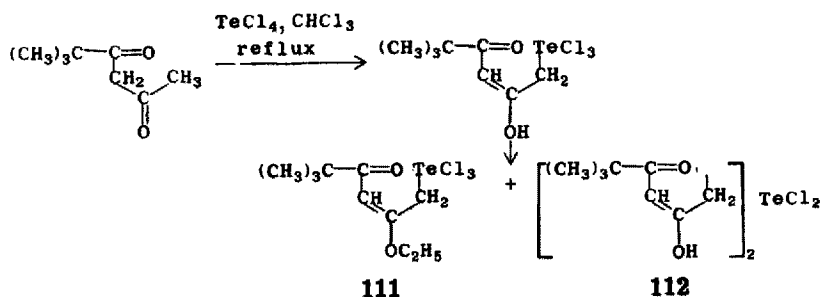


In the condensation of tellurium tetrachloride with 3-chloroacetylacetone, two products were obtained, 109 and 110, from the two possible enol forms.

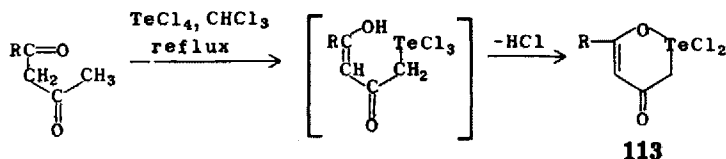
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Two products (**111** and **112**) were also obtained from the reaction of tellurium tetrachloride with pivalylacetone. Similar products were obtained from benzoylacetone and no oxatellurin resulted.

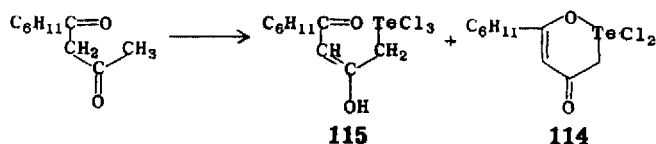


In a study of homologous diketones in this reaction, Morgan with Drew,⁶¹ Thompson^{61a} and Holmes^{62b} found that unbranched diketones led to the oxatellurin, as did also the diketones substituted on the carbon between the two carbonyls; branching at other carbon atoms favored the production of other products. Thus, *n*-butyrylacetone, *n*-valerylacetone, and caproylacetone similarly to propionylacetone, yielded the 6-alkyl-2, 2-dichloro-3, 4-dihydro-1, 2-oxatellurin-4-one (**113**) as the main product.



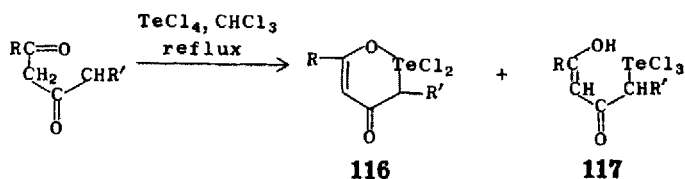
In the next higher homolog, *n*-heptanoylacetone, the oxatellurin (**114**) was a by-product (15% yield), the main product being the tellurium trichloride enol (**115**).

Ring Systems containing Selenium and Tellurium

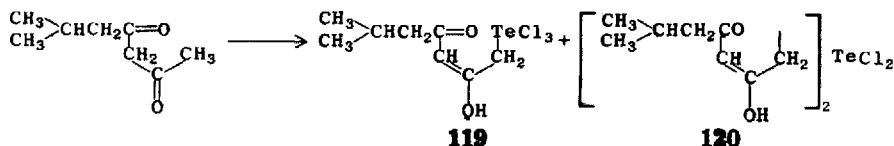
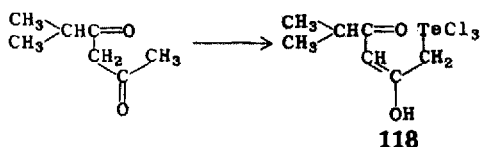


With ascent in the homologous series, $\text{RCOCH}_2\text{COCH}_3$, the melting point of the oxatellurin decreases and its solubility in chloroform and other organic solvents increases.

Dipropionylmethane and propionyl-*n*-butyrylmethane condensed with tellurium tetrachloride to give 78% and 19% oxatellurin (116), respectively, the other product being the tellurium trichloride enol (117).



No oxatellurin was obtained from branched diketones. Depending upon the branching, whether $\text{>CHCOCH}_2\text{COCH}_3$ or $\text{>CHCH}_2\text{COCH}_2\text{COCH}_3$, either the tellurium trichloride enol (118) alone or with the bisdiketone tellurium dichloride (120) were obtained.



Whereas the homolog $\text{RCOCHR}'\text{COR}$ condenses smoothly to give the oxatellurin, the homolog $\text{RCOCR}'_2\text{COR}$, such as 3, 3-diethylacetylacetone, yields exclusively the 6-methylene-3, 4, 5, 6-tetrahydro-1, 2-oxatellurin (121).

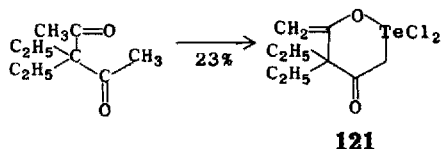
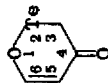


TABLE 4. 3, 4-Dihydro-1, 2-oxatellurin-4-ones



Substituent	Yield (%)	M.p. (°C)	Ref.
6-CH ₃ -	70	182	55, 58
6-CH ₃ -2, 2-(Cl-) ₂	62		55, 58
6- <i>n</i> -C ₃ H ₇ -	100	110-112	61
6- <i>n</i> -C ₃ H ₇ -2, 2-(Cl-) ₂	58	153-154	61
6- <i>n</i> -C ₄ H ₉ -	50	80	62b
6- <i>n</i> -C ₄ H ₉ -2, 2-(Cl-) ₂	70	125	62b
6- <i>n</i> -C ₅ H ₁₁ -		86	62b
6- <i>n</i> -C ₅ H ₁₁ -2, 2-(Cl-) ₂		102	62b
6- <i>n</i> -C ₆ H ₁₃ -		86	61
6- <i>n</i> -C ₆ H ₁₃ -2, 2-(Cl-) ₂	15	87	61
6- <i>n</i> -C ₉ H ₁₉ -		64	62b
6- <i>n</i> -C ₉ H ₁₉ -2, 2-(Cl-) ₂		49	62b
3-CH ₃ -6-C ₂ H ₅ -		151	61
3-CH ₃ -6-C ₂ H ₅ -2, 2-(Cl-) ₂	78	162 (dec.)	61
3-CH ₃ -6- <i>n</i> -C ₃ H ₇ -		101-102	61

3-CH ₃ -6- <i>n</i> -C ₃ H ₇ -2, 2-(Cl-) ₂	19	156 (dec.)	61
3-C ₂ H ₅ -6- <i>n</i> -C ₃ H ₇ -		97	61a
3-C ₂ H ₅ -6- <i>n</i> -C ₃ H ₇ -2, 2-(Cl-) ₂		120-139 (from C ₂ H ₅ OH or CHCl ₃ /Petr.)	61a
		137-138 (from CHCl ₃ /Petr.)	61a
		148 (from CH ₃ OH)	61a
5, 6-(CH ₃ -) ₂	76	170 (dec.)	58
5, 6-(CH ₃ -) ₂ -2, 2-(Cl-) ₂	80	>190 (dec.)	58
5, 6-(CH ₃ -) ₂ -2, 2-(Br-) ₂		152-153 (dec.)	58
5, 6-(CH ₃ -) ₂ -2, 2-(I-) ₂		175-176 (dec.)	58
5-CH ₃ -6-C ₂ H ₅ -		125-126 (dec.)	61
5-CH ₃ -6-C ₂ H ₅ -2, 2-(Cl-) ₂	80	166-167 (dec.)	61
5-C ₂ H ₅ -6-CH ₃ -	88	142	58
5-C ₂ H ₅ -6-CH ₃ -2, 2-(Cl-) ₂			58
5-C ₂ H ₅ -6-CH ₃ -2, 2-(Br-) ₂		161-170 (dec.)	58
5-C ₂ H ₅ -6-CH ₃ -2, 2-(I-) ₂		176 (dec.)	58
5, 6-(C ₂ H ₅ -) ₂		109	61a
5, 6-(C ₂ H ₅ -) ₂ -2, 2-(Cl-) ₂	63	167 (dec.)	61a
5-C ₂ H ₅ -6- <i>n</i> -C ₃ H ₇ -		113 (dec.)	61
5-C ₂ H ₅ -6- <i>n</i> -C ₃ H ₇ -2, 2-(Cl-) ₂	54	140 (dec.)	61
5- <i>n</i> -C ₃ H ₇ -6-CH ₃ -		108-107	61a
5- <i>n</i> -C ₃ H ₇ -6-CH ₃ -2, 2-(Cl-) ₂		180° (indefinite)	61a

TABLE 4. 3,4-Dihydro-1,2-oxatellurin-4-ones (cont).

Substituent	Yield (%)	M.p. (°C)	Ref.
5- <i>i</i> -C ₃ H ₇ -6-CH ₃ -		152-153	61a
5- <i>i</i> -C ₃ H ₇ -6-CH ₃ -2,2-(Cl)- ₂		150° (blackened)	61a
5- <i>n</i> -C ₄ H ₉ -6-C ₂ H ₅ -		93	62b
5- <i>n</i> -C ₄ H ₉ -6-C ₂ H ₅ -2,2-(Cl)- ₂	30	103	62b
5- <i>n</i> -C ₄ H ₉ -6-CH ₃ -		129	62b
5- <i>n</i> -C ₄ H ₉ -6-CH ₃ -2,2-(Cl)- ₂		155	62b
5-Cl-6-CH ₃ -	51	153-154 (dec.)	58
6-CH ₃ -2,2,5-(Cl)- ₃	5	161-162 (dec.)	58
3-CH ₃ -5,6-(C ₂ H ₅ -) ₂		137-138 (dec.)	61
3-CH ₃ -5,6-(C ₂ H ₅ -) ₂ -2,2-(Cl)- ₂	76	182 (dec.)	61
5,6-(H)- ₂ -5,5-(C ₂ H ₅ -) ₂ -6-(=CH ₂)		85-86	61
5,6-(H)- ₂ -5,5-(C ₂ H ₅ -) ₂ -6-(=CH ₂)-2,2-(Cl)- ₂	23	178-180	61

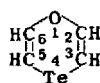
Ring Systems containing Selenium and Tellurium

With $\text{CH}_3\text{COCH}_2\text{COCH}_2\text{COCH}_3$, the condensation took a different course, yielding no oxatellurin. The course of the condensation of ethyl acetoacetate was also different, giving only the tellurium trichloride enol and no oxatellurin.

