

THE UNIVERSITY OF MANITOBA

STUDIES IN THE 1,2,4-DITHIAZOLE SYSTEM

presented by

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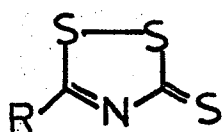
CONTENTS

<u>ACKNOWLEDGEMENT</u>	ii
<u>GENERAL INTRODUCTION</u>	1
Preparation of 1,2,4-Dithiazole-3-Thione	5
Preparation of The 1,2,4-Dithiazolium Cation	10
Reactions of 1,2,4-Dithiazole-3-thione	
(a) Effect of heat	11
(b) Reactions with ammonia and amines	11
(c) Reaction with mercuric acetate	12
(d) 1,3-dipolar cycloaddition	13
Reactions of 1,2,4-Dithiazolium cation	19
<u>OBJECT OF RESEARCH</u>	21
<u>DISCUSSION ON THE SYNTHESSES OF THE 1,2,4-DITHIAZOLE RING</u>	22
<u>DISCUSSION ON REACTIONS</u>	
Reactions of 5-phenyl-3-alkylthio-1,2,4- dithiazolium cation:	
(a) with aniline	32
(b) with N,N-dimethyl aniline and N-methyl aniline	35
(c) with 2-methyl-4,6-diphenyl pyrulium perchlorate	37
(d) with sodium benzoyl acetate	39
(e) with perchloric acid	42
Reactions of 5-phenyl-1,2,4 Dithiazole-3-thione:	
(A) Reactions of the exocyclic thione function:	
(i) Oxidation	43
(ii) Chlorination	44
(B) Alkylation reactions by various compounds	46

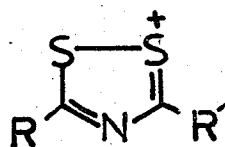
(C) Reactions with activated Dipolarophiles	
(a) Hexafluoro-2-butyne	47
(b) Dibenzoyl acetylene	48
(c) Dicyano acetylene	49
(d) Benzoquinone	49
(e) Dimethyl azodicarboxylate	49
(f) Phenyl isothiocyanate	49
(g) Propargyl bromide	51
1,4-Addition reactions of the Monoadducts	52
Sulfurization reactions of the monoadducts	54
Conversion of the C=S group into C=O group	56
Salt formation with triethyloxonium perchlorate	56
<u>EXPERIMENTAL</u>	58
<u>REFERENCES</u>	87
<u>INFRARED SPECTRA</u>	90

GENERAL INTRODUCTION

The 1,2,4-dithiazole system is a heterocyclic ring consisting of two sulfur, one nitrogen, and two carbon atoms. Two examples of this system were of interest: the 1,2,4-dithiazole-3-thiones (I) and the 1,2,4-dithiazolium cation (II). Some examples of both of these are known and will be dealt with later.

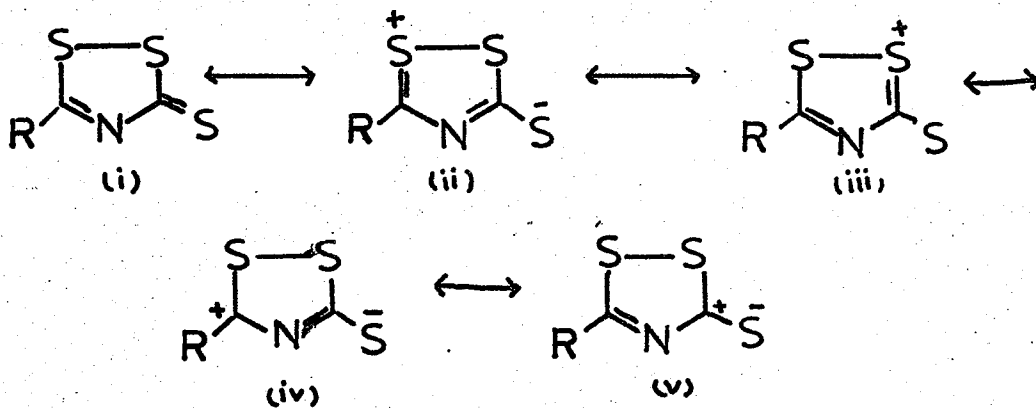


(I)

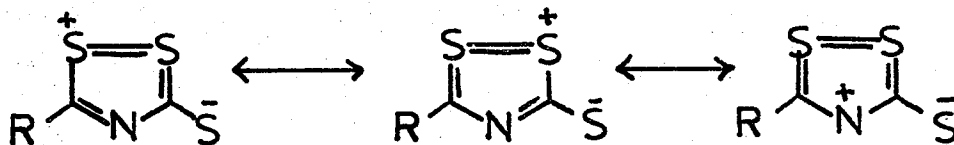


(II)

The thione compound exists as a resonance hybrid of the following contributing structures:



Structures involving sulfur d-orbitals can also be proposed, but they are probably less important.

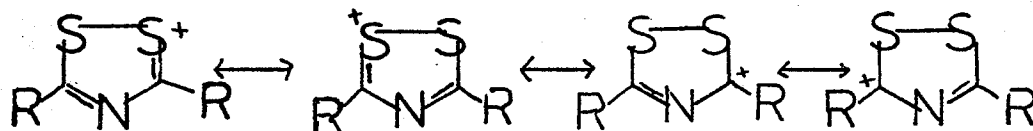


It will be noted that several of these forms indicate that this system will be potentially highly aromatic in character. Also, the exo-

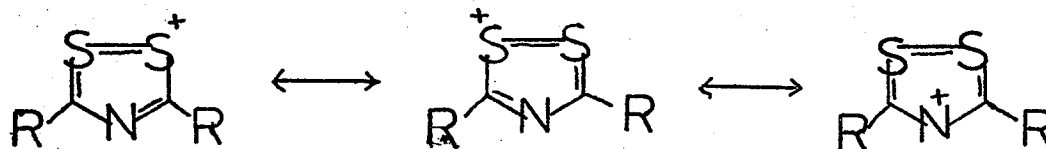
cyclic double bond should have a fairly high polar character, and the sulfur atom may function as a nucleophile in certain reactions.

Calculations of resonance energy of this system have not so far been reported.

