THE CHEMISTRY OF 1,2-DITHIOLE-3-THIONES

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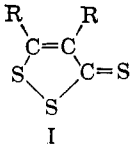
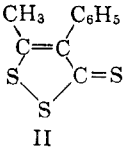
CONTENTS

I. INTRODUCTION

1,2-Dithiole-3-thiones are pseudo aromatic heterocyclic compounds having the structure shown in formula I. A wide variety of alkyl and aryl derivatives are known, the large majority of them having been synthesized since 1940.



I



II

Current *Chemical Abstracts* nomenclature and numbering are used throughout this review, *e.g.*, compound II is 4-phenyl-5-methyl-1,2-dithiole-3-thione. A brief review by German workers summarized work in this field through 1951 (3). Much of this early work utilized the name trithione as descriptive of the heterocyclic ring.

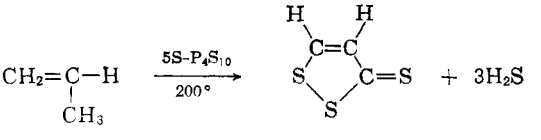
This review summarizes the present status of research on the synthesis and properties of these compounds.

II. SYNTHESIS OF 1,2-DITHIOLE-3-THIONES

A. 4- AND 5-SUBSTITUTED DERIVATIVES

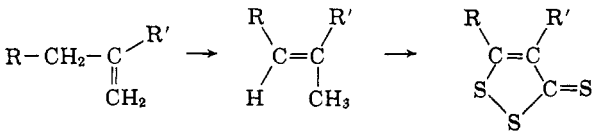
1. From Allylic Hydrocarbons

1,2-Dithiole-3-thiones have been synthesized from a wide range of starting materials. In most cases sulfur or phosphorus pentasulfide is utilized to dehydrogenate and sulfurize an allylic methyl group (5, 7, 9–11, 15, 37, 41, 45–47, 64, 71, 76–78, 83, 87) as illustrated by the formation of the parent compound from propylene.



When aromatic ring systems are conjugated with the double bond, high yields of the dithiole-3-thione are obtained by reaction of the olefin with sulfur. Thus, α-methylstyrene or isopropenylthiophene give nearly quantitative yields of the 4-aryl-1,2-dithiole-3-thione. With aliphatic olefins chain branching enhances thione formation, particularly in those cases where double bond isomerization is restricted.

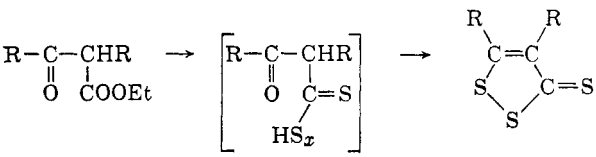
Olefins which readily isomerize to methyl-substituted derivatives similarly yield dithiole-3-thiones (10, 37, 41, 64, 87). Again, branched chain olefins generally provide higher yields of the appropriate derivative.



There is evidence that isomerization of the olefin, either thermally or catalyzed by sulfur, occurs before initial incorporation of sulfur into the molecule (18, 78).

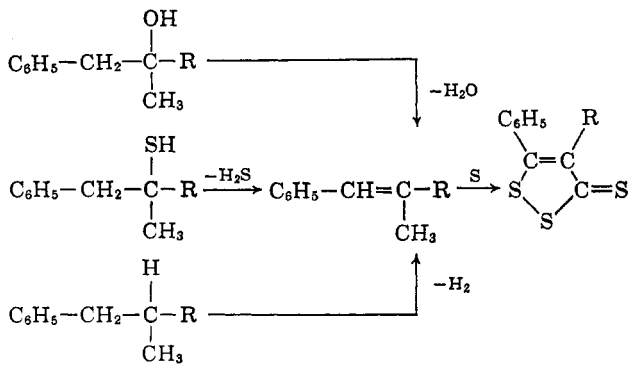
2. From β-Ketoesters

One of the more recently developed, widely used routes to 1,2-dithiole-3-thiones is the reaction of β-keto-esters with phosphorus pentasulfide (40, 44, 47, 57, 66, 82–85). While yields from this reaction are only fair, the reaction has utility since the 1,2-dithiole-3-thione can easily be separated by conversion to a metal salt complex from which the thione can be regenerated with hydrogen sulfide. The reaction is believed to proceed through an intermediate β-ketodithiocarboxylic acid.



3. From Structures Leading to Intermediate Olefins

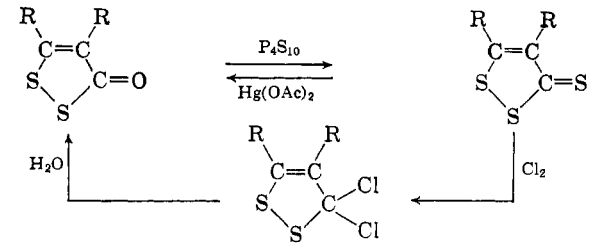
Other organic structures which readily dehydrate (73, 83), dehydrogenate (18), dehydrosulfurize (36, 85), or easily yield an olefin structure containing an α-methyl group react with sulfur to produce 1,2-dithiole-3-3-thiones. Basic catalysts facilitate the reactions, probably by catalyzing the olefin-forming reaction as well as the sulfurization reaction.