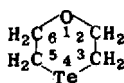
The 2, 2-dichloro-3, 4-dihydro-1, 2-oxatellurin-4-ones are readily converted to the corresponding 3, 4-dihydro-1, 2-oxatellurin-4-ones by treatment with potassium metabisulfite. The phenol coefficients of several oxatellurins indicated that they are growth inhibitors but not true germicides.⁵⁸ 2, 2-Dibromo- and 2, 2-iodo derivatives are prepared by treating the oxatellurin with bromine or iodine.⁵⁸

B. p-OXATELLURO COMPOUNDS

1. C_4OTe 1, 4-Oxatellurin (122) and 1, 4-Oxatellurane (123)



122

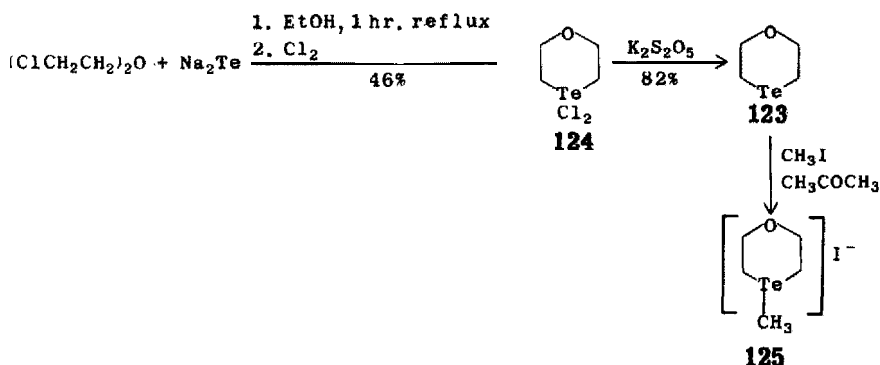


123

(RRI 260)

The parent compound (122) is not known. Its tetrahydro derivatives (123) listed in Table 5 were reported by Farrar and Gulland²³ in 1945 who used the 1, 4-telluroxan nomenclature. Chemical Abstracts indexed the tetrahydro derivatives under *p*-oxatellurane.

Farrar and Gulland²³ prepared 1, 4-oxatellurane (123) in 82% yield by the reduction of 4, 4-dichloro-1, 4-oxatellurane (124) which they had obtained in 46% yield on refluxing β, β' -dichlorodiethyl ether with sodium telluride (prepared *in situ* from tellurium and formaldehyde-sulfoxylate in aqueous sodium hydroxide), and then treating with chlorine.



1, 4-Oxatellurane was described as a foul-smelling, yellow solid, melting at 6° , which is slowly oxidized in air when impure, but when pure it is capable of being stored in a sealed tube without undergoing change. It reacted readily with halogens to form stable crystalline dihalides and

TABLE 5. 1,4-Oxatelluranes

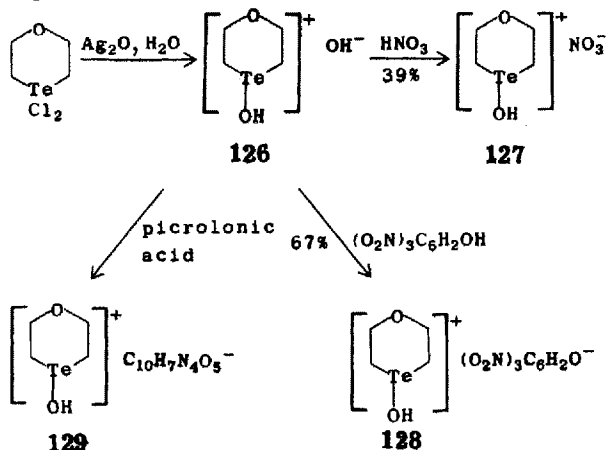


Substituent	Yield (%)	M.p. (°C)	B.p. (°C)	(mm)	Other properties	Ref.
None	82	6	90	21	n^{18}_D 1.6340	23
(4-Cl) ⁺ Cl ⁻	46	179.5 (some dec.)			d^{20}_D 1.8	23
(4-Br) ⁺ Br ⁻		157-158 (dec.)				23
(4-I) ⁺ I ⁻		155 (dec.)				23
(4-OH) ⁺ OH ⁻						23
(4-OH) ⁺ NO ₃ ⁻	39	190 (dec.)				23
(4-OH) ⁺ picrate ⁻	67	238 (dec.)				23
(4-OH) ⁺ picrolonate ⁻		216 (dec.)				23
(4-CH ₃) ⁺ I ⁻		199 (dec.)				23

Ring Systems containing Selenium and Tellurium

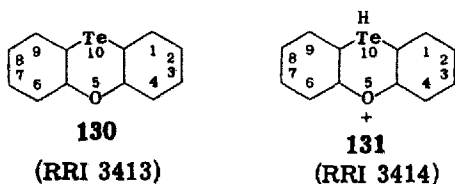
with methyl iodide to give the water-soluble methiodide (125).

4, 4-Dichloro-1, 4-oxatellurane dissolved in boiling water to give an acid solution which deposited a scanty amorphous white precipitate on cooling. When it was ground with excess moist silver oxide, silver chloride and the dihydroxy derivative (126) formed. 126 was obtained as a deliquescent, waxy mass of radiating needles, freely soluble in water giving an alkaline solution.



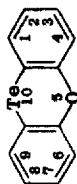
Farrar and Gulland pictured the products from the reaction of the aqueous solution of the dihydroxy compound (126) with nitric acid, picric acid, and picrolonic acid as having an oxatellurylium form (127, 128, and 129) as he did for the methiodide (125). They did not picture the dichloro or dihydroxy compounds as having this form. It is likely that these two are also oxatelluryliums, as the dihalides, for example, are not soluble in nonpolar solvents and their melting points are in the order $\text{Cl} > \text{Br} > \text{I}$ and much higher than that which is expected for similar covalent dihalides.

2. $\text{C}_4\text{OTe-C}_6\text{-C}_6$ Phenoxatellurin (130) and Phenotelluroxonium (131)



Phenoxatellurin was first reported in 1926 by Drew¹⁵ who called it phenoxatellurine. Chemical Abstracts has indexed it and its derivatives under phenoxatellurin and its salts under phenoxatellurylium compounds. These compounds are listed in Table 6.

TABLE 6. Phenoxatellurins

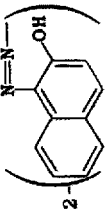
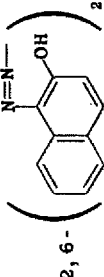
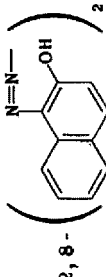
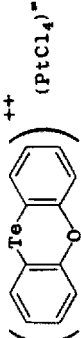


Substituent	Yield (%)	M.p. (°C)	Other properties	Ref.
None	99	78-79		15
	100	79		66
		79	$d_4^{25} = 1.770-0.00117t$	10
10-Monoxide				16, 21
10, 10-Dioxide				16
10, 10-(Cl) ₂	50	265		15
10, 10-(Br) ₂		290 (dec.)		15
10, 10-(I) ₂		270 (dec.)		15
10, 10-Diacetate	90	205-207		16
(10, ONO ₂) ⁺ NO ₃ ⁻		258 (dec.)		16
2-CH ₃ ⁻	93	50-52		10b
2-CH ₃ -10, 10-(Cl) ₂	80	274-275		10b
2-CH ₃ -8-Cl		67-68		10b
		59		17
2-CH ₃ -8, 10, 10-(Cl) ₃	14	284		10b
2-COOH		231-233		10b
2-COOH strychnine salt		198-200 (dec.)		10b

Ring Systems containing Selenium and Tellurium

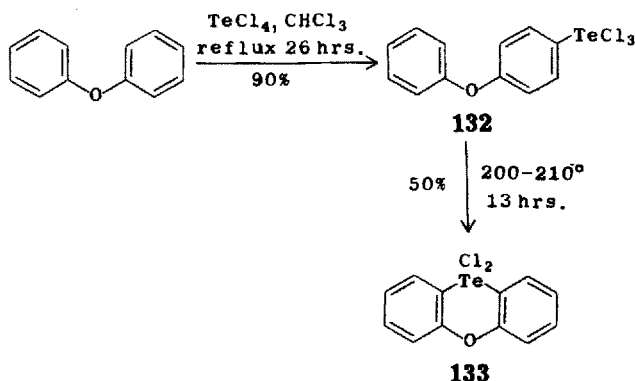
2-COOH quinine salt	211	10b
2-COOH cinchonidine salt	206	10b
2-COOH <i>d</i> - α -phenethylamine salt	205	10b
2-COOH <i>l</i> -menthol ester	123-125	10b
2-COOH-10, 10-(Cl-) ₂	319	10b
2-NO ₂	129	17
	128-129	10b
2-NH ₂ <i>d</i> -tartrate	158-159	10b
2-NH ₂ <i>d</i> -camphorsulfonate	182-185 (dec.)	10b
(2-NO ₂ -10-ONO ₂) ⁺ NO ₃ ⁻	196-197	16, 17
4-NO ₂	104	17
4-NO ₂ -10, 10-(Br-) ₂	302 (dec.)	17
(4-NO ₂ -10-ONO ₂) ⁺ NO ₃ ⁻		17
(4-NO ₂ -10-OH) ⁺ NO ₃ ⁻	243 (dec.)	16
2, 6-(NO ₂ -) ₂	198	17
(2, 6-(NO ₂ -) ₂ -10-OH) ⁺ NO ₃ ⁻	237-239	16
2, 8-(NO ₂ -) ₂		17
(2, 8-(NO ₂ -) ₂ -10-ONO ₂) ⁺ NO ₃ ⁻	259 (dec.)	16, 17
2-NH ₂ -	157	17
	157	10b
2, 8-(NH ₂ -) ₂	198	17
2, 6-(NH ₂ -) ₂	156	17

TABLE 6. Phenoxatellurins (cont).