The 1,2,4-dithiazolium cation should have four main contributing structures:

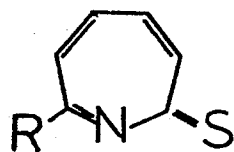


Structures utilizing d-orbitals can also be proposed:

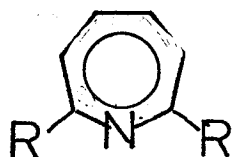


but these are less likely.

In accordance with the Longuet-Higgin theory of isosterism, each sulfur atom in the ring is equivalent to a $-\text{CH}=\text{CH}$ group and therefore the systems (I) and (II) will be isoelectronic with



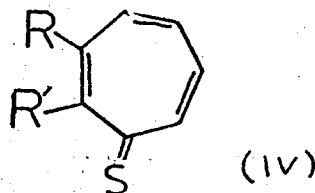
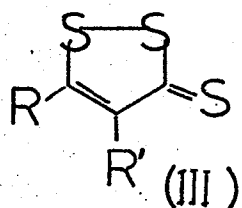
and



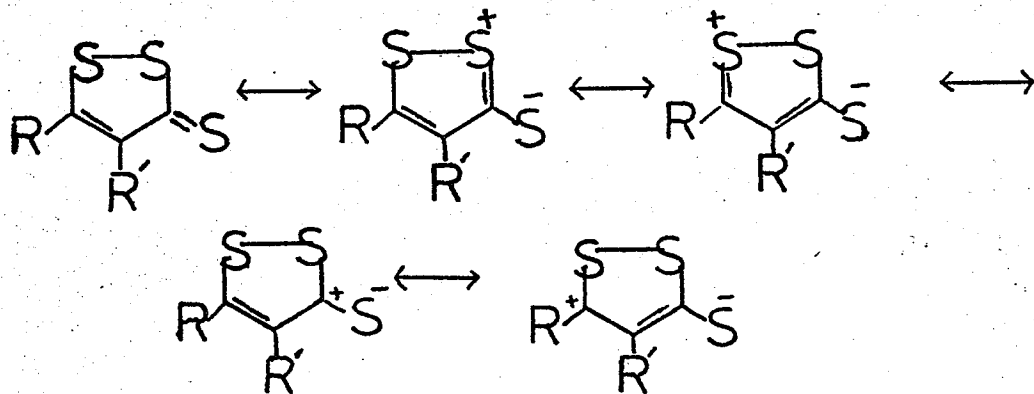
respectively

in the same way that thiophene is isoelectronic with benzene, with

which it has quite a few similar chemical properties. They may also be regarded as 4-aza derivatives of the 1,2-dithiole system (III) which is isoelectronic with the 1,3,5-cyclohepta triene system (IV). This is not confirmed directly, but the suggestion is in conformity with experimental results. It is to be expected therefore, that in many of their reactions these compounds (I & II) will be similar to the corresponding 1,2-dithioles.



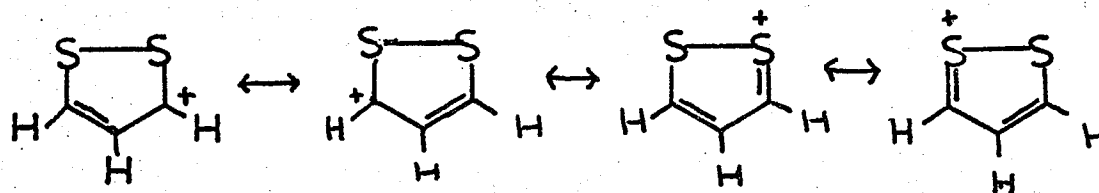
A number of derivatives of the carbon analogue (III) of (I) have long been prepared, and their physical and chemical properties investigated. Kehl and Jeffrey² have made a complete structural analysis of 4-methyl-1,2-dithiole-3-thione (III, R' = CH₃, R = H) determining the bond lengths and the conjugative interactions of the three groups S-S, C=C, and C=S, each of which has pi orbitals perpendicular to the plane of the dithiole ring. The main resonating forms of this compound may be represented as:



This suggests that in the analogous compound (I) pi orbitals of C=S, S-S, and C=N should be perpendicular to the plane of the dithia-

zole ring. On this basis of analogy, it may reasonably be suggested that the first three resonance forms of the 1,2,4-dithiazole thione system (i - iii) contribute most to the structure.

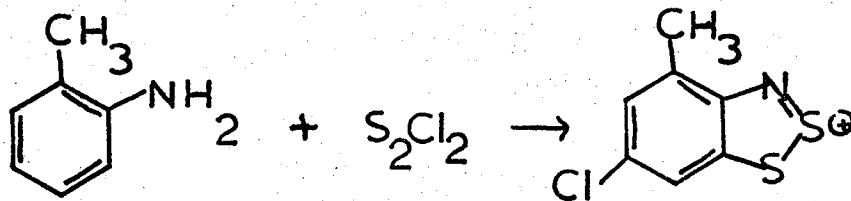
The 1,2-dithiolylium cation, built up with three trigonal carbon atoms and two sulfur atoms has a pronounced aromatic character together with a fair stability. Recently dithiolylium ions without any alkylthio substituents have been described^{3,4,5} which can be represented as the following canonical forms:



The above structure is isosteric with cyclohepta-trienylium ion.

However in the above structures, no canonical form involves positive charge on carbon 4, whereas in the tropylium ion, all the seven atoms of the ring are equivalent.

Only a few derivatives of the 1,2,4-dithiazolium system are known, probably due to lack of suitable preparative methods, rather than instability, since the derivatives of the isomeric isosteric system, the 1,2,3-dithiazolylium cation are known. It is formed in the Herz reaction.

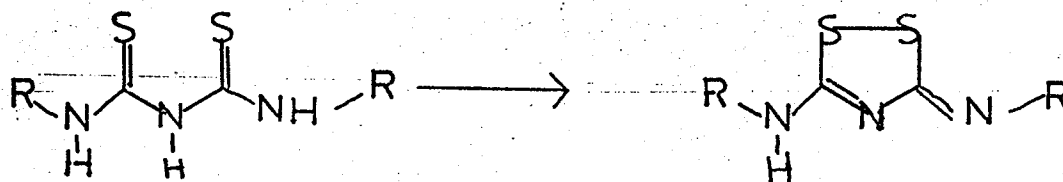


Different aryl amines have been used^{6,7} to obtain several 1,2,3-dithiazolylium cation derivatives.