4. From α,β-Unsaturated Esters and Mercaptans

α,β-Unsaturated esters and mercaptans are reported to produce low yields of 1,2-dithiole-3-thiones on reaction with sulfur in xylene (11, 46, 53). Ultraviolet and infrared absorption studies have been used to detect small quantities of 1,2-dithiole-3-thiones in the products obtained from high temperature sulfurization of aliphatic mercaptans, sulfides, and polysulfides (76).

When the 1,2-dithiol-3-one derivative is available, it can easily be converted to the 3-thione either with sulfur or phosphorus pentasulfide (9, 30, 53). This reaction can be reversed by chlorinating the thione to produce a desthio derivative which can be hydrolyzed to the ketone (37, 67, 78). Controlled oxidation using mercuric acetate (6) or potassium permanganate (22, 41) has also been used to convert the thiocarbonyl group to a carbonyl group.



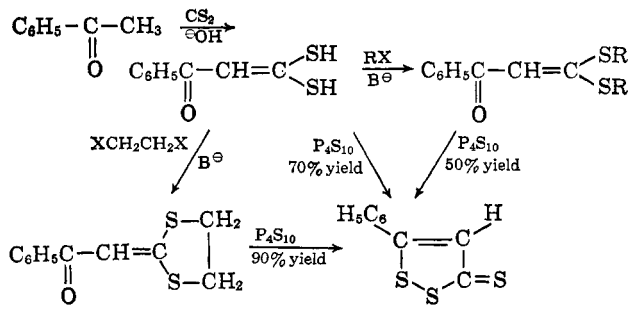
5. From Acetylenes

Methylacetylenes react with sulfur at elevated temperatures to yield a variety of products including 1,2-dithiole-3-thiones (42). Thus, methylphenylacetylene is converted to 5-phenyl-1,2-dithiole-3-thione. Acetylene itself produced low yields of the parent compound, 1,2-dithiole-3-thione, when heated with sulfur at 450°. This product must have arisen from addition of both sulfur and co-product carbon disulfide to acetylene (12).

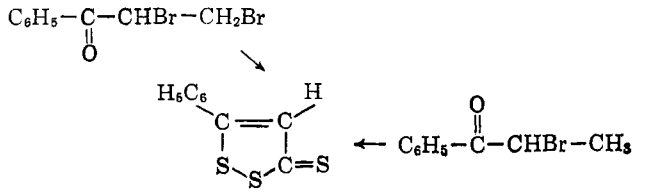
6. From Other Organic Intermediates

In a number of cases ketones which can be easily converted to methyl-substituted enols yield 1,2-dithiole-3-thiones on sulfurization (42, 69). Yields are only 2 to 5% but are improved by using as starting materials ketones in which the β-position is substituted by one or more sulfide groups. This technique has proved useful in the synthesis of 5-aryl-1,2-dithiole-3-thiones (69, 85).

In a somewhat analogous system, the sodium enolates of β-ketoaldehydes have been used as a source of 5-



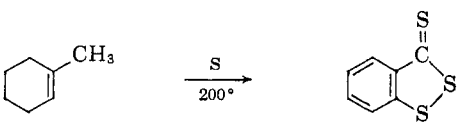
substituted 1,2-dithiole-3-thiones by reaction with phosphorus pentasulfide (85). Indeed, a wide range of β-ketoaldehydes have themselves been converted directly to 1,2-dithiole-3-thiones by reaction with a mixture of sulfur and phosphorus pentasulfide in biphenyl. Yields vary from 5 to 44% (38). A related reaction of 2-halo- and 2,3-dihaloketones with sulfur also yields 1,2-dithiole-3-thiones, presumably by dehydrohalogenation or dehalogenation to form olefinic precursors (39).



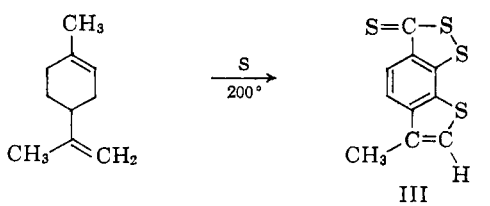
Recently 1,3-dimercaptopropanes have been dehydrogenated and sulfurized to 1,2-dithiole-3-thiones (59). Reaction of the dimercaptan with sulfur at 200 to 350° provides yields of 7 to 65% of the thione derivative, yields being lowest with low molecular weight derivatives and highest with aryl derivatives.

B. CONDENSED RING DERIVATIVES

Condensed rings in which the 1,2-dithiole-3-thione ring is part of the aromatic system have been prepared using many of the techniques for the preparation of the simpler analogs. Sulfur reacts with 1-methylcyclohexene to provide dehydrogenation and sulfur ring formation yielding 4,5-benzo-1,2-dithiole-3-thione (45).