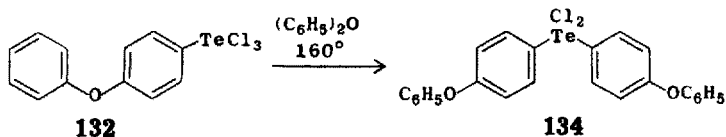
Substituent	Yield (%)	M.p. (°C)	Other properties	Ref.
 2-			insol. red azo dye	17
 2, 6 -			insol. red azo dye	17
 2, 8 -			insol. red azo dye	17
Chapter 13				
 $(\text{PtCl}_4)^{2-}$				21
 $[\text{Cl}_2(\text{NH}_3)_2\text{Pt}]_2\text{SO}_4$				21

Ring Systems containing Selenium and Tellurium

Drew¹⁵ found that diphenyl ether and tellurium tetrachloride in chloroform underwent a slow but almost complete condensation on heating, with evolution of hydrogen chloride, to give the *p*-telluritrichloride (**132**), which, when heated to about 200°, was converted to 10, 10-dichloro-phenoxatellurin (**133**), obtained from boiling toluene in colorless, nacreous platelets, melting at 265° to a transparent, yellow liquid. **133** is stable to heat and can be vaporized without suffering appreciable decomposition; it is almost insoluble in ether or petroleum, sparingly soluble in chloroform or ethyl alcohol, more soluble in benzene or toluene, and easily soluble in acetone; it slowly hydrolyzes in boiling water to give a white oxide; boiling aqueous alkali converts it to diphenyl ether.



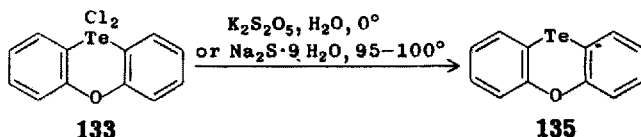
In view of the fact that phenetole is substituted exclusively in the *para* position by the telluritrichloride group, diphenyl ether undoubtedly reacts similarly to give **132**. On being heated above its melting point, **132** must isomerize to the *ortho* isomer preliminary to ring closure. Drew¹⁵ attempted to isolate the *o*-telluritrichloride by heating **132** to about 160° in an atmosphere of nitrogen. He obtained a telluritrichloride different from **132** but, because of impurities, he could not establish positively that it was the *ortho* isomer, although it probably was. A colorless noncyclic telluridichloride always occurred as a minor by-product in the condensation of diphenyl ether and tellurium tetrachloride in chloroform which was identical with the product resulting from heating **132** with diphenyl ether at about 160° and which was considered to be *p, p'*-diphenoxydiphenyl telluridichloride (**134**).



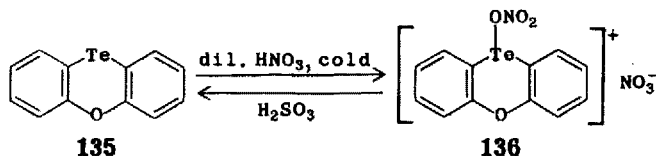
Drew¹⁵ obtained phenoxatellurin (**135**) in almost quantitative yield by reducing the 10, 10-dichloride (**133**) with potassium metabisulfite. Reichel and Kirschbaum⁶⁶ obtained a quantitative yield on heating **133** with

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sodium sulfide hydrate at 95-100° for 10 minutes. Phenoxatellurin re-crystallizes from hot light petroleum in long spear-like needles and from the cold solvent in large, transparent prisms, both forms being lemon-yellow to orange in color, melting at 78-79°. It has a delicate floral odor. It is stable to heat and can be vaporized unchanged. It is insoluble in water, but easily soluble in ethyl alcohol, ether, benzene, and carbon tetrachloride giving yellow solutions. It is stable towards hot concentrated hydrochloric acid and towards dilute aqueous alkali.



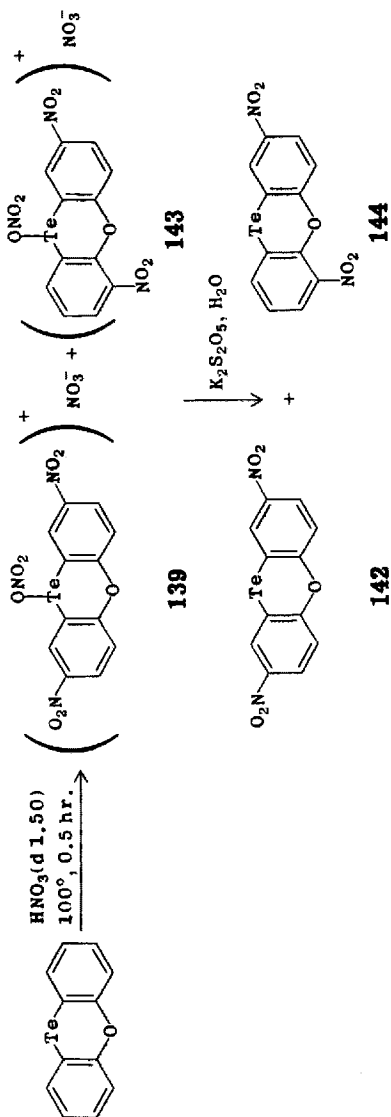
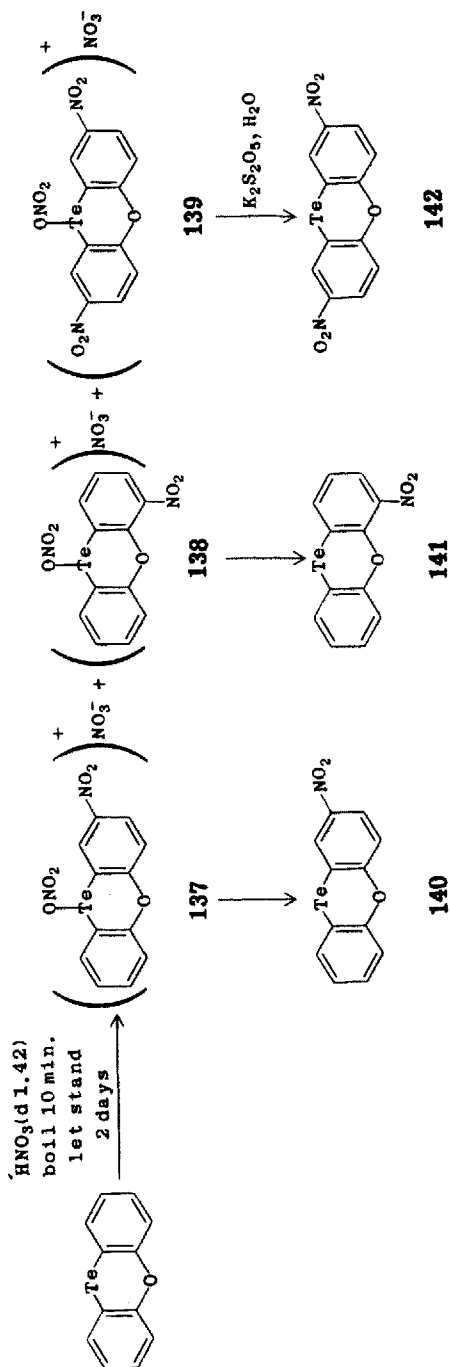
On treating phenoxatellurin with nitric acid under conditions which preclude nitration of the nucleus, the solution became intensely bluish-violet, then colorless on formation of the nitrate (136). Reduction of the nitrate with sulfurous acid gave a similar bluish-violet intermediate which changed to yellow on formation of phenoxatellurin.¹⁵⁻¹⁷



The intense blue-violet colored intermediate was formed on mixing and rubbing together dry 135 and 136 between two glass plates; the color was discharged on addition of water, ether, alcohol, benzene, or chloroform.

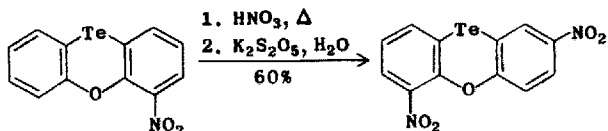
Treatment of phenoxatellurin with concentrated nitric acid (density 1.42) led chiefly to the formation of 2-nitrophenoxatellurin-10-nitrate (137) as the main product and 4-nitrophenoxatellurin-10-nitrate (138) and 2,8-dinitrophenoxatellurin-10-nitrate (139) as minor products.¹⁷

Ring Systems containing Selenium and Tellurium

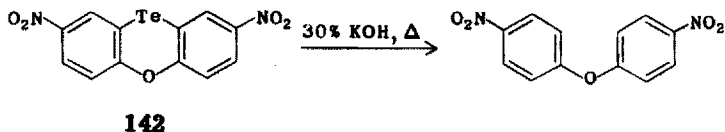


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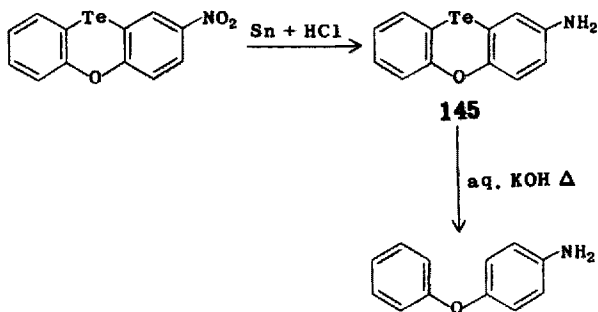
On using boiling fuming nitric acid, Drew and Thompson¹⁷ obtained 2, 8-dinitrophenoxatellurin-10-nitrate (**139**) as the main product and 2, 6-dinitrophenoxatellurin-10-nitrate (**143**) as a minor product. No nitration product higher than the dinitro was obtained. Nitration of 2-nitrophenoxatellurin (**140**) with boiling fuming nitric acid yielded the 2, 8-dinitro compound (**139**); similar nitration of 4-nitrophenoxatellurin gave 2, 6-dinitrophenoxatellurin in 60% yield and a by-product, probably 4, 6-dinitrophenoxatellurin, in small amount.



The nitro- and dinitrophenoxatellurins are yellow to orange-red crystalline compounds, soluble in organic compounds, and quite stable. They readily yield the 10-nitrates with dilute nitric acid with formation of an intensely colored intermediate. The 10-nitrates, chlorides, and similar derivatives are decomposed by warm aqueous alkali leading to formation of a corresponding diphenyl ether derivative. The nitrodiphenyl ethers, being known compounds, were used to characterize the nitrophenoxatellurins.