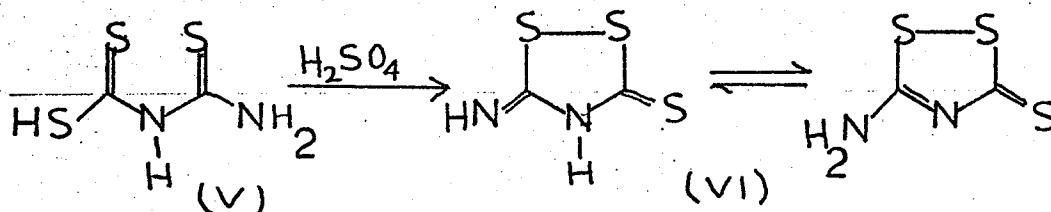
PREPARATION OF 1,2,4-DITHIAZOLE-3-THIONES

Although various derivatives^{9,10} of the system 1,2,4-dithiazole-3-thione have been made during the last two decades, synthesis of the unsubstituted ring itself has not so far been reported.

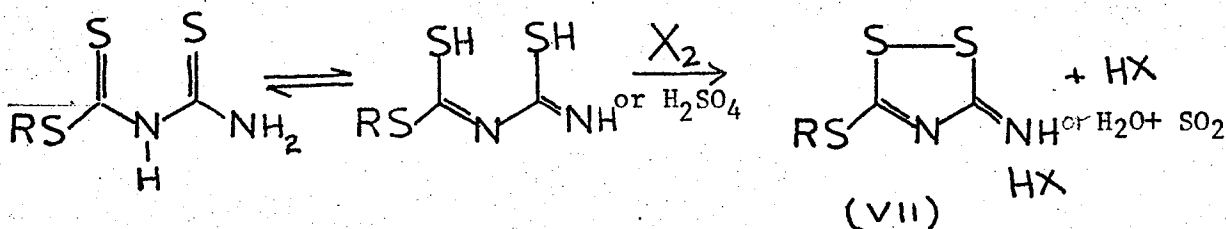
E. Fromm¹¹ reported the synthesis of cyclic disulfides of thiurets by the oxidation of the thiurets with iodine.



Later, Rosenheim et al¹² obtained 5-imino-1,2,4-dithiazolidine-3-thione by treatment of trithioallophanic acid (V) with conc. sulfuric acid:



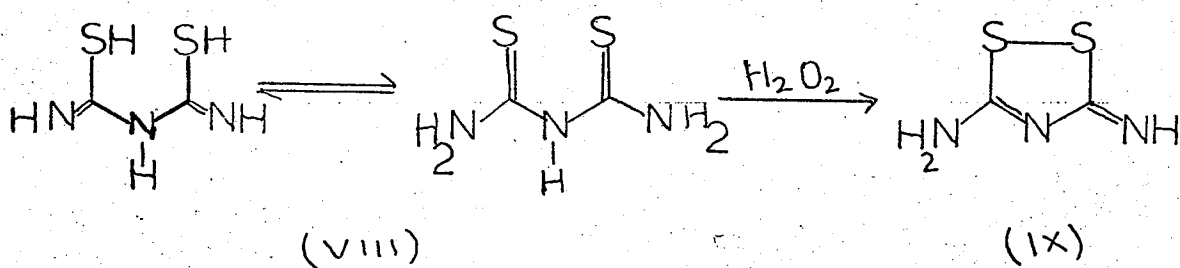
Oxidation of several alkyl esters of trithioallophanic acids with halogens or sulfuric acid gives 3-imino-5-alkylmercapto-1,2,4-dithiazoles¹³ (VII) as their hydrohalides or sulfates.



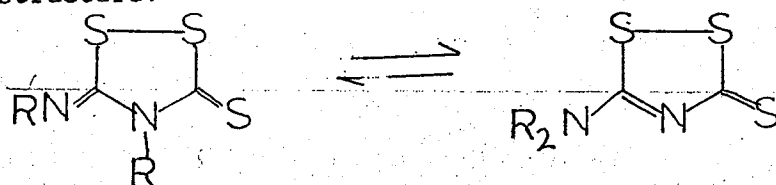
R = CH₃, n-C₃H₇ 1-C₃H₇, n-C₄H₉, OH.CH₂.CH₂, C₂H₅

X = Halogen,

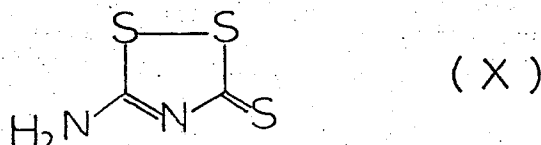
Preisler et al¹⁴ obtained the 3,5-diimino derivative of 1,2,4-dithiazole (IX) as its hydrochloride by suspending the dithiobiuret (VIII) in normal hydrochloric acid and subsequent treatment with hydrogen peroxide. Dithiobiuret may be obtained by the condensation of two moles of thiourea.



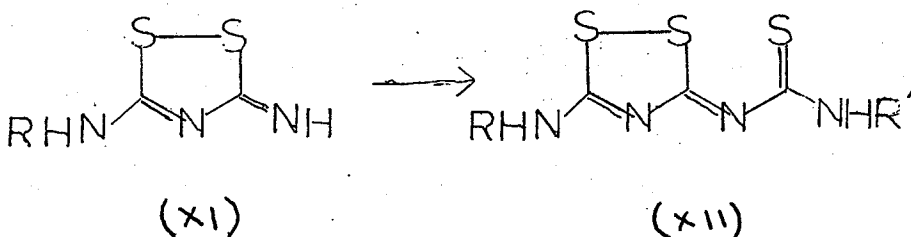
Freund¹⁵ isolated compounds of the type $(RNCS)_2Br_3$, which on digestion with water or alcohol gave compounds of the type $(RNCS)_2S$ having structure:



Hantzsch and Wolfenkamp¹⁶ postulated that isoperthiocyanic acid exists as (X), which was confirmed by crystallographic studies by Emelèus et al¹⁰.