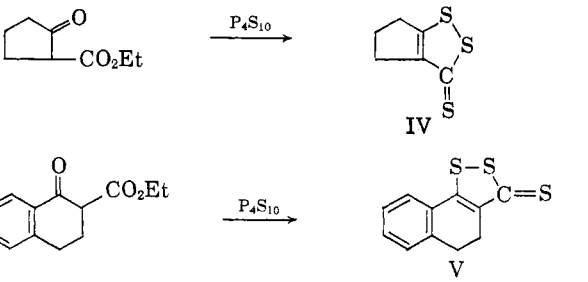
Terpenes behave in a similar fashion (5, 9, 14, 15, 89) as illustrated by the synthesis of III from dipentene.



III

1,2-Dithiole-3-thiones fused in the 4- and 5-positions by polynuclear aromatic rings have been prepared by treating the appropriate β-ketoester with phosphorus pentasulfide (40, 57). This technique has been used to prepare cyclopenteno (IV) and cyclohexeno (V) fused rings.

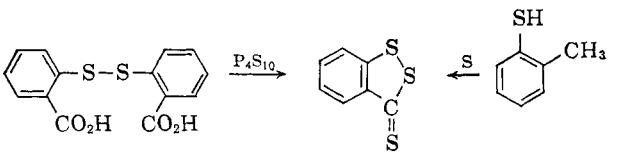
o-Thiocresol provides 4,5-benzo-1,2-dithiole-3-thione on reaction with sulfur at 200° (25). This same compound has been obtained from the reaction of phosphorus pentasulfide with the disulfide of thiosalicylic acid (20). This latter technique has been used for the



IV

V

synthesis of heterocyclic condensed ring systems as exemplified by 2,3-pyrido-1,2-dithiole-3-thione (50).



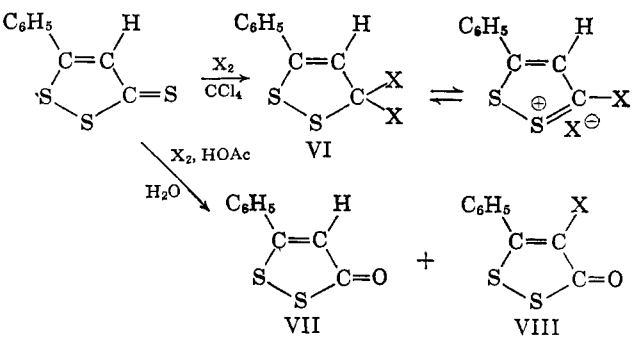
Eneamines condense with carbon disulfide and elemental sulfur at low temperatures in the presence of polar solvents such as dimethylformamide, forming 1,2-dithiole-3-thiones (16, 70). The reaction is particularly effective for the synthesis of derivatives fused in the 4,5-positions.

III. REACTIONS OF 1,2-DITHIOLE-3-THIONES

A. INORGANIC COMPLEXES

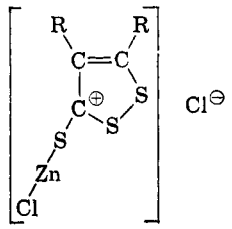
1. Halogens

1,2-Dithiole-3-thiones undergo many of the reactions typical of heterocyclic sulfur compounds; *i.e.*, they form adducts with halogens, alkyl halides, metal salts, and sulfur halides. Chlorine and bromine, in the presence of inert solvents, replace the thione sulfur to produce dihalo-desthio derivatives (VI) (37, 63, 78). Iodine yields a mixture of the diiodo adduct and a disulfide involving the thione sulfur atom (43). The action of chlorine or bromine on 5-aryl-1,2-dithiole-3-thiones in boiling acetic anhydride or aqueous acetic acid leads to 5-aryl-1,2-dithiol-3-one (VII) and 5-aryl-4-halo-1,2-dithiol-3-ones (VIII) (67). The choice of solvent affects the proportion of products.



2. Metal Salts

Metal salts that form insoluble sulfides complex readily with the thione portion of the nucleus forming colored coordination compounds whose structure has been assigned as IX. Either 1:1 or 2:1 molar ratios

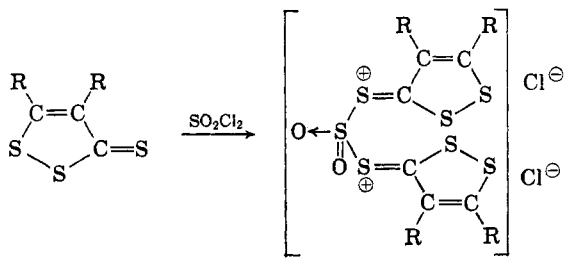


IX

of thione to metal salt are observed using $HgCl_2$, $HgBr_2$, $CdCl_2$, CdI_2, $ZnCl_2$, $FeCl_3$, $AgNO_3$, $SbCl_3$, $CuCl_2$, Cu_2Br_2, $AuCl_4$, $PdCl_2$, $PtCl_4$, $BiCl_3$, or $SnCl_4$ (10, 37, 43, 48, 63, 87, 88). The complexes frequently are yellow, but in some cases are brown ($FeCl_3$) or green ($ZnCl_2$).

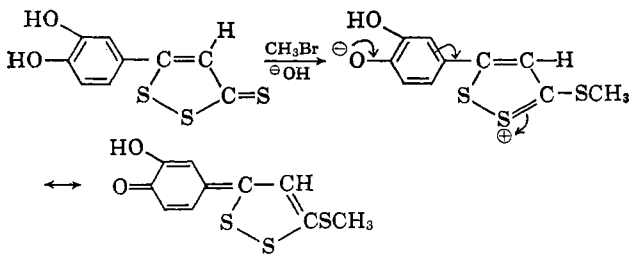
3. Sulfur Halides

Thionyl chloride and sulfuryl chloride react in a rather similar fashion to produce hygroscopic ionic adducts (63).

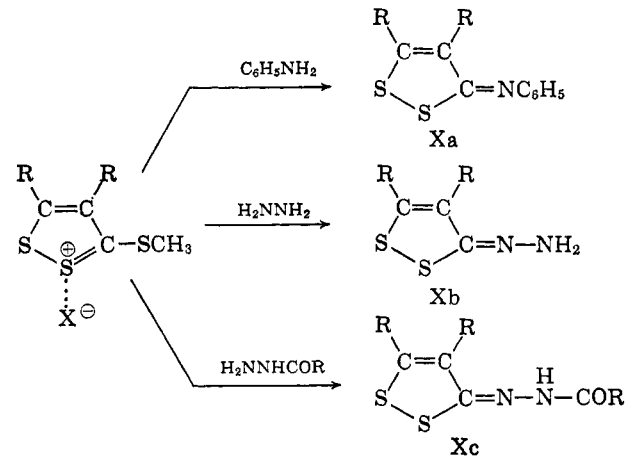


B. QUATERNARY SALT FORMATION

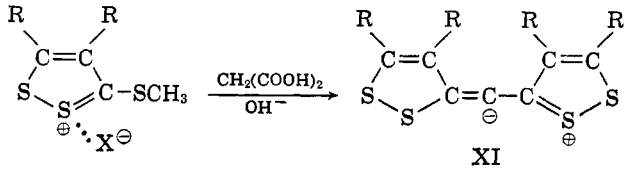
Alkyl halides, sulfates, and perchlorates (3, 9, 10, 41, 48, 51) combine with 1,2-dithiole-3-thiones to produce dithiolium salts in a manner analogous to the addition of halides to thiones. By appropriate substitution of the groups attached to the 1,2-dithiole-3-thione ring it has been possible to synthesize highly colored molecules with dye properties (55, 56, 72), as illustrated below. The methanethiol group of the quaternary salt



can be removed by reaction with nitrogen bases producing dithioimides (Xa,b,c).

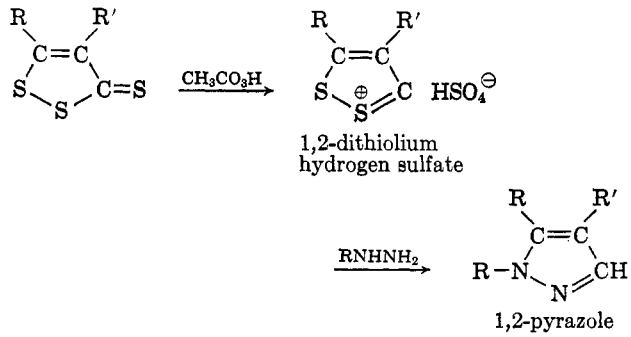


Compounds containing active methylene groups also remove methanethiol from the quaternary salt (55) yielding a zwitterion containing a carbon–carbon double bond (XI).



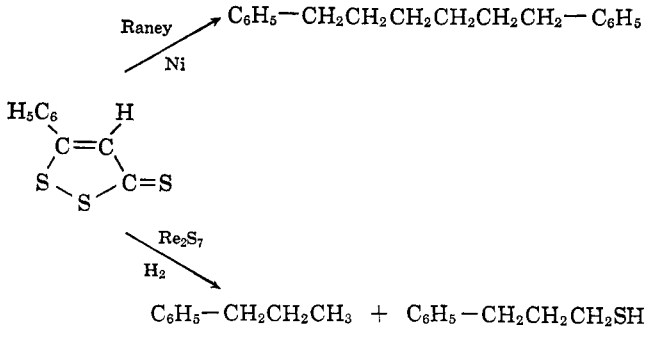
XI

Peracetic acid oxidation of 1,2-dithiole-3-thiones yields the pseudo-aromatic 1,2-dithiolium salts which are isosteric with the tropylium cation (30). The structures have been confirmed by ultraviolet spectroscopy (interannular conjugation provides a bathochromic shift and yields principal absorption maxima at 356 and 242 mμ) and by nuclear magnetic resonance. Hydrazines react with the 1,2-dithiolium cation to produce pyrazoles (31).



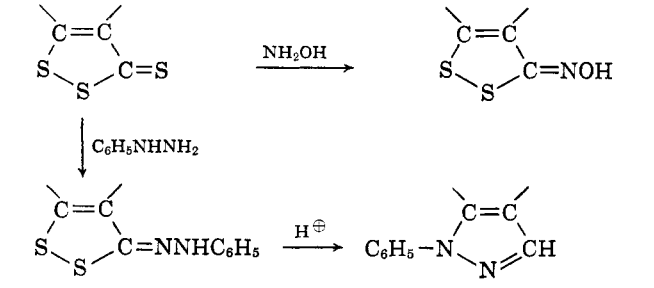
C. HYDROGENATION

Desulfurization of 1,2-dithiole-3-thiones by Raney nickel results in complete removal of sulfur and dimerization of the hydrocarbon portion of molecule (51), *e.g.*, 5-(*p*-methoxyphenyl)-1,2-dithiole-3-thione produces 1,6-bis(*p*-methoxyphenyl)hexane. Rhenium heptasulfide and hydrogen catalyze the hydrogenation of dithiole-3-thiones to equal parts of a hydrocarbon and a mercaptan (2).

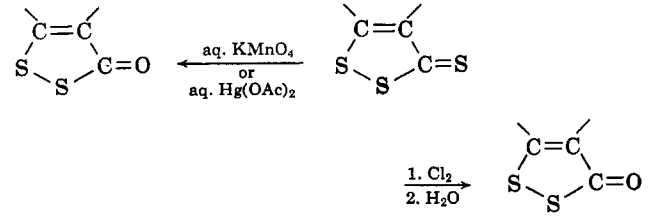


D. REACTIONS OF THE THIOCARBONYL GROUP

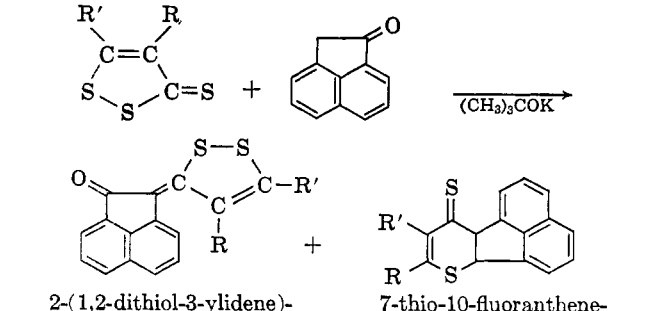
The 1,2-dithiole-3-thiones behave more like ketones than anhydrides in that the thiocarbonyl group undergoes reactions typical of ketones. Oximes and phenylhydrazones (3, 10, 55) have been obtained from a variety of 1,2-dithiole-3-thiones, although the latter easily undergo further rearrangement to form pyrazoles.



The thiocarbonyl group can be readily converted to a carbonyl group by treatment with aqueous potassium permanganate (22, 41) or aqueous mercuric acetate (6) or by chlorination followed by hydrolysis (37, 67, 78).



The thiocarbonyl group is also displaced in base-catalyzed reactions with compounds containing activated methylene groups. For example, 5-phenyl-1,2-dithiole-3-thione reacts with malonic ester derivatives to provide 5-aryl-1,2-dithiolylidene-3-malonic esters (67). These condensations proceed best when the 4- and 5-positions are substituted by aryl groups. When these positions are substituted by methyl groups, monothiothiones are sometimes observed (64).

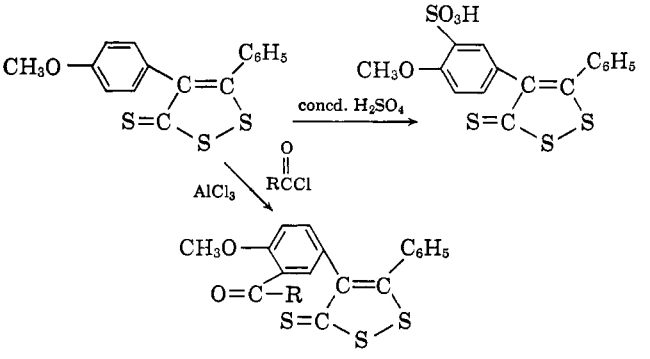


2-(1,2-dithiol-3-ylidene)-1-acenaphthenones
R and R′ = Ar

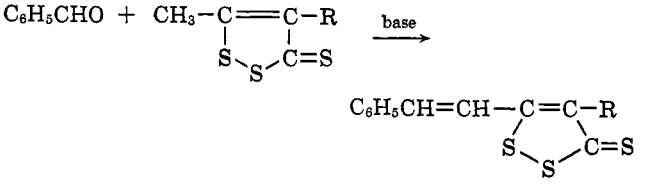
7-thio-10-fluoranthenethiones
R and R′ = CH_3

E. ELECTROPHILIC SUBSTITUTION REACTIONS ON ARYL GROUPS ATTACHED TO 1,2-DITHIOLE-3-THIONES

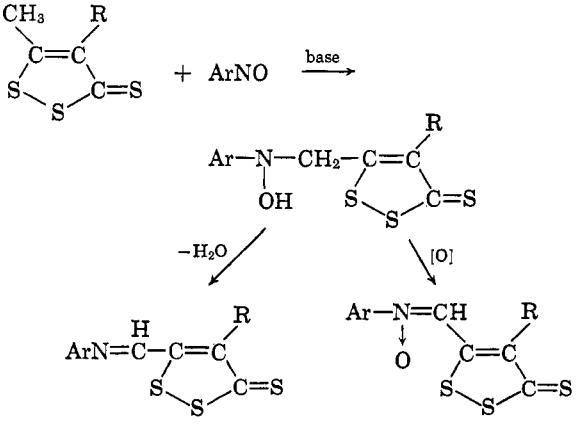
When the ring system is substituted in both the 4- and 5-positions by aryl groups, the resulting remarkable stability provides a source for a range of electrophilic substitution reactions on the attached aromatic ring. Thus, aryl-1,2-dithiole-3-thiones have been sulfonated by concentrated sulfuric acid and acylated under Friedel–Crafts conditions (74).



5-Methyl-1,2-dithiole-3-thiones undergo piperidine-catalyzed condensation with benzaldehyde and its derivatives forming aldol condensation products (66).



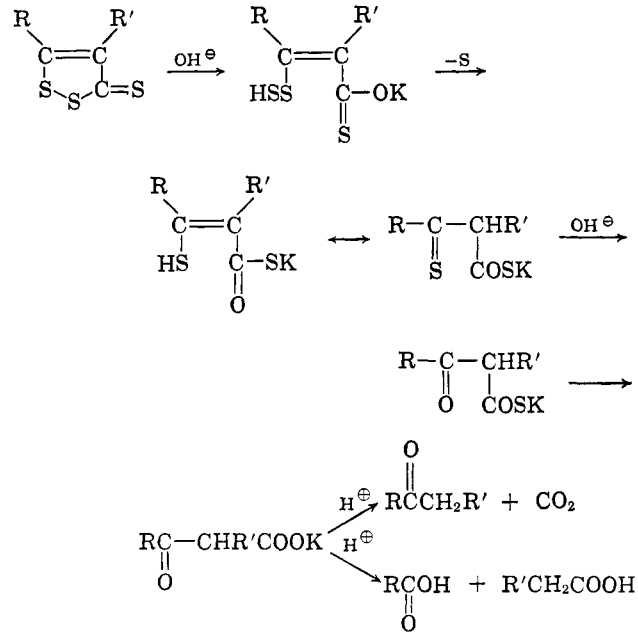
p-Nitroso-N,N-dimethylaniline is reported to react with 5-methyl-1,2-dithiole-3-thiones to produce hydroxylamine derivatives which can be dehydrated to anils or oxidized to nitrones (65).



F. HYDROLYSIS

Basic hydrolysis of 1,2-dithiole-3-thiones removes two atoms of sulfur as sulfide and a third atom as free sulfur (10). The organic product is a derivative of

acetoacetic acid which may be hydrolyzed to yield a ketone and carbon dioxide or to produce two different organic acids.



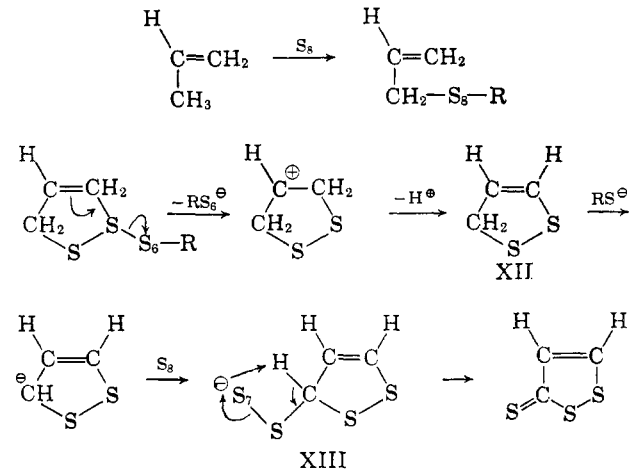
This hydrolysis has proved useful in structural studies (22, 37, 49, 76–78, 87) and has been suggested as a novel route to unusual organic acids. Thus γ,γ-dimethylvaleric acid has been obtained in good yield from 4-neopentyl-1,2-dithiole-3-thione (77, 78).

G. OXIDATION

Inorganic oxidizing agents convert 1,2-dithiole-3 thiones to carboxylic acids. Chromic acid or nitric acid oxidize 4,5-dimethyl-1,2-dithiole-3-thione to acetic acid (49). 5-*p*-Methoxyphenyl-1,2-dithiole-3-thione is oxidized to anisic acid (22). At low temperatures the oxidation can be controlled so that the thiocarbonyl group is converted to a carbonyl group. Peroxidic reagents oxidize the thione sulfur to dithiolium salts (30, 31).

IV. MECHANISM OF THE FORMATION OF 1,2-DITHIOLE-3-THIONES

It is known that reaction of sulfur with olefins to form 1,2-dithiole-3-thiones is catalyzed by base (18) and is not affected by ultraviolet light (33). This suggests a polar reaction mechanism of which many of the intermediates have been isolated in low temperature sulfurizations. In this scheme the reactions leading to XII are intramolecular variations of established low temperature sulfurization reactions with deprotonation leading to XII being favored by the conjugation of the resulting double bond with the adjacent sulfur atom. The allylic CH_2 group in XII will undergo facile proton transfer to a sulfenyl anion as will the CH group in XIII, thus inducing the formation of the thione group.



XIII

V. PHYSICAL PROPERTIES

A. GENERAL PROPERTIES

Many of the 1,2-dithiole-3-thiones are highly colored crystalline solids. Those with aromatic substituents are high melting solids and possess orange to deep red colors, while the aliphatic derivatives are yellow. High molecular weight alkyl derivatives frequently are oils.

The dithiole-3-thiones are characterized by high thermal stability. They can be distilled without decomposition often at atmospheric pressure. They are odorless, stable to air oxidation, and possess a bitter taste.

The thiones are essentially insoluble in most polar solvents, sparingly soluble in aliphatic solvents, and soluble in aromatic hydrocarbons. They are also soluble in concentrated sulfuric acid and can be recovered unchanged on dilution.

B. SPECTRAL PROPERTIES

The ultraviolet and visible absorption spectra of 1,2-dithiole-3-thiones show strong bands at 225, 250, 280, 335, and 417 mμ (14, 37, 49, 54, 68, 90) (see Figure 1).

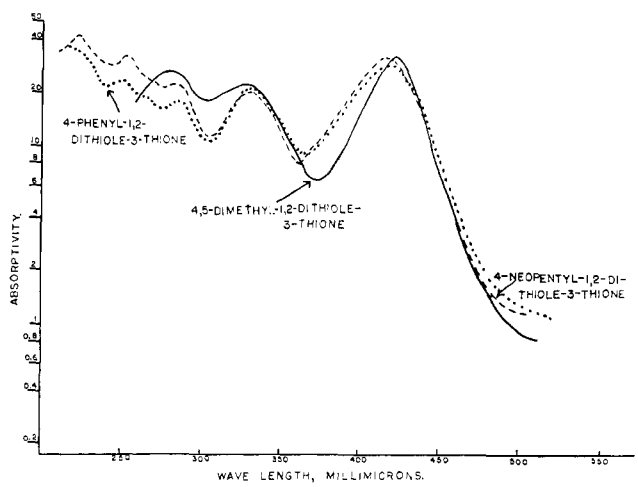


Figure 1.

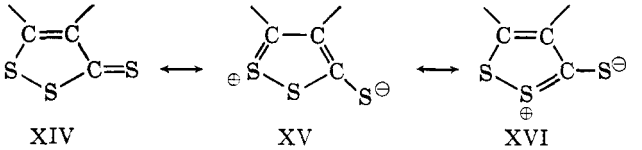
Infrared spectra have been used to substantiate structures of the 4-neopentyl-, the 4-methyl-5-*t*-butyl-, and 4-*t*-butyl-5-neopentyl-1,2-dithiole-3-thione (37, 78). Optical rotatary dispersion data were obtained for 1,2-dithiole-3-thiones derived from (+)-camphor and (+)-α-pinene. The data show a series of four negative Cotton effects (14).

High voltage mass spectra fragmentation patterns show that the ring system degrades by loss of S and CS ions.

C. CRYSTAL STRUCTURE STUDIES

The crystal structure of a 1,2-dithiole-3-thione was first reported by Zaslovski and Kondroshov (91) who worked with the 4-methyl-5-phenyl derivative. They established that four molecules with reasonable assumed dimensions could be fitted to the unit cell and space group to give a qualitative agreement with some 70 observed X-ray intensities.

More recently Kehl and Jeffrey (29) did a complete structural analysis of 4-methyl-1,2-dithiole-3-thione (see Figure 2), determining the bond lengths and the conjugative interactions of the three groups S–S, C=C, C=S, each of which has π-orbitals perpendicular to the plane of the dithiole ring. Resonance forms XIV, XV, and XVI, in the ratio of 5:4:1, qualitatively account for the observed bond lengths.



XIV XV XVI

Bergson has evaluated the π-electron structures of the parent compound, 1,2-dithiole-3-thione, and the 1,2-dithiolium cation, calculating the partial double bond character and net charges for overlap and for nonoverlap (4).

D. ANALYTICAL PROPERTIES

A paper chromatographic separation of mixtures of 1,2-dithiole-3-thiones has been developed utilizing Whatman No. 1 paper impregnated with 30% formamide in ethanol, with petroleum ether or 80% ethanol as the mobile phase. The spots were fixed with a solution of ferricyanide and ferric chloride (27).

Polarographic studies have established that the 1,2-dithiole-3-thiones give a cathodic wave with a half-wave potential of −0.9 v. (23).

A number of aryl-1,2-dithiole-3-thiones have been used to study the structural dependence of poisonous effects of organic compounds on Raney nickel hydrogenations (26).

Nuclear magnetic resonance spectra of 4-phenyl-1,2-dithiole-3-thione and 5-phenyl-1,2-dithiole-3-thione (Figure 3) illustrate the aromaticity of the dithiole ring.

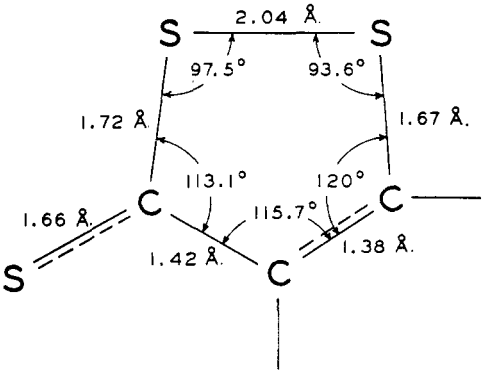


Figure 2.

In each of these compounds, as well as in their ketone analogs, the protons attached to the dithiole ring showed a resonance in the 6.86 to 8.27 c.p.s. region (tetramethylsilane reference). When the proton was located in the 4-position, the resonance occurred at lower fields than observed with the analogous compound containing a proton in the 5-position (35).

VI. PHYSIOLOGICAL PROPERTIES

The physiological properties of 5-*p*-methoxyphenyl-1,2-dithiole-3-thione have been studied extensively. It showed low toxicity when taken orally (21). Guinea pigs tolerated 3 to 4 g. per kg. of weight. Dosages greater than 0.15 g. caused mild digestive disturbances in humans. The compound showed activity in lowering blood pressure in hypertensive rats and in depressing the pressor action of noradrenaline (75). Promising results were observed in treating intestinal allergy and jaundice. The compound also stimulated the liver, increased bile secretion (21, 32, 34, 61), and caused an increase in nitrogen metabolism (24). At concentrations of 10^{-3} *M* in ethanol it caused inhibition of oxidation and phosphate consumption on oxidative

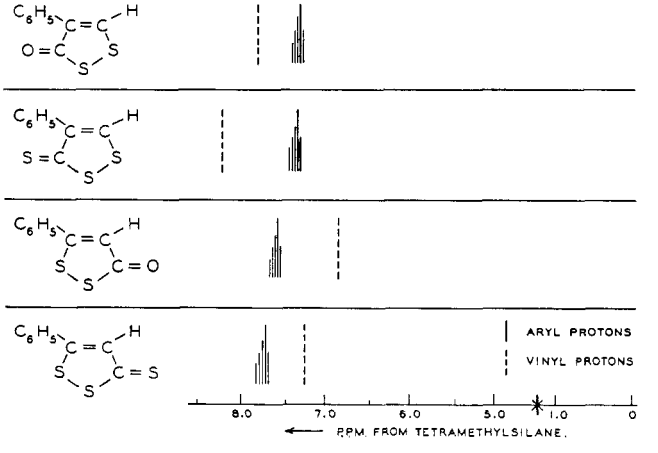


Figure 3.—Chemical shifts for aryl and vinyl protons in some 1,2-dithiol-3-ones and 1,2-dithiole-3-thiones.

phosphorylation studies in mitochondria of rat liver (17). The compound is also reported to stimulate chlororesis and intensify chromatogenic function (58). Sulfonium derivatives have been patented for their therapeutic value in suppressing growth of staphylococci and streptococci and for tuberculostatic properties (8).

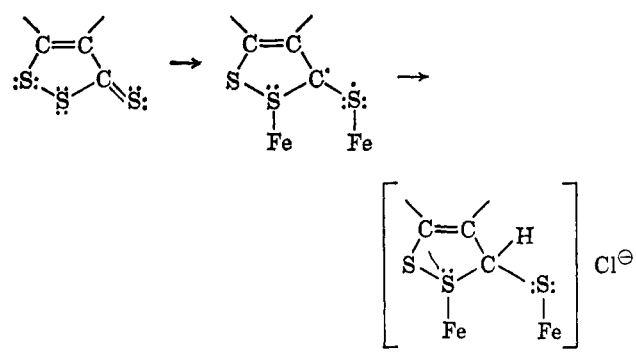
The 1,2-dithiol-3-one ring system had strong choleretic action, increasing cholesterol in the bile, accelerating the excretion of bromsulphalein, and augmenting urea formation (61).

The parent compound, 1,2-dithiole-3-thione, and a 5-polyhydroxyphenyl derivative were isolated from *Brassica oleracea* (mustard family) (28).

VII. USES

Their stability to air oxidation has suggested the use of 1,2-dithiole-3-thiones as antioxidants in fuels (78, 80) and in lubricating oils (1, 25). They have also been used as additives for high pressure lubricants (1) and for cutting oils (81), and as polymerization inhibitors for free-radical reactions.

The reactivity of 1,2-dithiole-3-thiones with metal surfaces and with metal salts has prompted their use in spot testing for Cu^{+}, Ag^{+}, Sn^{+2}, Pd^{+2}, Pt^{+2}, Pt^{+4}, and Hg^{+2} (88). They are protective agents for iron surfaces. Concentrations as low as 0.1 to 0.2 mmole $l.^{-1}$ of solvent provide complete protection against attack of iron by hydrochloric acid (52). This protection has been related to the identity of the S—C=S bond distance to that of Fe-Fe in the structural lattice.



The sulfur–iron bond prevents acids from attacking the metal surface in aqueous systems.

The 1,2-dithiole-3-thiones are also suggested for use in rubber and plastic to filter ultraviolet and blue light (25).

4-Alkyl- and aryl-1,2-dithiole-3-thiones and their sulfonium salts have been patented as agents to speed the rate of development in the silver halide diffusion process of photography (86).

Two 5-chloro-4-aryl-1,2-dithiole-3-thiones are reported to be fungitoxic to a wide variety of pathogens at low concentrations. They show promise in soil and seed treatment applications (13).

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