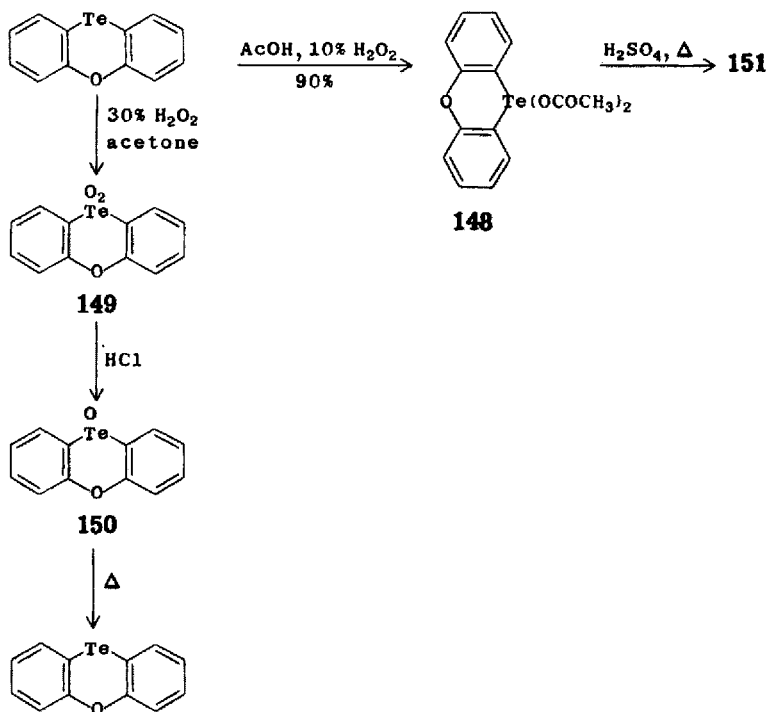
The nitrophenoxatellurins are readily reduced by treatment with tin and hydrochloric acid. Thus, Drew and Thompson¹⁷ prepared 2-amino- (**145**), 2, 8-diamino-, and 2, 6-diaminophenoxatellurin.



The aminophenoxatellurins are crystalline, stable compounds, recrystallized from alcohol. Their hydrochlorides are readily diazotized, giving yellow to red diazonium salts, which may be coupled with β-naphthol to give insoluble, red azo dyes.

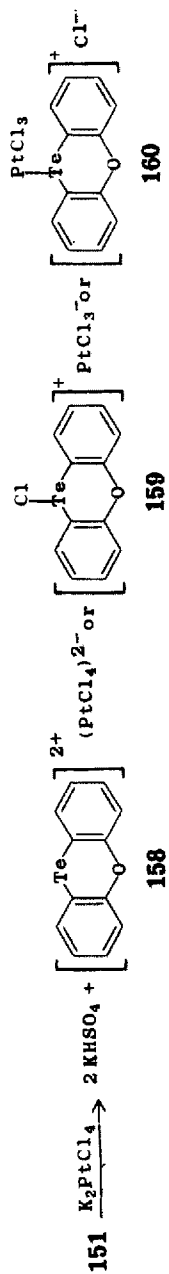
Drew noted the halochromism of phenoxatellurin and its derivatives from the very beginning of his work in this series, and concentrated much of his attention to the products obtained with sulfuric acid.^{15,16,19} The products, unfortunately, were not sufficiently well defined for structure assignment. The discussion of the halochromism of thianthrene (Chapter 12, section III J-1d) undoubtedly is applicable here.

Drew¹⁶ prepared phenoxatellurin-10, 10-diacetate (**148**) as colorless needles soluble in organic solvents by the action of hydrogen peroxide or of sodium nitrite on a glacial acetic acid solution of phenoxatellurin. Excess hydrogen peroxide yielded the 10, 10-dioxide (**149**), a white, amorphous powder, insoluble in acetone or water and soluble in hot acetic acid, which was reduced to the 10-monoxide (**150**) by concentrated sulfuric acid, hydrochloric acid, or hydriodic acid. The 10-monoxide also has been obtained by grinding 10, 10-dichlorophenoxatellurin with silver oxide.²¹ On treating the 10,10-diacetate (**148**) in boiling water with sulfuric acid, Drew obtained a crystalline sulfate (**151**) which, on recrystallization from sulfuric acid, gave crystals whose composition depended on the concentration of acid present.



On treatment of the sulfate with sodium bisulfite, Drew obtained phenoxatellurin; thus, nuclear sulfonation had not occurred.

Drew postulated that the product he obtained on rubbing phenoxatellu-



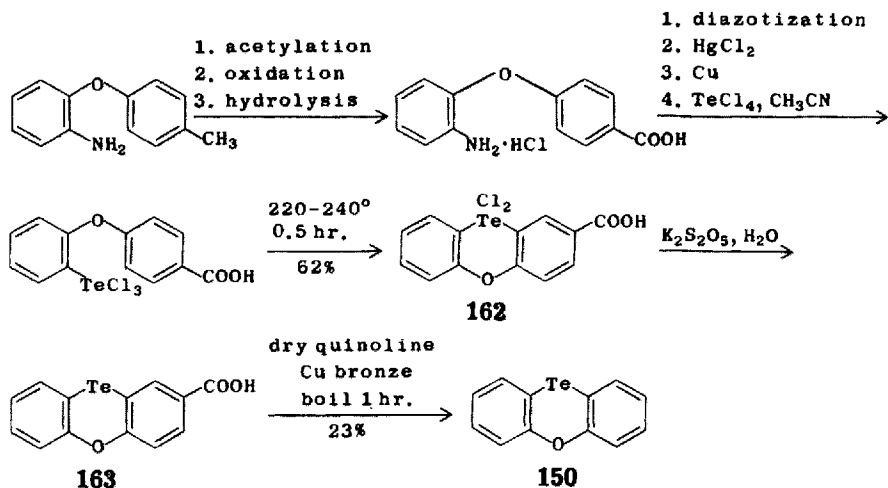
Ring Systems containing Selenium and Tellurium

rin sulfate (**151**) with ammonium or potassium chloroplatinite was phenoxatellurylium chloroplatinite (**158**, **159**, or **160**).

The chloroplatinite could not be recrystallized. It was shown to be a definite compound by elemental analysis and by its reaction with hydrochloric acid. It reacted with hydrochloric acid to give 10, 10-dichlorophenoxatellurin and chloroplatinous acid and with aqueous potassium chloride to give 10, 10-dichlorophenoxatellurin and potassium chloroplatinite. These two reactions indicated to Drew the presence of **158**, which, however, as it should be colored red, does not account for the black color of the product. Consequently, Drew assumed that **158** is tautomeric with **159** or with **160** which would account for the black product. These structures remain to be elucidated.

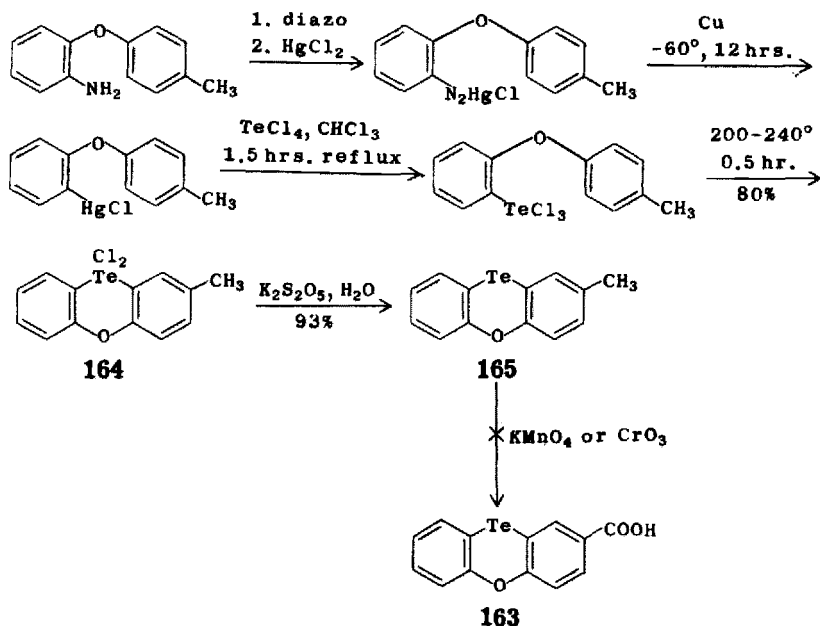
On reacting **151** with platinum (II) diammines in cold 75% sulfuric acid, Drew obtained an intensely purple-black substance, which, on analysis, had the composition $C_{36}H_{40}O_{23}N_4Cl_4S_5Te_3Pt_2$, but whose structure remains to be elucidated.

Campbell and Turner^{10b} attempted to resolve 2-nitro- and 2-amino-phenoxatellurin and phenoxatellurin-2-carboxylic acid without success. They concluded that, although phenoxatellurins have a folded configuration, the folding is unstable with rapid interconversion of the *d*- and *l*-forms. They prepared the 2-carboxylic acid (**163**) by the following series of reactions:



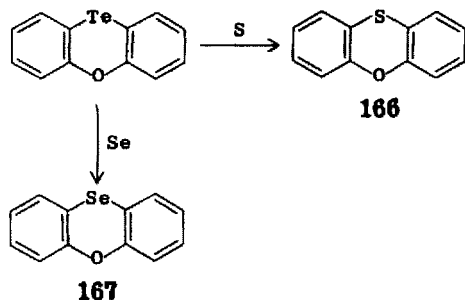
They were not able to prepare the 2-carboxylic acid by permanganate or chromic oxide oxidation of 2-methylphenoxatellurin (**165**), which they obtained by the following series of reactions:

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They prepared the *d*-tartrate and *d*-camphorsulfonate salts of 2-amino-phenoxatellurin and the *l*-menthol, strychnine, quinine, cinchonidine, and *d*- α -phenethylamine derivatives of **163**.

Phenoxatellurin reacts with sulfur and with selenium exothermally to give phenoxathiin (**166**) and phenoxaselenin (**167**), respectively. This reaction has been important in the preparation of these homologous ring systems (see section IX B-2a and Chapter 11, section III I-1).