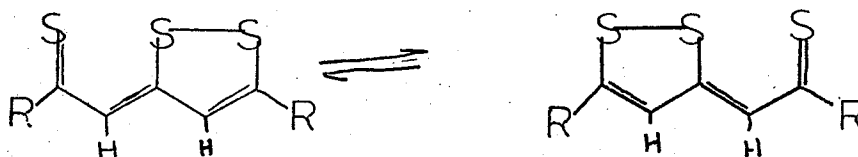


Behringer and Weber¹⁸ reacted N-substituted-5-amino-3-imino-1,2,4-dithiazole (XI) with various isothiocyanates, and obtained the imino derivatives (XII), which may also be considered as 1,2,4-dithiazole derivatives.

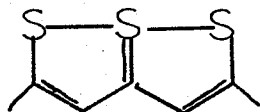


- (a) R = Ph R' = Ph
(b) R = Ph R' = p-methoxy-phenyl
(c) R = p-OMe.C₆H₄ R' = Ph

The compound (XII) is an aza analogue of the "thiothiophene"* system



where the two forms shown may either exist in tautomeric equilibrium¹⁷, or may represent two contributing structures to a resonance hybrid where the sulfur-sulfur bonds exhibit single bond - no-bond resonance⁶². Another possible resonance structure would involve d-orbital participation of the central S atom.

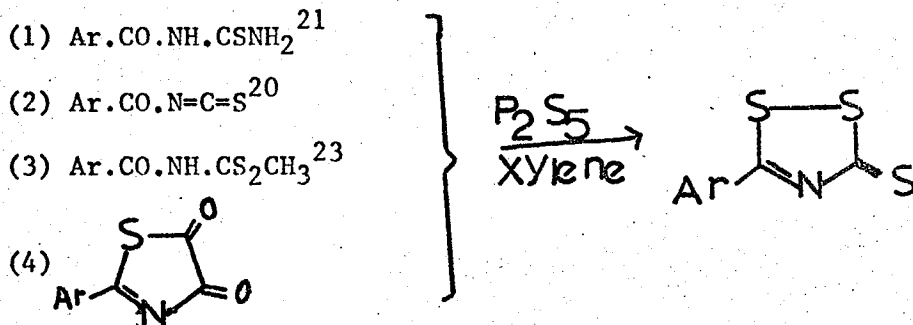


The sulfur-sulfur bonding has been investigated by K. Maeda²⁵ who suggests that it may involve $p_{\sigma} - p_{\delta}$ bonding.

* Some authors call it "thiathiophene", but in this thesis we will use "thiothiophene".

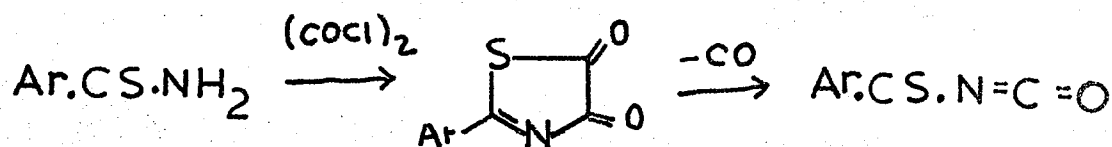
However, syntheses of the system 1,2,4-dithiazole-3-thione, containing carbon atom attached directly to the heterocyclic ring have been reported only recently.^{1,19}

Derocque and Vialle¹⁹ used four procedures to obtain the 5-aryl substituted compounds. In the first procedure, they used N-benzoyl thiourea as the starting material and reacted it with phosphorus pentasulfide, but the yield of 5-phenyl-1,2,4-dithiazole-3-thione was very low. In the second method they used N-arylisothiocyanate prepared by the method of Hoggarth²⁰, and reacted it with phosphorus pentasulfide. In the third procedure, they prepared various N-aryldithiocarbamates from the isothiocyanate, and then sulfurized the compound by refluxing it with phosphorus pentasulfide. In the fourth method, an N-thioaroyl isocyanate was sulfurized.



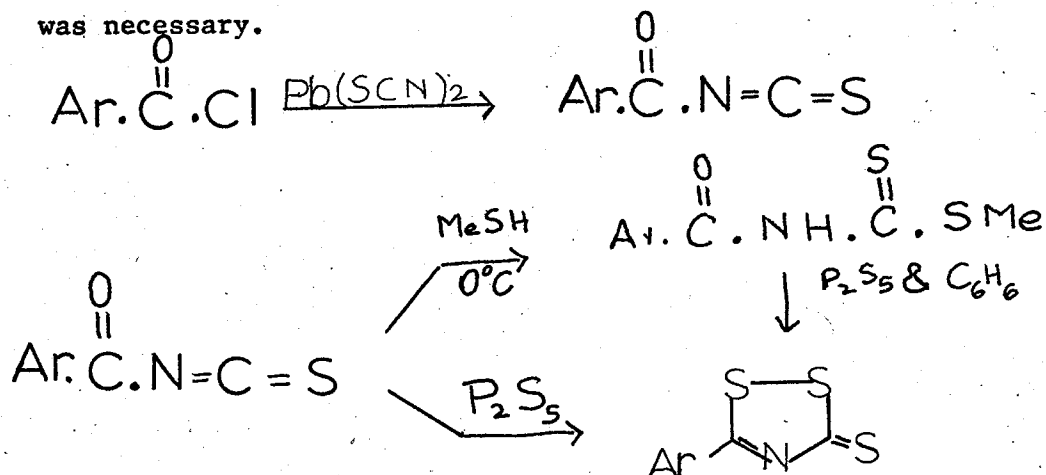
- | | |
|-------------------------|----------------------|
| Ar = (a) Phenyl | (b) 4-bromo-phenyl |
| (c) 2-chloro-phenyl | (d) 4-chloro-phenyl |
| (e) 2,4-dichloro-phenyl | (f) 4 methoxy-phenyl |
| (g) 4 nitro-phenyl | (h) 2-thienyl |

The thioaroylisocyanate was prepared by treatment of an aryl thioamide with oxalylchloride to provide a 5-aryl-thiazoline-4,5-dione, which was pyrolyzed.



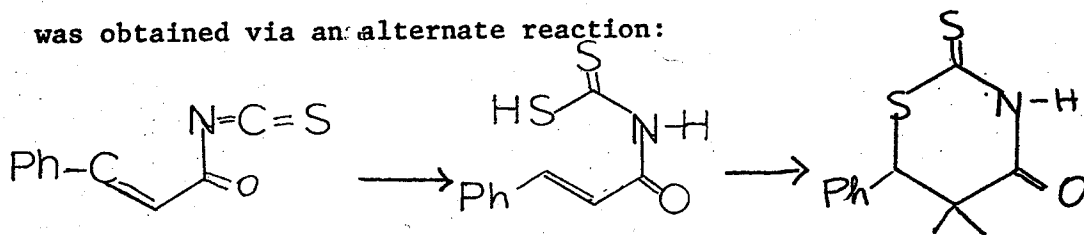
Other solvents besides xylene were used also, e.g. benzene, toluene and pyridine, but the yield was comparatively less.

MacDonald and McKinnon¹ prepared 5-aryl substituted dithiazole-3-thiones by rather similar methods, and also noted that sulfurization of benzoyl thionocarbamates gave 1,2,4-dithiazole-3-thiones but in low yield. They noted that the synthesis failed where the 5-substituent was aliphatic and suggested that a stabilizing aromatic substituent was necessary.



Ar = (a) Ph (b) p-methyl phenyl (c) o-toluyyl, (d) 2,5-dimethyl-phenyl, (e) p-methoxy-phenyl, (f) o-chloro-phenyl, (g) p-chloro-phenyl, (h) 2-furyl, (i) 2-thienyl, (j) 1-naphthyl, (k) 2-naphthyl

When cinnamoyl isothiocyanate was sulfurized, a 1,3-thiazine derivative was obtained via an alternate reaction:



Apart from these papers, which describe synthesis of the heterocyclic system there do not appear to be any reported in which other synthetic methods are used.

PREPARATION OF THE 1,2,4-DITHIAZOLIUM CATION

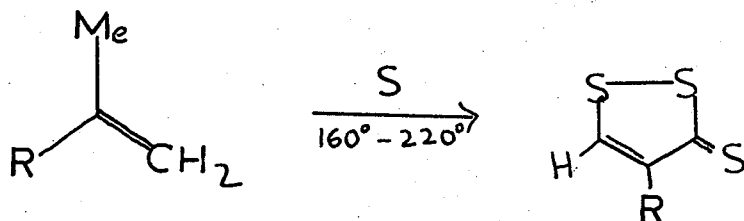
No preparations of this system from acyclic starting materials are reported, and it is hard to envisage syntheses analogous to those used for 1,2-dithiolium salts, e.g. action of hydrogen disulfide on a diacylamide, or oxidation of a dithiodiacylamide, since these precursors are not very well known. Successful methods used start from the corresponding dithiazole-3-thiones and are discussed under the reactions of these.

REACTIONS OF 1,2,4-DITHIAZOLE-3-THIONES:

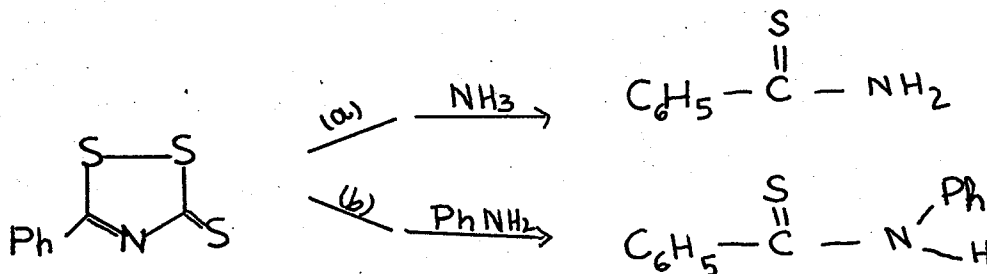
The system appears to be fairly stable, but probably less so than the 1,2-dithioles. Reactions of 1,2,4-dithiazole-3-thione so far reported in literature may be classified as:

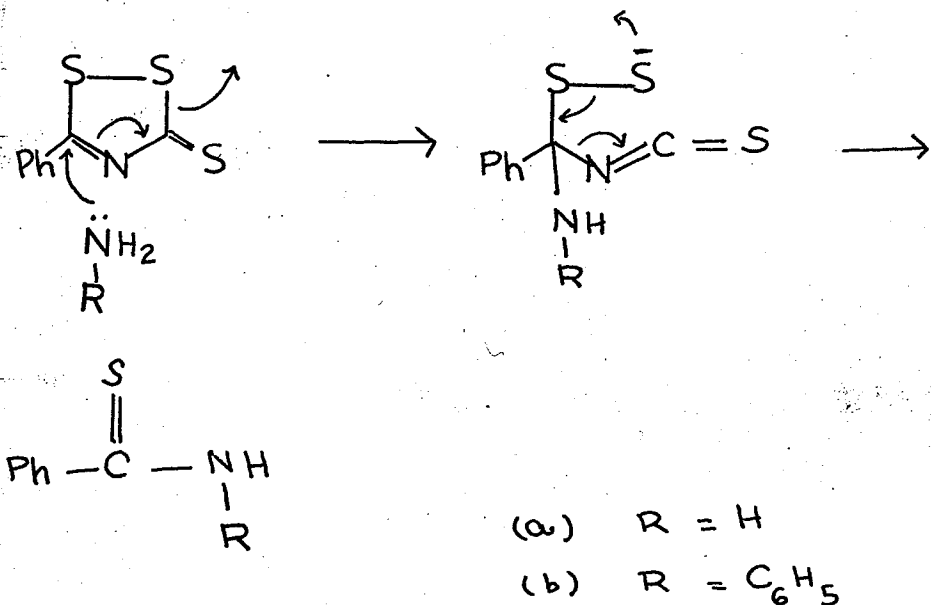
- (a) effect of heat
- (b) reaction with bases, e.g. ammonia and amines,
- (c) reaction with mercuric acetate,
- (d) reaction with acetylenes,
- (e) reaction with alkylating agents.

(a) On heating in a sealed tube. 5-phenyl-1,2,4-dithiazole-3-thione suffers decomposition¹, giving sulfur, carbon disulfide and benzonitrile. This may be contrasted with the dithiole thiones which appear to be fairly stable to heat as may be seen by some of the methods of synthesis⁵³.