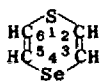


In the three homologous series, the 10-monoxide of **167** is the most stable and phenoxatellurin the least. The 10, 10-dihalides of phenoxatellurin, on the other hand, are the most stable and the sulfur analog (**166**) is so unstable that no one has isolated it. The selenium analog (**167**) is more like phenoxatellurin than like phenoxathiin.¹⁸ Phenoxathiin is colorless, melts at 58°, and its sulfuric acid solution has an intense violet color; phenoxaselenin is colorless, melts at 88°, and its sul-

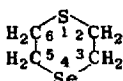
Ring Systems containing Selenium and Tellurium

furic acid solution has an intense olive-green color which becomes violet on diluting or heating; phenoxatellurin has a yellow to orange color depending on the solvent from which it is obtained, melts at 78-79°, and its sulfuric acid solution has a deep purplish-red color. The three analogs taken in pairs form mixed crystals and are inseparable by solvent extraction or recrystallization.²⁰ Moir⁵⁴ studied the halochromism of phenoxatellurin, phenoxaselenin, phenoxathiin, and their oxides in sulfuric acid solution. Wood, McCale, and Williams,⁸¹ in a crystallographic study of these analogs found that phenoxathiin appears to belong to the orthorhombic halohedral class but X-ray examination showed the crystals to be enantiomorphic, that there are four molecules in each unit cell, and that each analog is folded about the line joining the heterocyclic atoms. Burstall and Sugden¹⁰ found the parachor of phenoxatellurin to be 452.9.

XI. C_4SSe 1, 4-THIASELENIN (168) AND 1, 4-THIASELENANE (169)



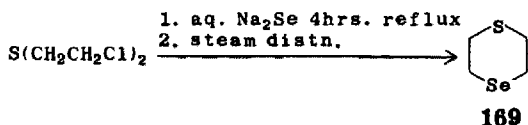
168



169

(RRI 264)

The parent compound (168) is not known. Gibson and Johnson³² prepared 1, 4-thiaselenane (169), which he named 1, 4-selenothian, by refluxing β, β' -dichlorodiethyl sulfide with aqueous sodium selenide.

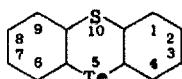


169

They were not able to prepare 1, 4-thiaselenane from the reaction of aqueous sodium sulfide with β, β' -dichlorodiethyl selenide. The interaction of β, β' -dichlorodiethyl sulfide with aluminum selenide gave only *p*-dithiane.

1, 4-Thioselenane, recrystallized from ethyl alcohol as colorless thin plates, melts at 107°. It resembles *p*-dithiane in its ready volatility in steam, and in odor and crystalline appearance. It reacted readily with bromine but the product was not described.

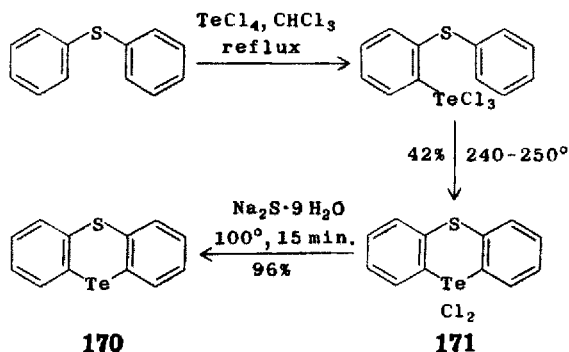
XII. C_4STe-C_6 PHENOTHIATELLURIN (170)



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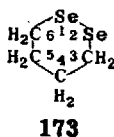
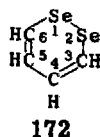
Petragnani,⁶⁵ in 1960, using Drew's¹⁵ synthesis for the preparation of 10, 10-dichlorophenoxatellurin, obtained 5, 5-dichlorophenothiatellurin (171) on heating *o*-thiophenoxyphe nyltellurium trichloride at 240-250° in a glass tube with stirring. On cooling, the dark liquid solidified to a dark yellow mass, which, dissolved in acetone, filtered, and crystallized, yielded needles, melting at 265-270° (a change in crystalline form was noted at 230°). Treatment of the 10, 10-dichloride (171) with hydrated sodium sulfide gave phenothiatellurin in 96% yield as pale yellow needles, melting at 122-123. 5°, from ethyl alcohol.



XIII. C_4Se_2

A. *o*-DISELENO COMPOUNDS

1. C_4Se_2 *o*-Diselenin (172) and *o*-Diselenane (173)



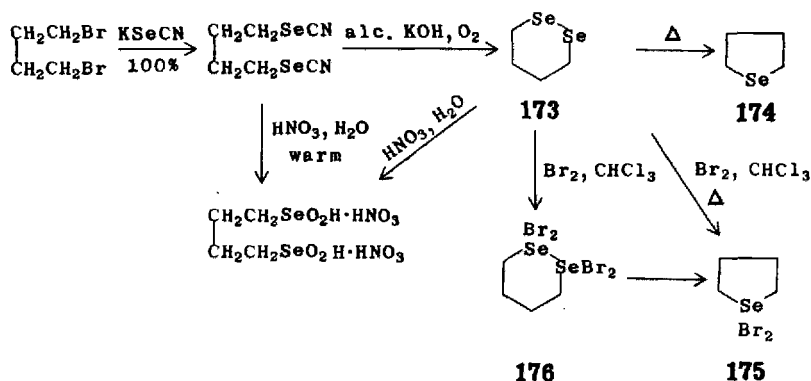
(RRI 269)

The parent compound (172) has not been reported. Its tetrahydro derivative (173) was first reported by Morgan and Burstall⁶³ in 1929, and only a relatively few substituted derivatives of *o*-diselenane have been studied. In addition to the diselenane nomenclature, which Chemical Abstracts has used, 173 has been named 1, 2-diselenacyclohexane, cyclo-diselenobutane, and cyclotetramethylene diselenide.

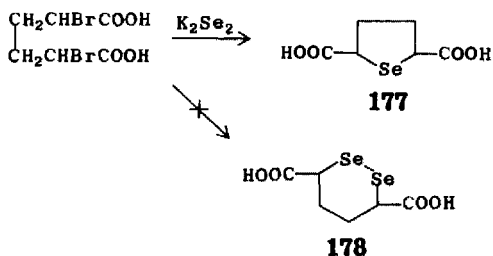
In studying methods for preparing tetrahydroselenophene (174), Morgan and Burstall found that the addition of an alcoholic solution of 1, 4-tetramethylenediselenocyanate to alcoholic sodium hydroxide in the presence of oxygen yielded *o*-diselenane (173) as a yellow powder, sparingly soluble in alcohol or acetone, readily soluble in benzene or chloroform. It was quite stable on standing, melted to a yellow liquid at 41-42°, and, when strongly heated, it decomposed to give 174. It reacts

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with bromine in chloroform to give 1,1-dibromotetrahydroselenophene (175) through the intermediate formation of 1,1,2,2-tetrabromo-*o*-diselenane (176), an unstable, orange compound, also prepared by the action of excess bromine on *o*-diselenane. The tetrabromide (176) decomposed so readily that it could not be analyzed. Treatment of *o*-diselenane or of the diselenocyanate with warm nitric acid yielded 1,4-tetramethylenediseleninic acid dinitrate, which decomposed explosively with liberation of selenium at 136°.

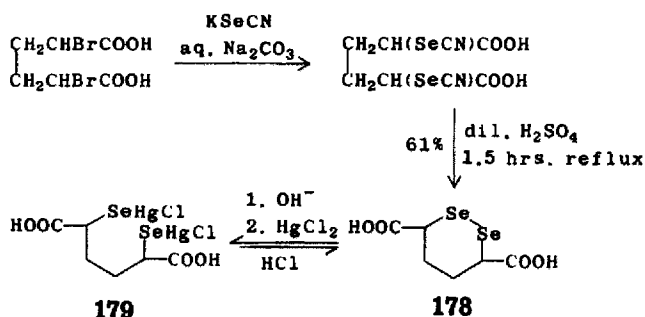


On reacting *meso*- and *rac*- α, α' -dibromoadipic acid with potassium diselenide, Fredga^{25,26} obtained tetrahydroselenophene-2,5-dicarboxylic acid (177), and not the expected *o*-diselenane (178).



The surprising nature of this reaction is commented on in section VI A-2. Fredga^{27,28} prepared *cis*-*o*-diselenane-3,6-dicarboxylic acid (178) from the reaction of *meso*- α, α' -dibromoadipic acid with potassium selenocyanate and refluxing the potassium salt of *meso*-adipic acid- α, α' -diselenocyanate with dilute sulfuric acid. Fredga,²⁹ on treating *o*-diselenane-3,6-dicarboxylic acid with mercuric chloride, obtained 179 as a heavy white precipitate, which on acidification reverted to 178.

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The *cis*-dicarboxylic acid (178) separated as orange-red crystals from water and decomposed at 200°; it showed strong brown-orange to yellow dichroism; its solubility in water at 25° is 0.694 g/l. The secondary strychnine salt, $\text{C}_6\text{H}_8\text{O}_4\text{Se}_2 \cdot 2(\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4) \cdot 5\text{H}_2\text{O}$ as yellow crystals, when acidified did not yield an active form of 178. Treatment of *trans*-178 with quinine yielded a salt which was resolved into (–)-178, $[\alpha]_D^{25} -351^\circ$, as yellow crystals from water or ether showing yellow to nearly colorless dichroism, and, from the mother liquor, (+)-178, $[\alpha]_D^{25} 351^\circ$ whose solubility in water is 2.37 g/l. Fredga³⁰ pointed out that *o*-dithiane-3, 6-dicarboxylic acid and 178 resemble each other closely. The (–)-isomer is best isolated in acetone solution as its quinidine salt and the (+)-isomer is best separated through its strychnine salt.

Djerassi, Fredga, and Sjöberg,^{14b} who studied the optical rotatory dispersion curve of (+)-*o*-dithiane-3, 6-dicarboxylic acid and of (–)-178, in which the hetero atoms are adjacent to the asymmetric center, noted a strong Cotton effect related to the ultraviolet absorption. They also point out that the vicinal action from the carboxyl group may be important with respect to the anisotropy of the disulfide and diselenide.

Bergson⁷ studied the ultraviolet and infrared adsorption of *o*-diselenane, *o*-diselenane-3, 6-dicarboxylic acid, and other diselenium compounds, paying particular attention to the interpretation of the spectral shifts caused by the dihedral angle of the C-Se-Se-C group, the inductive effect of the carboxylic acid group, and the hyperconjugative effect due to the presence of hydrogen atoms in the neighborhood of the Se-Se group. The steric effect is most pronounced for the Se-Se group in a five-membered ring. The steric effect in the six-membered ring is less pronounced, as the dihedral angle does not deviate so much from 90°. The dihedral angle in *o*-diselenane-3, 6-dicarboxylic acid has been determined to be 56° and the ultraviolet peak is at 345 mμ. In *o*-diselenane-3, 6-dicarboxylic acid, the carboxylic acid groups cause a hypsochromic shift, the absorption maximum for *o*-diselenane being 350 mμ. Bergson's measurements on cyclic diselenides are summarized in Table 7. The values of ΔE are a direct measure of the steric effect in the ultra-violet spectra of the diselenium compounds. The small difference in the spectra of *rac*- and (+)-*o*-diselenane-3, 6-dicarboxylic acid does not account for the deeper color for the racemic acid compared with the optically active acid in the solid state as observed by Fredga.²⁸ The

TABLE 7. Ultraviolet Absorption of Cyclic Diseleniums

Compound	λ_{max} $m\mu$	E_{excit} kcal/mol	ΔE_{excit} kcal/mol
1, 2-Diselenolane	444	64. 4	27. 3
4, 4-Bis(hydroxymethyl)-1, 2-diselenolane	443	64. 5	27. 2
6-Selenoctic acid	442	64. 7	27. 0
<i>o</i> -Diselenane	365	78. 3	13. 4
(+)- <i>o</i> -Diselenane-3, 6-dicarboxylic acid	341	83. 8	13. 7
<i>rac-o</i> -Diselenane-3, 6-dicarboxylic acid	343	83. 3	14. 2
<i>cis-o</i> -Diselenane-3, 6-dicarboxylic acid	345	82. 8	14. 7

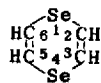
infrared absorption band Bergson attributed as being probably due to C-Se stretching in *o*-diselenane-3, 6-dicarboxylic acid occurred at 18.8μ (for 6-selenoctic acid $\lambda = 18.7\mu$).

Foss and Schotte,²⁴ in an X-ray crystallographic study of cyclic disulfides and diselenides, described *rac-o*-diselenane-3, 6-dicarboxylic acid as monoclinic and probably prismatic, having four molecules per unit cell, density 2. 27 g/cc; it and *rac-o*-dithiane crystallize in the same space group with very similar unit cell dimensions. They described (+)-*o*-diselenane-3, 6-dicarboxylic acid as orthorhombic spheroidal with four molecules per unit cell, density 2. 21 g/cc.

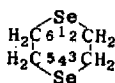
Schwarz and Foltz^{71a} found that *o*-diselenane-3, 6-dicarboxylic acid was inactive against dietary necrotic liver degeneration in rats.

B. *p*-DISELENO COMPOUNDS

1. C_4Se_2 *p*-Diselenin (180) and *p*-Diselenane (181)



180



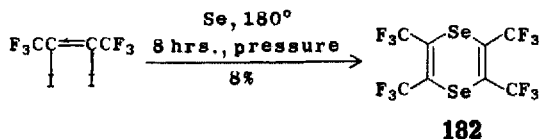
181

(RRI 270)

The parent compound (180) is known by only one derivative, 2, 3, 5, 6-tetrakis(trifluoromethyl)-*p*-diselenin (182). Its tetrahydro derivative (181) was first reported in 1951. The few derivatives of *p*-diselenane which have been reported are listed in Table 8. In addition to the diselenane nomenclature, which Chemical Abstracts has used, 181 and its derivatives have been referred to as 1, 4-diselenacyclohexanes.

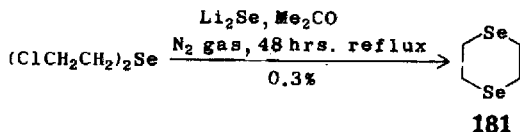
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The only derivative of *p*-diselenin which has been reported is 2, 3, 5, 6-tetrakis(trifluoromethyl)-*p*-diselenin (**182**) which Krespan^{45a} prepared in 1961 by heating 2, 3-diiodohexafluoro-2-butene with selenium at 180° under pressure. The isolation of **182** after exposure to a temperature at which the *p*-dithiin ring contracts shows that the *p*-diselenin is relatively stable toward loss of selenium to form the corresponding selenophene. Krespan explained the stability of *p*-diselenin by the greater length of the C-Se bonds.

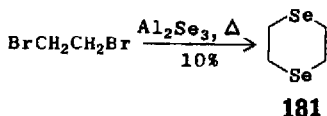


182, recrystallized from 95% ethanol, melted at 55° and boiled at 106-107°/110 mm; an infrared band for C=C occurred at 6.30 μ ; ultra-violet absorption was at $\lambda_{\text{max}}^{\text{EtOH}}$ 288 m μ ($\epsilon = 5,780$); a nuclear magnetic resonance peak for CF₃ was at -1252 c.p.s.

Gould and McCullough³³ were not able to prepare *p*-diselenane by the methods used for the preparation of *p*-dithiane. In these attempts, both ethylene bromide and β, β' -dichlorodiethyl selenide were treated with solutions of sodium or lithium selenide in aqueous alcohol. Using anhydrous acetone, they were successful in obtaining *p*-diselenane, although in very poor yield, 0.3%, from the reaction of β, β' -dichlorodiethyl selenide and powdered lithium selenide. *p*-Diselenane was identified through chemical analysis and its structure was determined through an X-ray diffraction study.⁵⁰



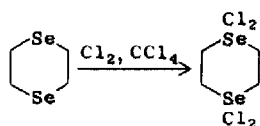
In attempting to increase the yield of *p*-diselenane, McCullough and Tideswell⁵¹ obtained a 2% yield from the reaction of aluminum selenide and ethylene bromide. On using magnesium selenide or ferrous selenide, the yield was negligible. By controlling the reaction conditions, Gould and Burlant³⁵ increased the yield to 10% by adding powdered aluminum selenide to ethylene bromide, heating the mixture at 80-85° the first hour, 85-95° the second hour, and 95-105° the third hour, then slowly bringing the temperature to 140° over an 8-hour period, and maintaining it there for an additional 5 hours.



p-Diselenane, recrystallized from methanol as a white crystalline compound and sublimed at 100° and 2mm, melted at 112.5–113.5°; its density, by flotation in mixtures of bromoform and ethylene bromide, was found to be 2.2.

Marsh and McCullough⁵⁰ studied the crystal structure of *p*-diselenane by X-ray diffraction. The volume of a unit cell is 3.13Å. The molecule is in a chair form, the only unanticipated feature being an unexpectedly long Se-C bonded separation which is 0.07Å longer than the sum of the single bond covalent radii for selenium and carbon. The corresponding bond distances are; Se-C₁ 1.99, Se-C₂ 2.04, C₁-C₂ 1.54, and Se-Se 3.66Å. The corresponding angles are: C₁-Se-C₂ 97.6°, Se-C₁-C₂ 108.5°, and Se-C₂-C₁ 107.8°.

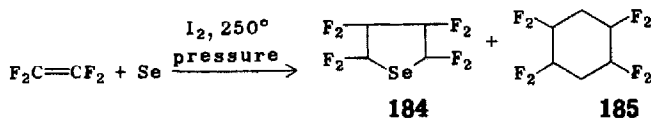
p-Diselenane readily reacts with halogens to form presumably 1,1,4,4-tetrahalo-*p*-diselenanes⁵¹ which are white (chloro), yellow (bromo), and brick-red (iodo) solids with relatively high melting points. They are insoluble in common organic solvents.



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McCullough, Chao, and Zuccaro,⁵² in their investigations of the structure of 1,1,4,4-tetraiodo-*p*-diselenane, found that the angle for Se-I-I is within a degree or two of 176°, the angle found in the I₃⁻ ion. From bond lengths, it is shown that *p*-diselenane forms a stronger iodine complex than *p*-dithiane, which in turn forms a stronger complex than the ICl and Br₂ complexes of dioxane. The halogen molecule entering a stronger complex should become itself more loosely bonded. The observed Se-I bond distance of 2.81Å is about 0.1Å longer than the anticipated length of a Se-I bond in axial I-Se-I bonding. In the latter case, Se would be expected to have a covalent radius of 1.39Å. The Se-Se-I angle was found to be 90° as compared to the S-S-I angle of 130° in *p*-dithiane. The apparent isomorphism of *p*-dithiane and *p*-diselenane is therefore surprising, as they must have different conformations.

On reacting tetrafluoroethylene with selenium, in the presence of iodine as a catalyst, at 250° under autogenous pressure, Krespan⁴⁵ obtained perfluoroselenolane (184) as the major product and perfluoro-*p*-diselenane (185) as a minor product.



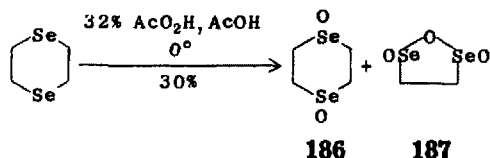
184

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Gould and Burlant³⁵ speculated that if the configuration of the bonds about the selenium atom is pyramidal rather than planar, then the 1,4-dioxide of *p*-diselenane should exist in both *cis* and *trans* forms. They

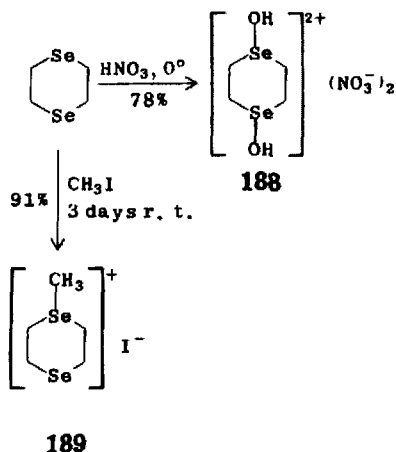
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were unable to isolate the isomers. Careful oxidation of *p*-diselenane with 32% peracetic acid at 0° yielded a compound, C₄H₈Se₂O₂, which was rapidly reduced to *p*-diselenane by reaction with sulfurous acid or hydroxylamine. The possibility that the product was the 1,1-dioxide was ruled out by its reaction with aqueous hydrogen halides to form 1,1,4,4-tetrahalides, and the compound was thus the 1,4-dioxide (186), which was previously reported by Gould and Post.³⁴



During the oxidation, particularly with 40% peracetic acid, some degradation of the ring occurs to give 14% *trans*-187 as a minor product (see section VII A). Both the dioxide and anhydride decompose rapidly if heated above 80°; both darken slowly if allowed to stand in moist air for more than two days, and both are extremely sensitive to base.^{34,35}

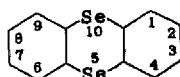
Oxidation of *p*-diselenane with concentrated nitric acid at 0° gives the dihydroxynitrate 188. Treatment of the dihydroxynitrate with hydrogen chloride or hydrogen bromide reduces it to *p*-diselenane with subsequent formation of the tetrahalide.³⁵ The high solubility of the dioxide in water and its sensitivity to base prevented its conversion to the methiodide (189) in a pure form.



1,4-Diselenane has marked but selective donor characteristics and thus forms complexes with cadmium chloride, palladium chloride, and mercuric chloride. It does not form complexes with nickel chloride, ferric chloride, cupric chloride, chromic chloride, or cobaltous chloride.

TABLE 8. *p*-Diselenanes

Substituent	Yield	M.p.(°C)	Other properties	Ref.
None	0, 3	112, 5-113, 5	$d = 2.2 \text{ g/cc}$	33
	10	112		35
1, 1, 4, 4-(Br-) ₄		149		33
	98	148-151 (dec.)		51
1, 1, 4, 4-(Cl-) ₄	100	178-181 (dec.)		51
		223		35
1, 1, 4, 4, -(I-) ₄	99	150-151 (dec.)		51
2, 2, 3, 3, 5, 5, 6, 6-(F-) ₈	1, 3		b.p. 108°	45
1, 4-(=O) ₂	30	109° (dec.)	$d = 2.58 \text{ g/cc}$	35
[1, 4-(HO-) ₂] ⁺⁺ (NO ₃ ⁻) ₂	30	111.5 (dec.)		35
[1-CH ₃ -] ⁺ I ⁻	91	133 (dec.)		35
C ₄ Se ₂ · 2CdCl ₂	55			35
C ₄ Se ₂ · PdCl ₂	100			35

2. C₄Se₂-C₆-C₆ Selenanthrene (190)

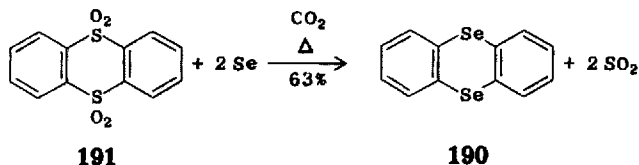
190

(RRI 3453)

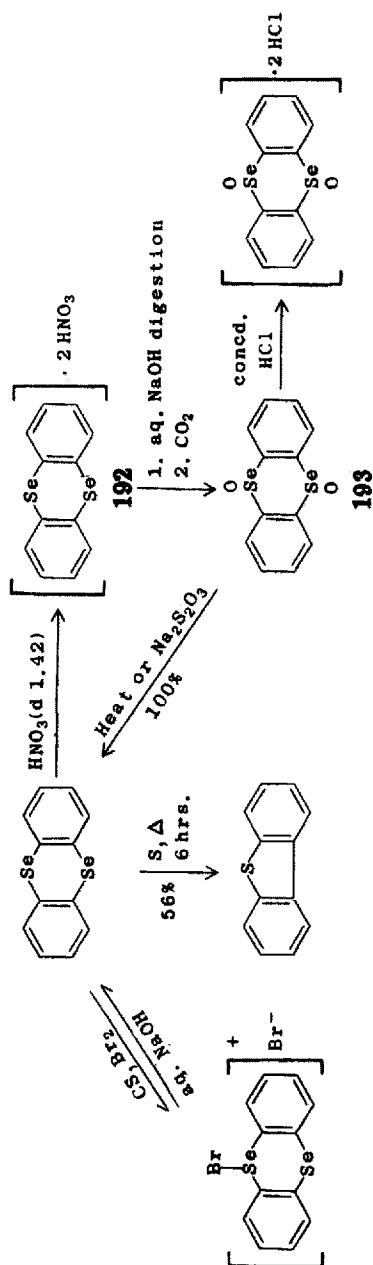
Selenanthrene is represented by a relatively few derivatives, listed in Table 9, in contrast to the large number of derivatives which have been reported for its analog thianthrene. In addition to the above name, which has been used by Chemical Abstracts, selenoanthrene, dibenzo-*p*-diselenin, and di-*o*-phenylene diselenide have been used.

Selenanthrene (190) was first reported in 1896 by Krafft and Kaschau,⁴⁴ who prepared it in 63% yield by heating thianthrene 5, 5, 10, 10-tetroxide (191) with selenium in an atmosphere of carbon dioxide. Cul-
linane, Morgan, and Plummer¹² obtained it in 44% yield by heating 191 with selenium for 50 hours.

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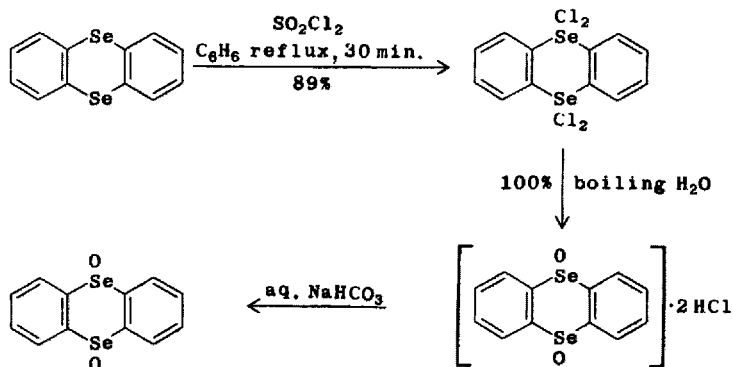


Selenanthrene was obtained from hot acetic acid, amyl alcohol, or amyl ether as colorless, flat needles or prisms with oblique terminal faces, melting sharply and without decomposition at 180-181° and boiling at 223°/11 mm. Treatment of selenanthrene with concentrated nitric acid yielded selenanthrene dinitrate (**192**) as colorless prisms, melting at 221° with decomposition; heating the dinitrate quickly caused it to burst into flame. Digesting the dinitrate with aqueous base, the base neutralized with carbon dioxide, and the product dried under vacuum yielded selenanthrene 5, 10-dioxide (**193**) as colorless crystals, melting at 270° with liberation of oxygen. Cullinane¹⁴ similarly prepared the 5, 10-dioxide, and obtained along with the 5, 10-dioxide, melting at 265° with decomposition, a product melting at 249° with decomposition which he speculated as possibly being a stereoisomeric form. According to Cullinane, the 5, 10-dioxide crystallizes from water as a hydrate. Inasmuch as Cullinane converted the dioxide to selenanthrene by heating it to its melting point or by treating it with sodium pyrosulfite, the dioxide had to be the 5, 10- and not the 5, 5-dioxide. Treatment of selenanthrene with hydrogen peroxide gave only a small yield of the 5, 10-dioxide; the dioxide could not be further oxidized with hydrogen peroxide or chromic acid. Treatment of the dioxide with excess concentrated hydrochloric acid gave a copious white precipitate of selenanthrene 5, 5-dioxide dihydrochloride.¹⁴ Selenanthrene is converted to dibenzothiophene on being heated with sulfur for 6 hours.¹³ Treatment of selenanthrene in carbon disulfide with bromine gave a dibromide, brownish-red prisms, melting at 140° with decomposition; treating the dibromide with sodium hydroxide converted it to selenanthrene in 90% yield; when kept in air or on being heated, the dibromide was transformed completely to selenanthrene.¹⁴ Similarly to thianthrene, selenanthrene and its derivatives dissolve in concentrated sulfuric acid with a blue color, which disappears on dilution.^{14, 44}

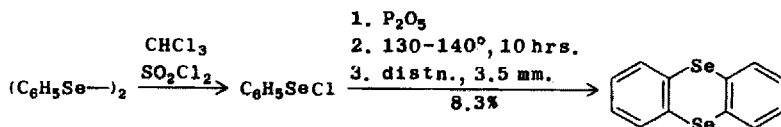


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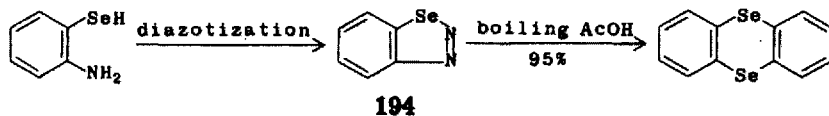
Bergson³ prepared selenanthrene 5, 10-dioxide by the reaction of selenanthrene in benzene with sulfuryl chloride under reflux, hydrolyzing the resulting selenanthrene tetrachloride with boiling water to the dihydrochloride, and treating the dihydrochloride with sodium bicarbonate.



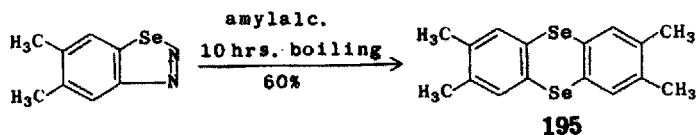
Keimatu and Satoda⁴⁰ prepared selenanthrene in 8.3% yield by treating phenylselenium chloride with P_2O_5 ; the phenylselenium chloride was obtained by decomposing diphenyl diselenide in chloroform with sulfuryl chloride.



They obtained a 95% yield on boiling an acetic acid solution of 1,2,3-benzoselenodiazole (194) which was obtained by diazotizing *o*-aminoselenophenol in a current of hydrogen at 0°.



By this method they prepared 2, 7- and 1, 6-dimethylselenanthrene from 5-methyl- and 7-methyl-1, 2, 3-benzoselenodiazole, respectively. 2, 3, 7, 8-Tetramethylselenanthrene (195) was prepared in 60% yield from 5, 6-dimethyl-1, 2, 3-benzoselenodiazole.⁴¹

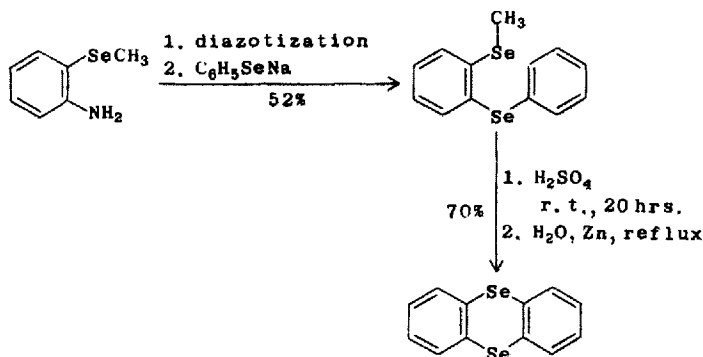


Sulfuric acid solutions of the alkyl selenanthrenes are blue.

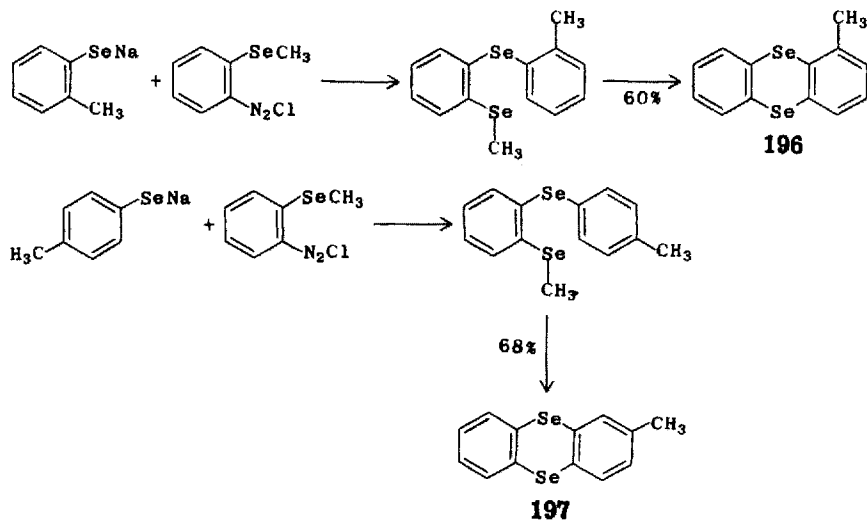
Keimatu, Satoda, and Tigano⁴¹ prepared selenanthrene in 70% yield by treating *o*-ethylselenodiphenyl selenide or *o*-methylselenodiphenyl sele-

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nide (obtained by treating diazotized seleno-*o*-anisidine with sodium selenophenolate) in concentrated sulfuric acid at room temperature for 20 hours and refluxing with water and a small amount of zinc.



In a similar manner, 1-methylselenanthrene (196) and 2-methylselenanthrene (197) were prepared from 2-methylseleno-2'- and 4'-methyl-diphenyl selenide, respectively.

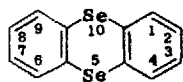


By this method, Keimatu, Satoda, and Kobayasi⁴² prepared 1-methyl- (196) and 2-methylselenanthrene (197) from 3-methyl- and 5-methyl-2-methylselenodiphenyl selenide, respectively; 1, 8-dimethylselenanthrene was prepared from 2, 3'- and 4', 5-dimethyl-6-selenomethyldiphenyl selenide; and 1, 6-, 2, 7-, 2, 8-, and 1, 7-dimethylselenanthrene were prepared from 2', 5-, 3, 4'-, 3, 3'-, and 3, 5'-dimethyl-6-selenomethyldiphenyl selenide, respectively.

It is generally accepted that the selenanthrene molecule is folded about the line joining the selenium atoms. Campbell and LeFèvre^{10a}

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TABLE 9. Selenanthrenes



Substituent	Yield	M.p.(°C)	B.p.		Ref.
			(°C)	(mm)	
None	63	180-181	223	11	44
	95	181			40
	70	181			41
	44	179.4			12
Dinitrate	90	221 (dec.)			44
Dibromide		140 (dec.)			14
Tetrachloride	89	208-209.5 (dec.)			3
5, 10-Dioxide	65	270 (dec.)			44
	68	265 (dec.)			14
	66	264-265 (dec.)			3
5, 10-Dioxide·2 HCl		213 (dec.)			14
	100	228-229 (dec.)			3
1-CH ₃ -	60	96-97			41
	76	97-98			42
2-CH ₃ -	68	78-79			41, 42
1, 6-(CH ₃ -) ₂	87	156	191-193	2	40
	65	156			42
1, 7-(CH ₃ -) ₂		78-79			42
1, 8-(CH ₃ -) ₂	48	77-78			42
2, 7-(CH ₃ -) ₂	95	111-112	209-210	2	40
	40	111-112			42
2, 8-(CH ₃ -) ₂		82-83			42
2, 3, 7, 8-(CH ₃ -) ₄	60	198-199			41

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estimated the angle of fold to be about 141° by assuming reasonable values for the valency angles of carbon and selenium and by the known radii of these atoms. In continuation of the work of Wood and Crackston,⁸⁰ Wood and Williams⁸² made a projection of the unit cell of selenanthrene on the (010) plane using photographically measured intensities of X-ray reflections, and assuming that the benzene rings are regular plane hexagons of side $1.41\text{\AA}$, calculated the angle of fold to be 127° , and interatomic distance of $1.96\text{\AA}$ for carbon and selenium, and a valency angle of 96° for selenium.

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- Disinfectant 262, 282
- Dispersing agent 782
- Dispiro [andro-4-ene-17β-ol-3, 3'-[1, 2, 4] trithiolane-5', 3''-andro-4''-ene-17''β-ol] 74s
- Dispiro [cholest-4-ene-3, 3'-[1, 2, 4] trithiolane-5', 3''-cholest-4''-ene] 74s
- Dispiro [fluoren-9, 3'-[1, 2, 4] trithiolane-5', 9''-fluorene] 74s
- Dispiro [indane-1, 3'-[1, 2, 4] trithiolane 5', 1''-indane], 3, 3''-diphenyl- 73s
- Dispiro [5.1.5.1] tetradecane-7, 14-dione 1024r
- Dispiro [xanthene-9, 4'-[1, 3] dithiolane-5', 9''-xanthene] 487s
- 2, 5-Dithia-7-azabicyclo [2. 2. 1] heptane, 7-anilino- 1095s
- 2, 5-Dithia-7-azabicyclo [2. 2. 1] heptane, 1, 4-dimethyl- 1107s
- 2, 5-Dithia-7-azabicyclo [2. 2. 1] heptane, 1, 4-dimethyl-7-phenyl- 1105rs
- 2, 5-Dithia-7-azabicyclo [2. 2. 1] heptane, 2, 5-dimethyl-7-phenyl- 253r
- 2, 5-Dithia-7-azabicyclo [2. 2. 1] heptane, 1, 4-dimethyl-7-ureido- 1106s
- 2, 5-Dithia-7-azabicyclo [2. 2. 1] heptane, 7-ethyl-1, 3, 4, 6-tetramethyl- 1106s
- 2, 5-Dithia-7-azabicyclo [2. 2. 1] heptane, 7-ureido- 1087s, 1095s, 1099s
- 3, 4-Dithiabicyclo [4. 1. 0] heptane, perfluoro- 964s
- 1, 4-Dithiacycloheptane, 6-hydroxy- 1053r
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- m*-Dithiane, 2, 2'-bis- 990s
- m*-Dithiane, 5, 5-bis (hydroxymethyl)- 991s
- m*-Dithiane, 5, 5-bis (*p*-hydroxyphenyl)- 1005s
- m*-Dithiane, 5-bromo- 1005s
- m*-Dithiane, 2-cyanomethylene- 995s
- m*-Dithiane, 5-dicyanomethylene- 1005s
- m*-Dithiane, 2, 2-dimethyl- 989s, 1007u
- m*-Dithiane, 5, 5-dimethyl- 991s, 1001r
- m*-Dithiane, 2, 2-dimethyl-5-benzoxo- 993s
- m*-Dithiane, 2, 2-dimethyl-5, 5-bis (hydroxymethyl)- 346s, 991s, 998r
- m*-Dithiane, 2-ethyl-2-methyl- 989s, 990s

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- s-Trithiane 1, 1, 3, 3-tetroxide, 2, 2, 4, 4, 6, 6-hexachloro- 744s, 745s, 758u
- s-Trithiane 1, 1, 3, 3-tetroxide, 2, 2, 4, 4, 6, 6-hexamethyl- 750s
- s-Trithiane 1, 1, 3, 3-tetroxide, 2, 2, 6, 6-tetrabromo- 743s
- s-Trithiane 1, 1, 3, 3-tetroxide, 2, 4, 6-trimethyl- 748s
- s-Trithiane 1, 3, 5-trioxide 729r, 740rs, 741r
- s-Trithiane 1, 3, 5-trioxide, 2, 4, 6-trimethyl- 747rs
- s-Trithiane 1, 3, 5-trioxide, 2, 4, 6-triphenyl- 750s
- s-Trithiane-4-carboxylic acid, 2, 6-bis (dibromomethylene)- 755s
- s-Trithianium chloride, 1-methyl- 752s
- s-Trithianium iodide, 1-methyl- 752s
- s-Trithianium trichloride, 1, 3, 5-tribenzyl- 752s
- s-Trithianium triiodide 729s, 741rs
- 2, 6, 7-Trithiaspiro [3. 4] octane 690rs
- Trithiocarbonate, sodium 530r, 996r
- 1, 2, 4-Trithiolane 69s
- 1, 2, 4-Trithiolane, 2, 5-bis (methylimino)- 72s
- 1, 2, 4-Trithiolane, 3, 5-dimethyl - 71s
- 1, 2, 4-Trithiolane, 3, 3, 5, 5-tetramethyl- 70s, 627s
- 1, 2, 4-Trithiolane, 3, 3, 5, 5-tetraphenyl- 71s, 72r
- 1, 2, 4-Trithiolane derivatives 69t
- 1, 2, 3-Trithiole 2-oxide, 4, 5-dicyano- 67s
- Trithiolo [4, 5-b] quinoxaline 68su
- Trithiolo [4, 5-b] quinoxaline 2-oxide 68su
- Trithione - see 1, 2-Dithiole-3-thione
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- Uracil, 6-methyl- 1116s
- Uscharin 1094r
- n-Valerylacetone 1310r
- Vanillin 814r
- Varnish 873
- Varnish solvent 838
- Varnish, stoving 756
- Vinyl acetate 811r
- Vinyl ethyl ether 830r, 832r
- Vinylidene fluoride 615r
- Vinylmercuric oxychloride 698r, 717r
- Vinylpyridine polymer 782s, 783s
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- Vulcanization accelerator 757
- Wetting agent 782
- Xanthogenate, ethylene-, diethyl 530r
- X-ray 412, 547, 866, 1052, 1056, 1064, 1100, 1125, 1126, 1141, 1161, 1275, 1301, 1329, 1333, 1335, 1343
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- p-Xylene 1170r
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- Xylose mercaptal 3r
- o-Xylylene dibromide 974r
- o-Xylylene, α , α' -dimercaptan 974r