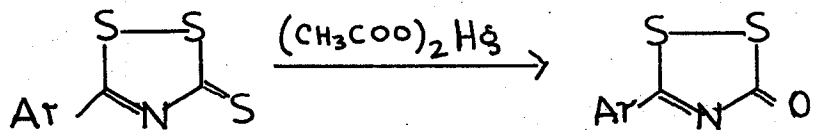


(b) 5-phenyl-1,2,4-dithiazole-3-thione reacts with ammonia and aniline¹ and gives as decomposition products thiobenzamide and N-phenyl thiobenzamide. Presumably they are formed via initial nucleophilic attack at position 5 with ring fission.





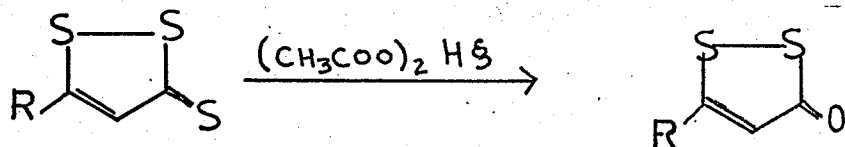
(c) Derocque and Vialle¹⁹ attempted conversion of the exocyclic C=S group of the thione to C=O. 5-aryl-1,2,4-dithiazole-3-thione was treated with mercuric acetate, and the product obtained was the 1,2,4-dithiazole-3-one. The IR spectrum of the compound showed strong absorption bands at 1670 cm^{-1} and 1700 cm^{-1} characteristic of the carbonyl group.



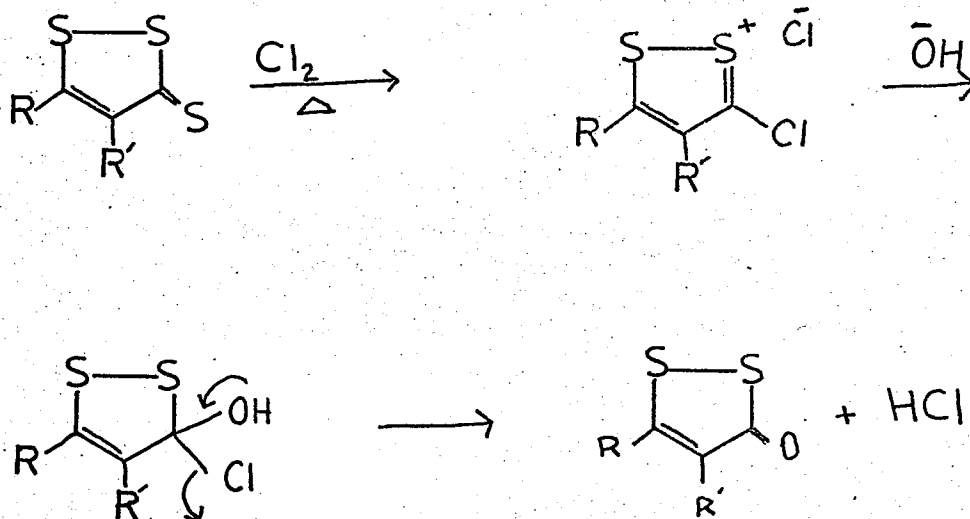
Ar = Phenyl, 4-bromo-phenyl; 2-chloro-phenyl; 4-chlorophenyl
 2,4-dichlorophenyl; 4-methoxyphenyl; 4-nitrophenyl;
 2-thienyl

This reaction is also found in the 1,2-dithiole-3-thiones, the carbon analog of the thiazole thione system, which have been reported⁷¹,

to undergo conversion to C=O group from C=S using mercuric acetate.



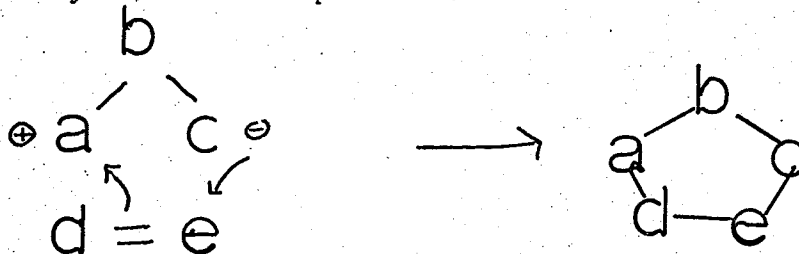
The ketones may also be made from the 1,2-dithiole-3-thiones²⁶ by chlorination followed by hydrolysis:



(d) A very interesting type of reaction which 5-phenyl-1,2,4-dithiazole-3-thione has been reported. This is their 1,3-dipolar cycloaddition reactions with activated acetylenes and benzyne.

1,3 addition reactions of diazoalkanes, azides and ozones have been known for over 50 years, and although they were reviewed²⁷ to a reasonable extent in the past, it is only recently²⁸ that the general concept of 1,3 dipolar cycloadditions has been presented more clearly.

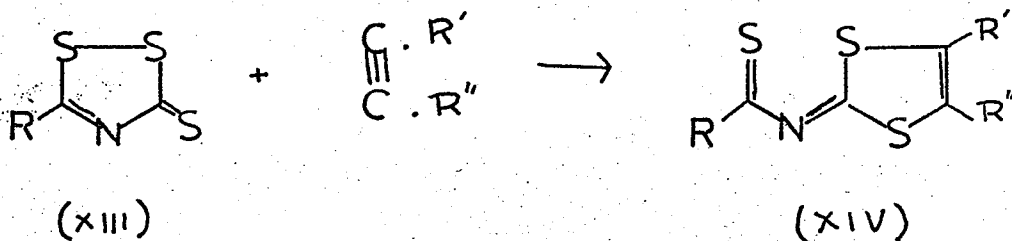
Most frequently in cycloadditions, two reactants unite to form a cyclic compound creating two new sigma bonds at the expense of two pi bonds. In cyclo addition of the type (3+2 = 5), a - b - c is a 1,3 dipole; atom 'a' possessing an electron sextet and 'c' is the negatively charged centre with an unshared pair of electrons. Combination of such a 1,3 dipole with a multiple bond system d = e, called dipolarophile, is referred to as a 1,3 dipolar cycloaddition. The dipolarophile may be any double or triple bond.



A large number of groups acting as dipolarophile, have been reviewed by Huisgen²⁸. Two mechanisms have been suggested for 1,3 dipolar cycloadditions. Huisgen²⁹ suggested that the reaction goes by a concerted rather than stepwise mechanism. According to him, 1,3 dipole is always an ambivalent compound, which displays electrophilic and nucleophilic activity in positions 1 and 3. The mesomerism of the octet and sextet resonance structures of the 1,3 dipole results in charge compensation or charge exchange, respectively, which makes it impossible to identify unequivocally an electrophilic and nucleophilic centre. This eliminates the possibility of the stepwise mechanism. Thus according to him a concerted addition, which can also be described in terms of molecular orbitals and in which the two new sigma bonds are formed simultaneously, offers the best explanation of the experimental

facts. Firestone³⁰ on the other hand suggested a two step mechanism, with a discrete intermediate a spin-paired diradical. Conjugation exerts the promoting effect on the dipolarophilic activity of all multiple bonds, which means that the intermediate, whether dipolar or diradical in nature derives some stabilization through conjugation. Both Huisgen and Firestone have their views substantiated by arguments, and it is not the purpose of this thesis to go into these arguments.

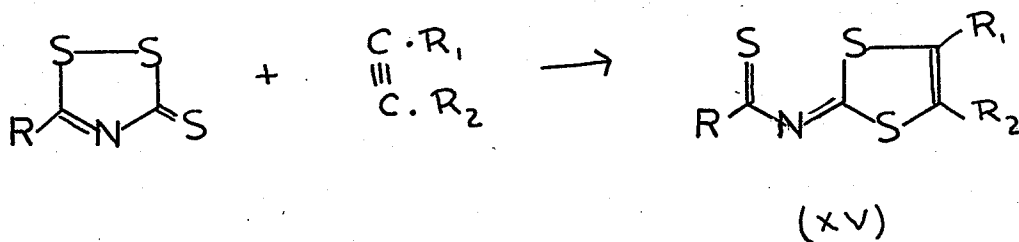
A number of instances have been reported in literature where $C \equiv C$ derivatives act as dipolarophile, and add to the cyclic 1,3 dipole causing ring opening of the initial starting material. Behringer and Deichmann³¹ reported the addition of acetylene derivatives to 5-phenyl-1,2,4-dithiazole 3-thione:



XIV

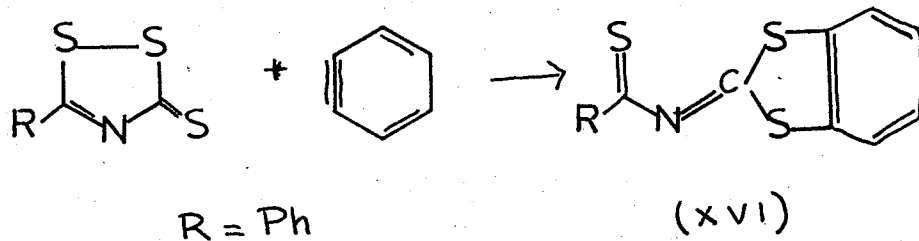
XIII - R=	R=	R' =	R'' =
(a) Ph	(a) Ph	COOCH ₃	COOCH ₃
(b) p-Cl .C ₆ H ₄	(b) Ph	H	COOH
(c) p-CH ₃ .C ₆ H ₄	(c) Ph	H	H++
(d) p-OCH ₃ .C ₆ H ₄	(d) Ph	H	CHO
	(e) Ph	H	Ph
	(f) p-Cl.C ₆ H ₄	COOCH ₃	COOCH ₃
	(g) p-Cl.C ₆ H ₄	H	CHO
	(h) p-CH ₃ .C ₆ H ₄	COOCH ₃	COOCH ₃
	(i) p-CH ₃ .C ₆ H ₄	H	CHO
	(j) p-CH ₃ .O.C ₆ H ₄	COOCH ₃	COOCH ₃
	(k) p-CH ₃ O.C ₆ H ₄	H	CHO

MacDonald and McKinnon¹ have also reported the formation of monoadducts of the type (XV).

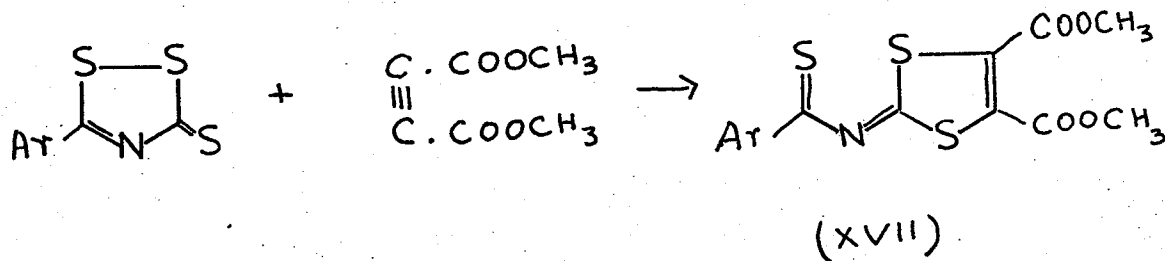


	R	R ₁	R ₂
(a)	Ph	COOEt	H
(b)	Ph	COOEt	Ph
(c)	Ph	COOMe	COOMe
(d)	thienyl	COOEt	H

They also reported the addition of benzyne on the ring in a similar fashion; benzyne acting as a dipolarophile:

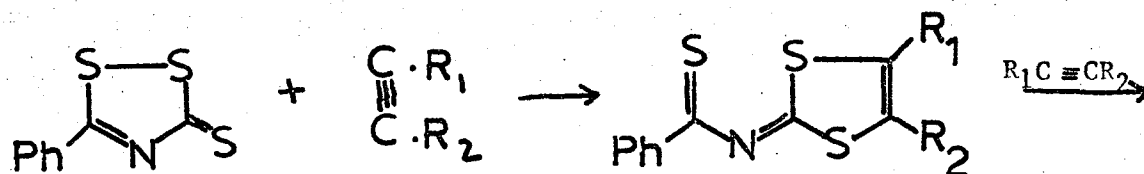


Lang and Vialle³² have also obtained 1,3 monoadduct of the following type:

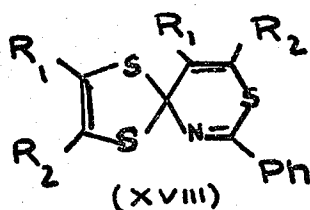


Ar =	(a)	(b)	(c)
	Ph	p-Cl.C ₆ H ₄	p-OCH ₃ .C ₆ H ₄

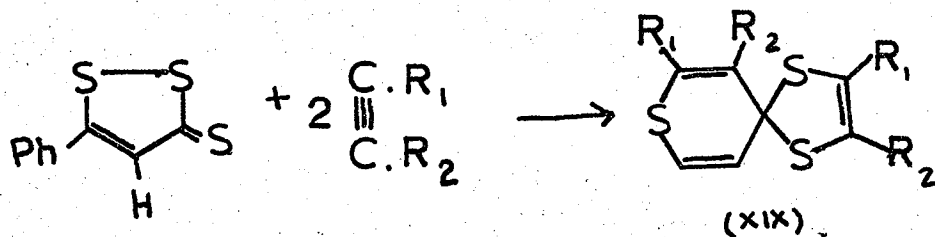
They have also reported the formation of a diadduct with acetylenic compound and 5-phenyl-1,2,4-dithiazole-3-thione:



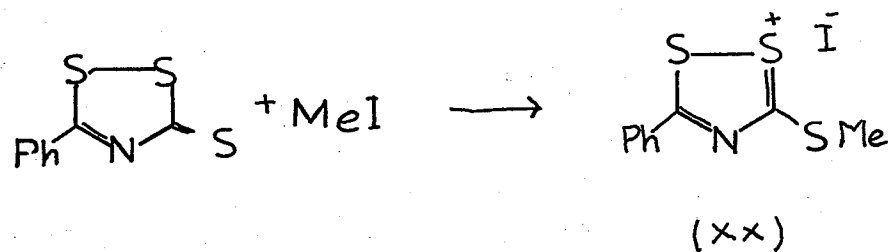
$R_1 = R_2 = \text{COOMe}$
 $\text{Ar} = \text{Ph}$



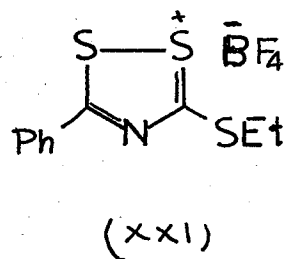
Similar type of addition reactions of activated dipolarophilic acetylenes have been reported for the carbon analogue of the dithiazole substrate.^{33,34,35} They are also reported^{33,34,36} to give a diadduct by the addition of one more acetylene molecule:



(e) Reactions with alkylating agents - Only a few reactions with alkylating reagents have so far been reported. MacDonald and McKinnon¹ obtained the methyl iodide salt of the thione (XIII-a), i.e. 5-phenyl-3-methylthio-1,2,4-dithiazolium iodide (XX), by dissolving the thione in methyl iodide and allowing the mixture to stand for 16 hours.

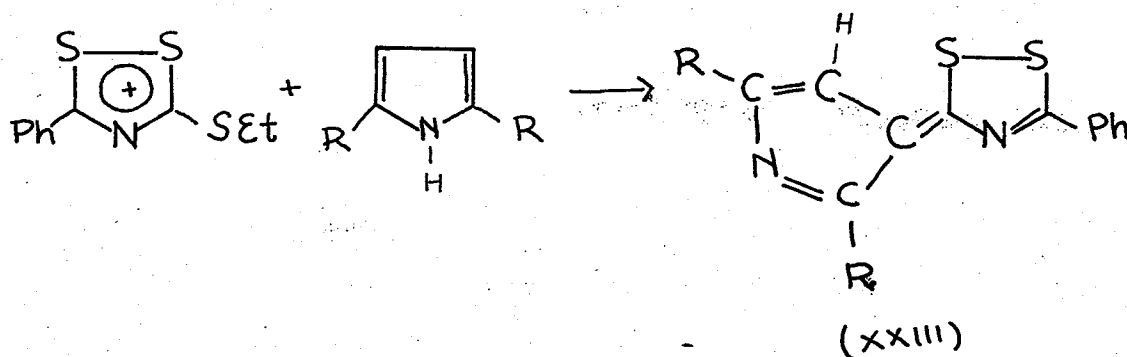
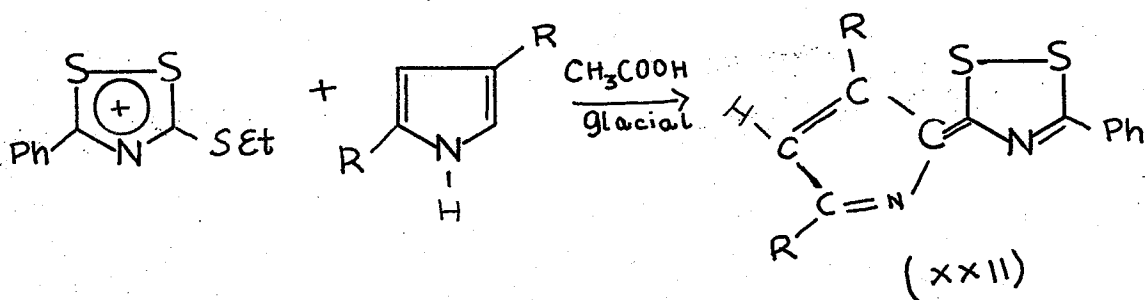


Similarly Gompper and Weiss⁸ prepared 5-phenyl-3-ethylthio-1,2,4-dithiazolium fluoroborate (XXI) by the reaction of triethyl-oxonium fluoroborate with dithiazole thione:



REACTIONS OF 1,2,4-DITHIAZOLIUM CATION

Not much work has been done on the 1,2,4-dithiazolium cation. Gompper and Weiss⁸ have reported the formation of azafulvenes by the action of dimethyl or diphenyl pyrroles with 3-ethylthio-1,2,4-dithiazolium salts (XXI).



These reactions obviously proceed via nucleophilic addition of the pyrroles to the 3 position of the heterocyclic ring, with elimination of ethanethiolate anion.

Analogously, 5-phenyl-3-methylthio-1,2-dithiolium and 4-phenyl-2-methylthio-1,3-dithiolium cations have been made⁸, which also on reaction with dimethyl pyrroles and diphenyl pyrrole in glacial acetic

acid give the corresponding fulvenes:

