THE UNIVERSITY OF MANITOBA

CHEMISTRY DEPARTMENT

STUDIES ON ISOTHIAZOLIUM SALTS AND RELATED COMPOUNDS

by

MOHAMED EZELDIN RASHAD HASSAN

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

WINNIPEG, MANITOBA

1976

"STUDIES ON ISOTHIAZOLIUM SALTS AND RELATED COMPOUNDS"

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ACKNOWLEDGEMENTS

I would like to express my gratitude to Dr. D. M. McKinnon for his patient guidance and advice. Special thanks also go to Drs. C. Wong and A. Queen for their help and stimulating suggestions.

I am also sincerely grateful to the various help and cooperation I received from Dr. S. Loosmore, Dr. E. Thompson, R. Smerchanski, Dr. J. Charlton, Dr. N. Hunter, Dr. H. Thimm, Dr. M. Chauhan, K. Lai, M. Razik, and K. Sadana.

ABSTRACT

A variety of isothiazolium salts has been prepared and allowed to react with sodium benzoylacetate. 2-Benzoylthiophenes were obtained, suggesting that the position of initial nucleophilic attack is at the sulfur atom of the heterocyclic cation. Reaction with hydrogen sulfide gave acyclic reduction products, or 1,2-dithiole derivatives, depending on the type of substituent on nitrogen in the isothiazolium salts. The study also included the reaction with other commonly available nucleophiles such as sodiodiethylmalonate, sulfonium ylids, Wittig reagents, cyclopentadienyl, and indenyl anions, and was found to be of synthetic value for the preparation of various heterocyclic systems especially pseudoazulenes and thienoisothiazolium salts.

Reactions of certain 3-bromothio-1,2-dithiolium bromides with primary amines produced isothiazoline-5-thiones. These compounds were found to form adducts of varying stability with acetylenic reagents. Comparison of their reactivity with the isomeric isothiazoline-3-thiones indicates that while the former react rapidly to form only monoadducts, the latter react more slowly to form monoadducts which react more rapidly to form diadducts. Thioacylmethylenethiazoles have been prepared and were found to form mono and/or diadducts with dimethyl acetylenedicarboxylate depending on the polarity of the solvent.

Thioacylmethyleneisothiazoles have been also prepared and their NMR spectra studied in comparison with those of 1,6,6a S^{IV} trithiapentalenes,

and evidence was found to favour the hypothesis that invokes the use of sulfur d-orbitals in the bonding of the central sulfur atom in the last system to explain its symmetry in solution.

INTRODUCTION

GENERAL INTRODUCTION

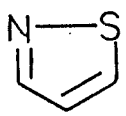
This thesis concerns the syntheses and reactions of a number of compounds containing the isothiazole nucleus, namely the isothiazolium salts, and the isothiazoline-3-, and -5-thiones.

Such compounds would be useful substrates for the investigation of various reactions, such as nucleophilic attack, and 1,3-dipolar cycloadditions. Moreover they may serve as a synthetic route to various other interesting heterocyclic systems, especially the 3-thioacylmethyleneisothiazoles which are aza-analogues of the 1,6,6aS^{IV}-trithiapentalenes.

ISOTHIAZOLES

I. DESCRIPTION OF THE MOLECULE

Isothiazole 1 , is an unsaturated five-membered heterocyclic molecule containing two adjacent heteroatoms, namely sulfur and nitrogen. The sulfur atom contributes a free pair of electrons to the mesomeric bond system.



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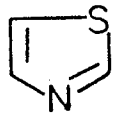

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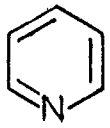

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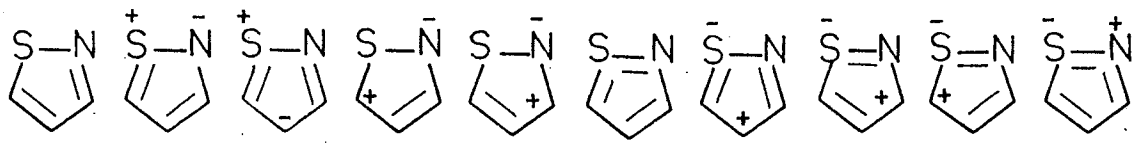
Both the isothiazole 1 , and the isomeric system, the thiazole 2 , have a physical and chemical similarity to pyridine 3 , from which they can be formally derived by replacement of the 2 - 3 , or 4 - 5 carbon to carbon double bonds by a formally bivalent sulfur atom -S-[1]. However, taking into account the participation of sulfur d-orbitals, the replacement of =S= group for a =CH-CH= group is also possible. Like pyridine, these systems may also be represented by delocalized structures.

The following contributing structures [1_i - 1_x] may be drawn for the isothiazole molecule. Structures [1_{vi}- 1_x] utilize the sulfur 3d-orbitals.



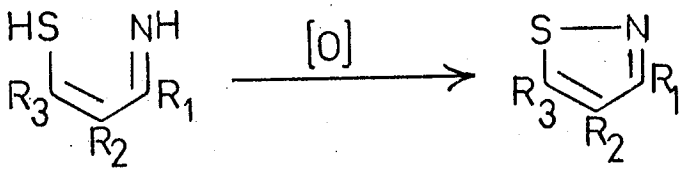
1i 1ii 1iii 1iv 1v 1vi 1vii 1viii 1ix 1x

II. SYNTHESES OF ISOTHIAZOLES

Since the first preparation of the systems by Adams and Slack[2], numerous routes have been devised for the syntheses of isothiazoles. These have been a subject of a recent review by Wooldridge[3]. Two of these methods are closely related to the preparation of isothiazolium salts and therefore will be discussed briefly in the following:

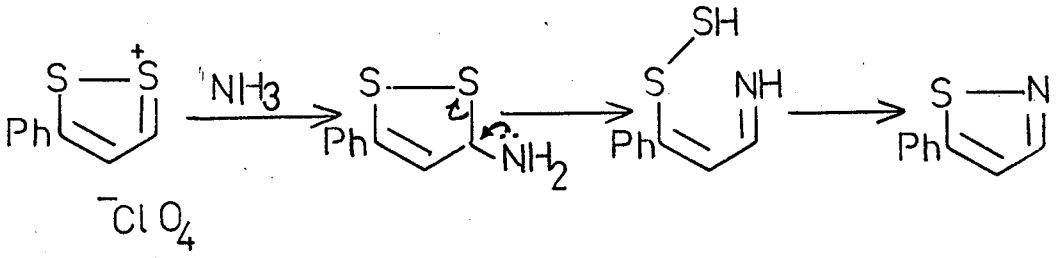
1. Syntheses involving an oxidative N-S bond formation :

In this approach the isothiazoles are obtained by the oxidation of acyclic intermediates formed in an addition or condensation reaction.



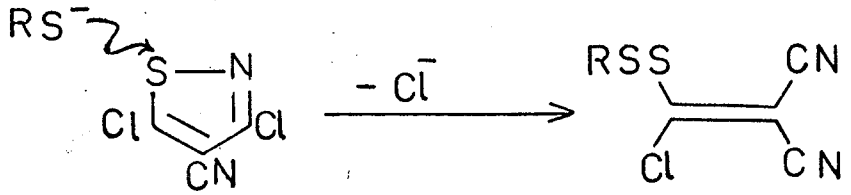
Numerous routes have been devised to these precursors including the addition of hydrogen sulfide to β-iminopropionitriles[4], the addition of isocyanates to primary and secondary enamines[5-7], the thionation of β-iminoketones[8], and the reduction of isoxazole by Raney Nickel, followed by thionation[9]. Various oxidizing agents have also been used including hydrogen peroxide, chloramine, halogens, persulfate, or elemental sulfur.

2. Syntheses from dithiolium salts: Leaver et al.[10-12] obtained the isothiazoles by treatment of 1,2-dithiolium salts with ammonia.

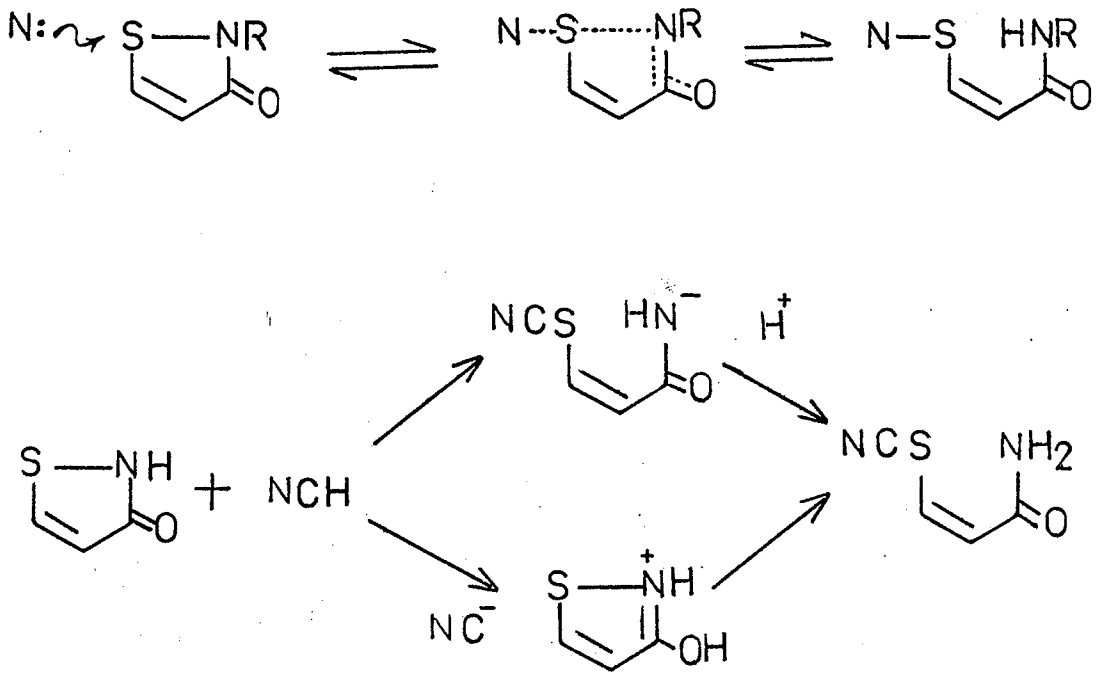


III. THE CHEMICAL PROPERTIES OF ISOTHIAZOLES

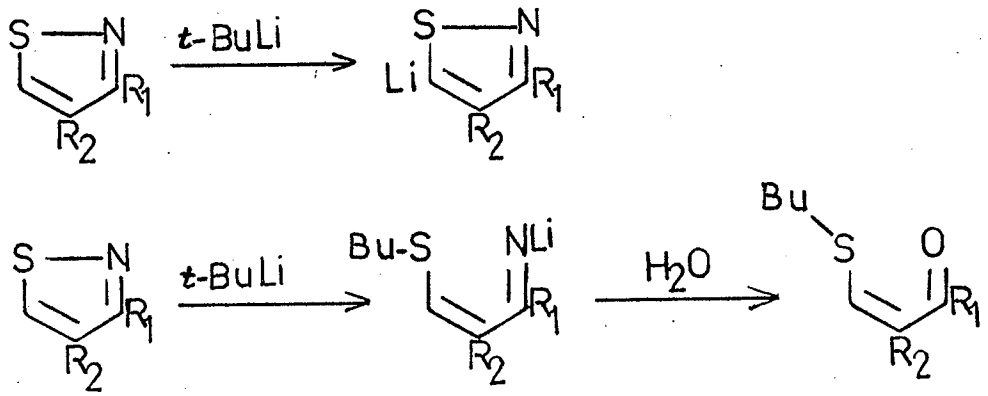
The chemistry of isothiazoles have been discussed in detail in the review by Wooldridge[3] mentioned earlier. Although the ring nitrogen is only weakly basic (pKa = -0.51 ± 0.04 at 25°C)[3], it can be induced to form quaternary derivatives[16]. This observation is of special interest for the preparation of isothiazolium salts. Electrophilic attack is reported to take place at the 3-position[13]. Nucleophilic attack was found to take place at the ring sulfur atom[14].



Crow et al.[15] found that while the nucleophilic attack upon the S-N bond of 3-hydroxyisothiazole has a reversible character, previous protonation of the substrate results in a thousand-fold increase in the rate constant. This was explained by the weakening of S-N bond in the isothiazolium cation.



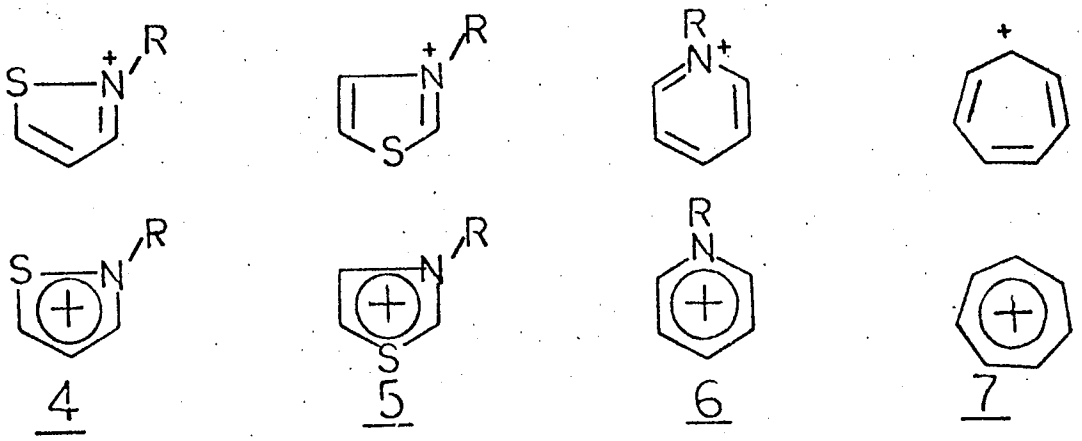
Hydrogen exchange is reported to take place at 5-position very rapidly under basic conditions, and therefore treatment of isothiazoles with butyllithium affords the 5-lithio derivatives[17]. However nucleophilic attack on the ring sulfur also takes place leading to ring cleavage[3].



ISOTHIAZOLIUM SALTS

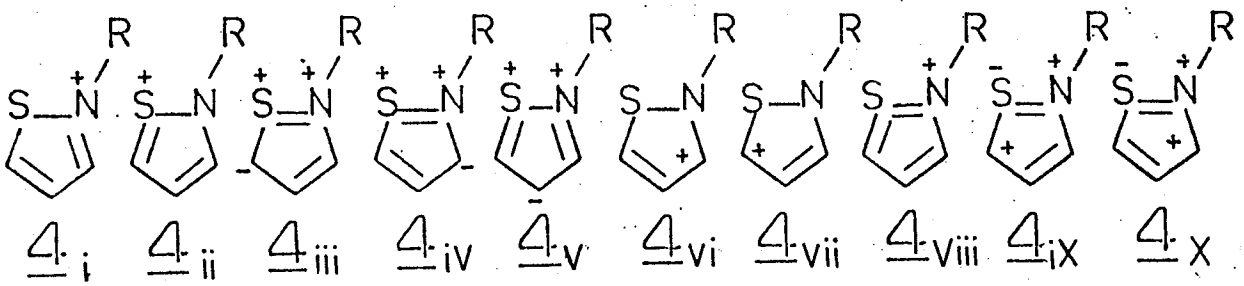
I. DESCRIPTION OF THE MOLECULE

The isothiazolium cation 4 , is the quaternization product of the isothiazole's ring nitrogen. It is isoelectronic with the thiazolium 5 , and pyridinium 6 , as well as tropylium 7 cations.



4 5 6 7

The resonance structures of isothiazolium system may be represented by the following contributing structures [4i - 4x] , in which the structures [4viii- 4x] utilize sulfur d-orbitals. Structures [4iii- 4v] with two adjacent positive centers are of negligible importance.



4i 4ii 4iii 4iv 4v 4vi 4vii 4viii 4ix 4x

According to the inductive, coulombic or LCAO molecular orbital considerations, most of the positive charge should be on the nitrogen. However deprotonation studies[19] have shown proton loss to occur at position 3 and 5 , with higher exchange rates for the 5-position,

which suggests that another factor such as sulfur d-orbital overlap would stabilize the deprotonated species. This stabilization would be greater when the carbanion center is adjacent to the sulfur atom.

Nuclear magnetic resonance studies on isothiazolium hydrogen sulfate also suggest a lower electron density at the 5-position than at the 3-position[18]. (τ for H_5 = 0.4 , τ for H_3 = 0.9 , and τ for H_4 = 2.1) .

Structural investigations of 1,2-dithiolium salts[20] have shown that the sulfur-sulfur bond in the 1,2-dithiolium cation 8 is shortened through π bonding. The sulfur-sulfur bond in 8 is 2.00 A , as compared with the sulfur-sulfur single bond length of 2.10 A in a cis planar disulfide group. By analogy, the sulfur-nitrogen bond in an isothiazolium cation 4 is expected[21] to be 1.65 A in comparison with a nitrogen-sulfur single bond of 1.75 A [22].

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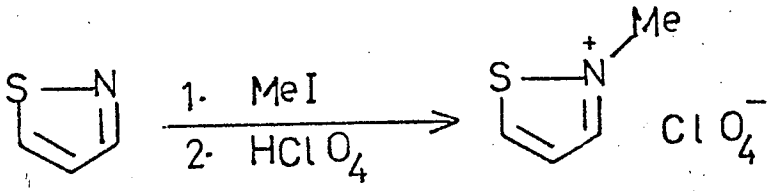
II. SYNTHESIS OF ISOTHIAZOLIUM SALTS

The several methods available for the preparation of this system could be classified under four general approaches.

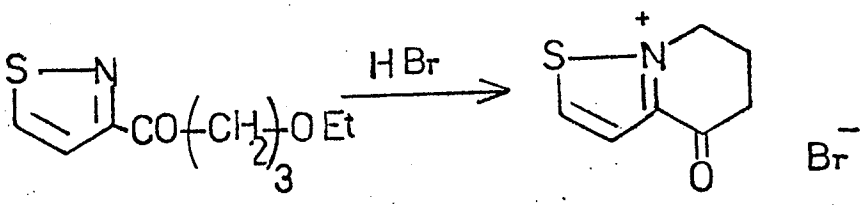
1. The Alkylation of Isothiazoles:

Isothiazoles were found[16] to undergo alkylation to isothiazolium iodides when kept for prolonged periods with simple alkyl iodides. Heating led to gross decomposition, while the presence of solvent would slow the reaction. Other reagents were also successfully used including

benzyl halides[16], triethyloxonium fluoroborate[23], dimethyl sulfate[24] and methyl tosylate[16],[25].



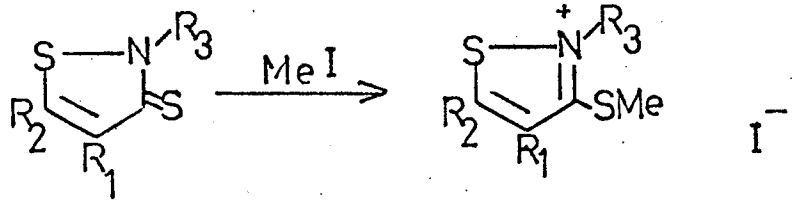
Intramolecular quaternization of isothiazoles afforded a bicyclic system[28].



This approach, however, presupposes the availability of a suitable alkylating agent and the required isothiazole, and has the obvious disadvantage of being inapplicable to the synthesis of N-aryl isothiazolium salts.

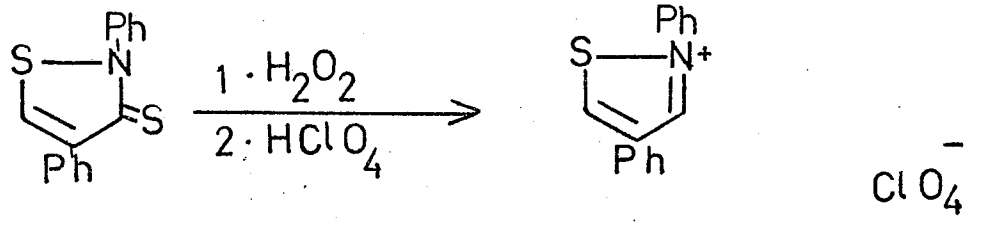
2. The Alkylation of Isothiazolinethiones:

Both 3- and 5-thiones have been alkylated by alkyl halides to give the corresponding alkylthioisothiazolium salts[25-27]. The approach is restricted, however, to the preparation of isothiazolium salts carrying an alkylthio substituent on the 3- or 5-position.



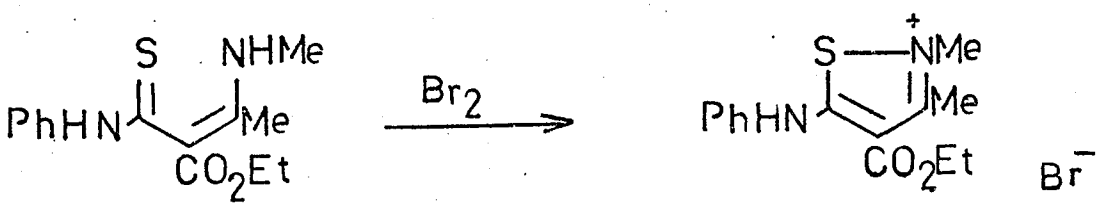
3. Oxidation of Isothiazolinethiones:

Bachers and co-workers[29] obtained 2,4-diphenylisothiazolium perchlorate by the oxidation of the corresponding 2,4-diphenyl-3-thione with hydrogen peroxide in acetic acid. The method was extended later by Loosmore[30] to other thiones.

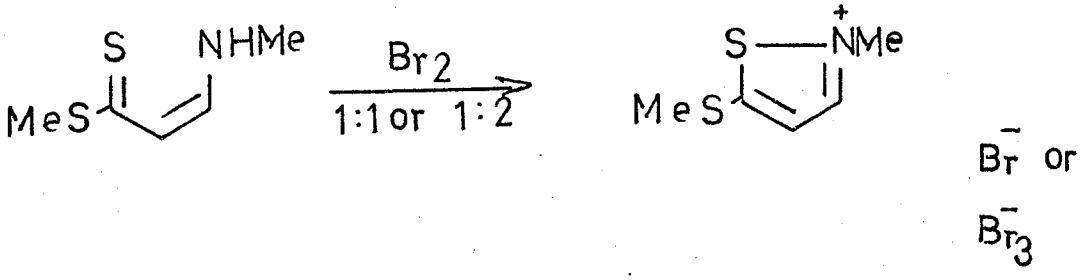


4. Oxidative Formation of the N-S Bond:

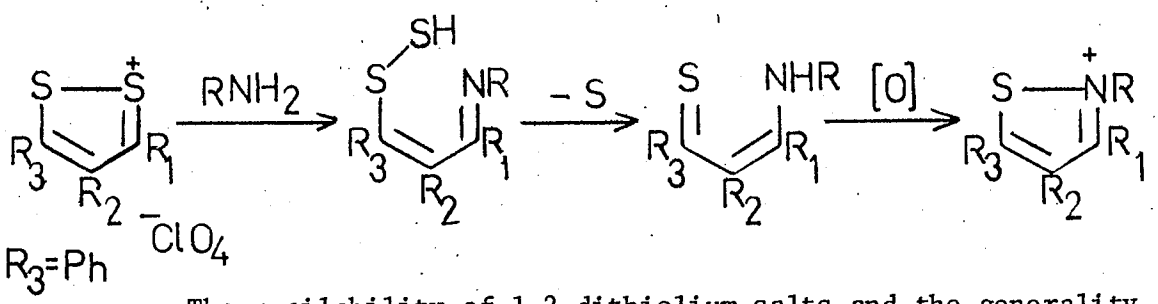
Goerdeler et al.[31], prepared the first isothiazolium cation by dehydrogenation of 3-methylamino-N-phenylbut-2-ene-thioamide derivative with bromine.



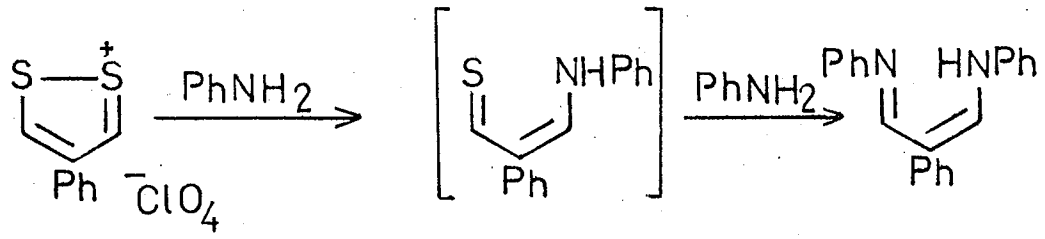
Following the same approach, Faust[32] synthesized the 2-methyl-5-methylthioisothiazolium bromide and the corresponding tribromide.



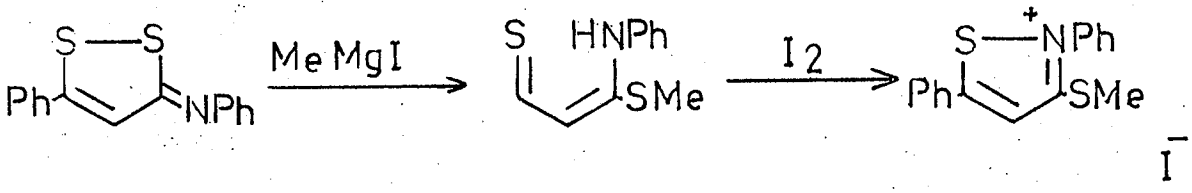
By treating 1,2-dithiolium salts with primary amines, McKinnon and Robak[24] obtained 1-aminopropene-3-thiones. By oxidation with iodine, a variety of isothiazolium triiodides were obtained which were converted into the corresponding perchlorate on treatment with perchloric acid in acetic acid or nitromethane.



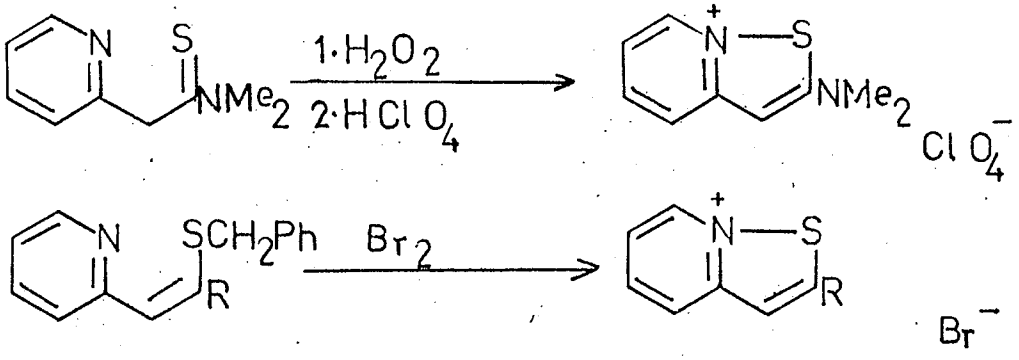
The availability of 1,2-dithiolium salts and the generality of the reaction make this approach a convenient one for the preparation of N-aryl isothiazolium salts. However if R_3 = H , the reactivity of the intermediate thial precludes the synthesis of 5-unsubstituted isothiazolium salts by this method, and phenylmalondialdehydedianils are obtained instead[33].



N-aryl-3-alkylthio (or phenylthio) were also obtained[34] by the iodine oxidation of the 3-alkylthio or (arylthio)-1-arylamino-2-propen-1-thione, which were obtained from the reaction of Grignard reagents with N-(5-aryl-3-H-1,2-dithiole-3-ylidine)arylamines.



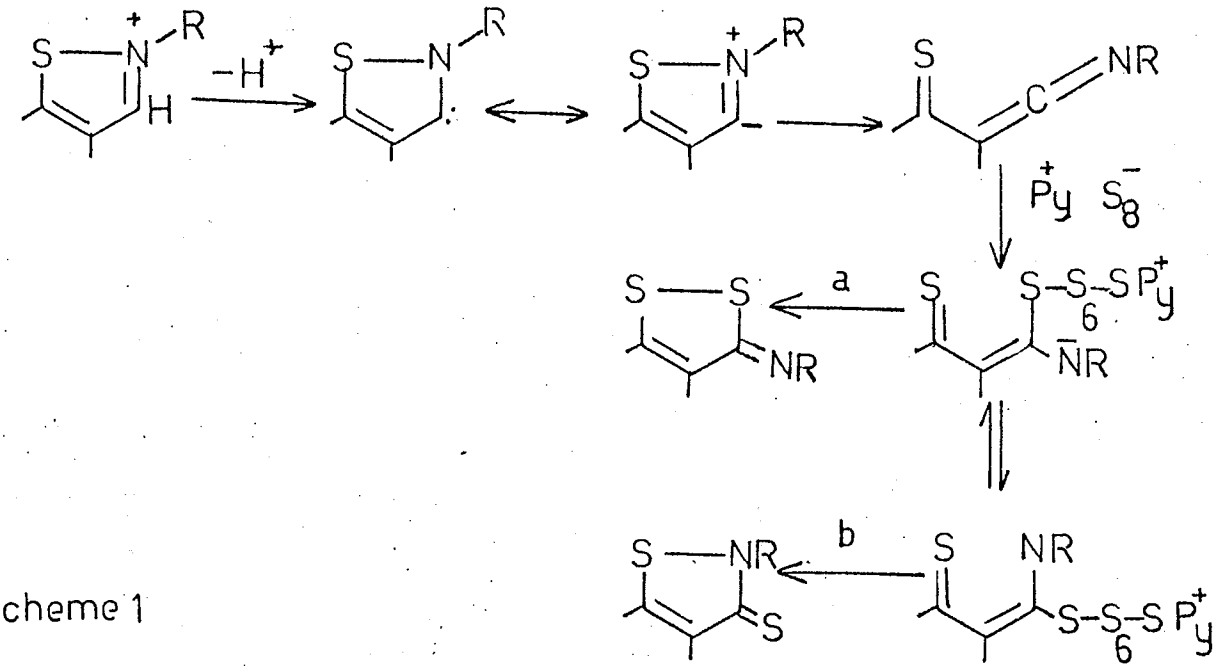
Oxidation of 2-pyridylthioacetamide or 2-(2-benzylthiovinyl) pyridines afforded isothiazolo [2,3-a] pyridinium salts[35], which could be regarded as an isothiazolium cation fused with a pyridine ring.



III. REACTIONS OF ISOTHIAZOLIUM SALTS

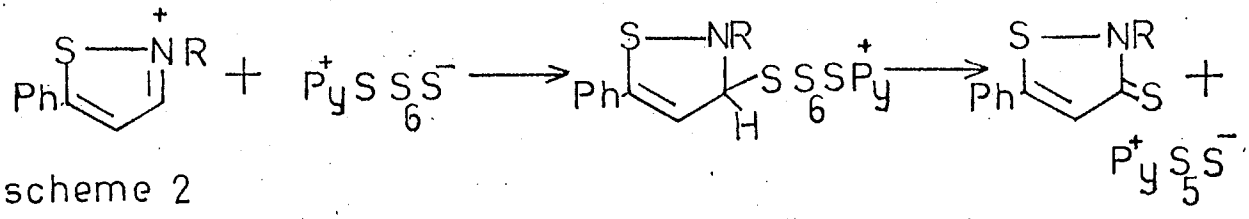
The deprotonation studies mentioned earlier[19] showed that the proton on the 5-position is lost at higher rate than the proton on the 3-position.

Similarly to a reaction of 1,2-dithiolium with sulfur in pyridine[36], McKinnon and Robak[24] found that certain isothiazolium salts reacted also under the same conditions to give isothiazoline-3-thiones. In a more detailed investigation, Bachers and co-workers[29] found that while 5-unsubstituted isothiazolium salts give the corresponding isothiazoline-5-thiones, the 3-unsubstituted salts give either the corresponding isothiazoline-3-thione if the nitrogen is alkyl substituted, or 1,2-dithiole-3-imines if the nitrogen is aryl substituted. The mechanism shown in [scheme 1] was suggested to explain the formation of the different products, with [path 1a] being favored when the substituent on nitrogen is aryl, and [path 1b] being favored when the substituent is alkyl. Inductive effects appear to be important.



scheme 1

Alternatively the reaction could involve direct nucleophilic attack by the activated polysulfide anion [scheme 2][33].

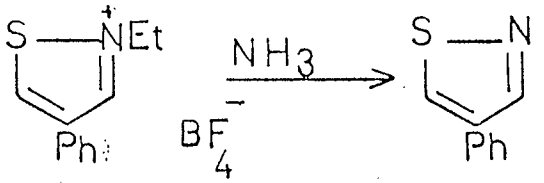


scheme 2

However, an isothiazolium salt with both 3 and 5 positions unsubstituted gave only a product derived from attack at the 5 position. This was taken by the authors as evidence for deprotonation as the first stage in the reaction. Nucleophilic attack on a carbon atom would be favored at the 3-position by inductive and coulombic consideration[29].

Landesberg and Olofson[23] examined the nucleophilic attack of ammonia on isothiazolium salts. They suggested that the reaction takes

place at the 3-position, causing ring cleavage followed by ring closure to form isothiazoles.



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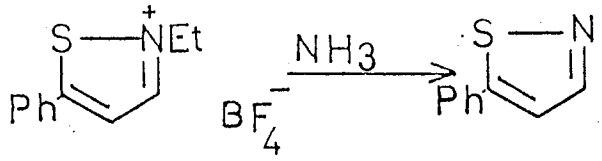

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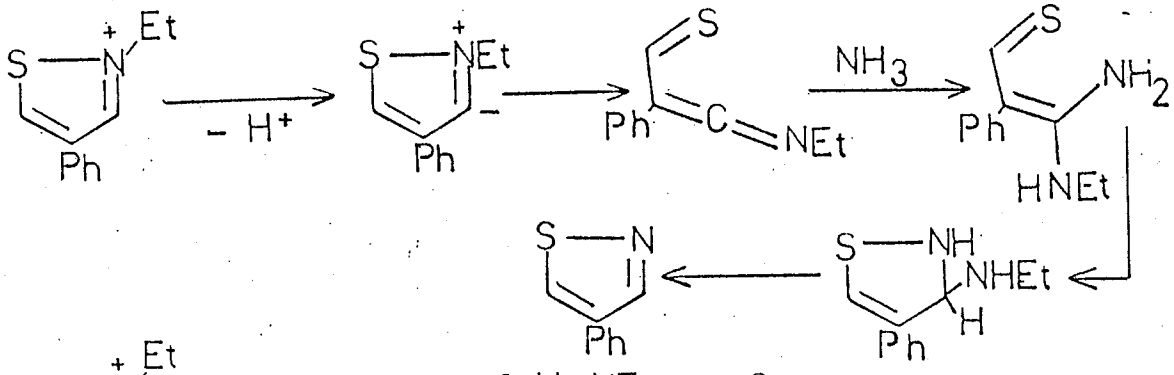
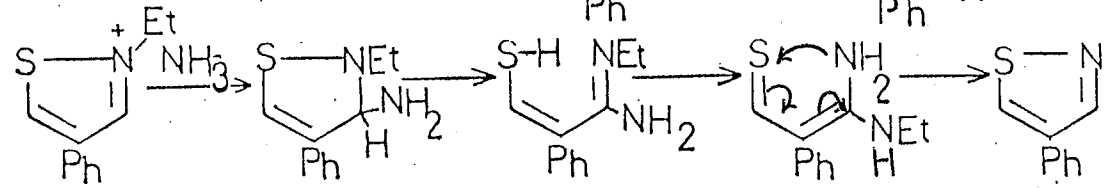
Of the four plausible mechanisms for the reaction [scheme 3], "a" and "b" have been excluded on the basis that the 3-phenylisothiazolium salt, though it does not have the proton in the 3-position required by these mechanisms, still reacts to yield 3-phenylisothiazole. Path "d" is less favorable than path "c" since 5-phenylisothiazole 10 is formed in higher yield than the 4-phenyl 9. The 4-phenylisothiazolium cation should be less sterically hindered in the displacement mechanism "d".

a:



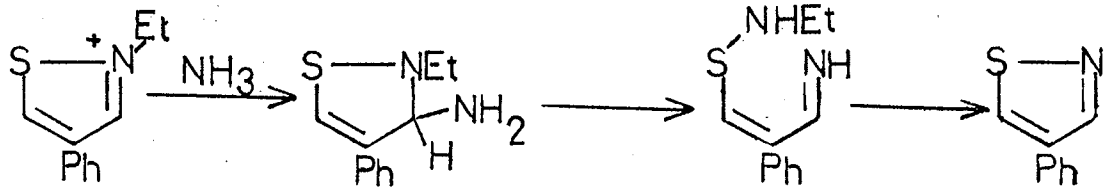
b:



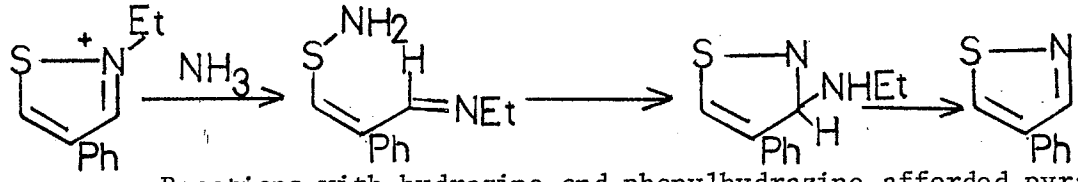
scheme 3

scheme 3 cont.

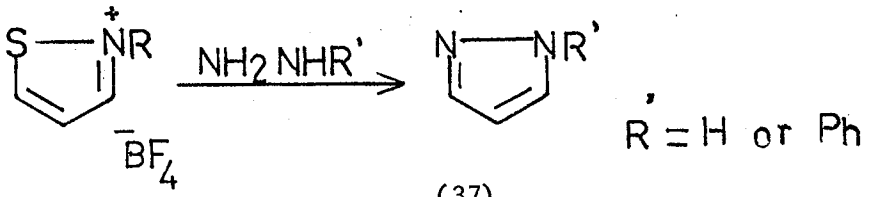
c:



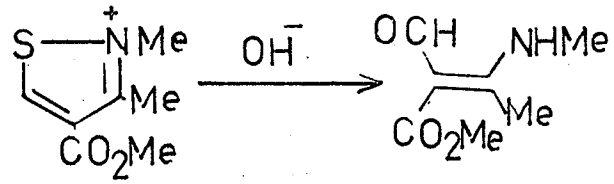
d:



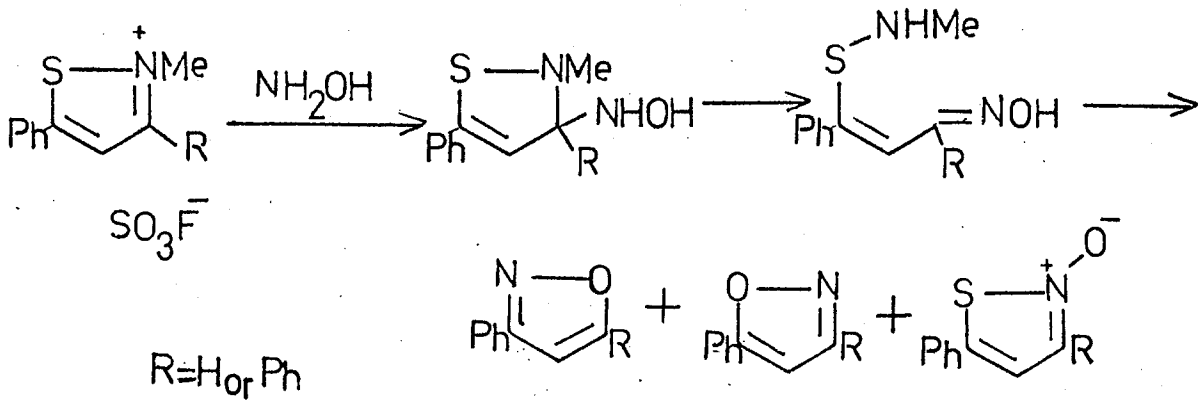
Reactions with hydrazine and phenylhydrazine afforded pyrazoles and phenylpyrazoles respectively[23],[38].



Hydroxyl ions are reported[37] to attack the quarternary isothiazoles on the carbon atom 5 , leading to the formation of an enaminoaldehyde.



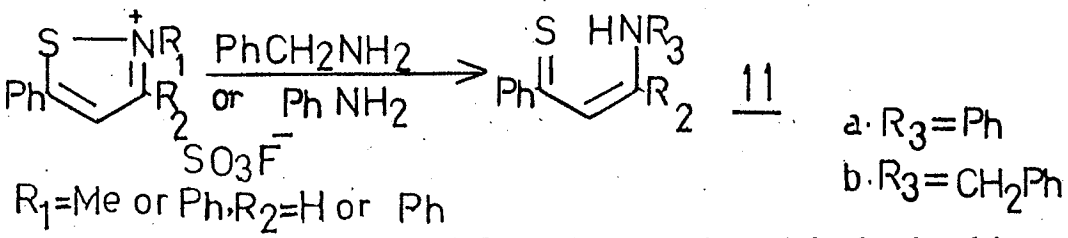
Recently, Sykes and Ullah[38] studied the nucleophilic reactions of hydroxylamine with 5-phenyl or 3,5-diphenyl substituted isothiazolium cations which afforded isoxazole and isothiazole N-oxide. The reaction seems to proceed by initial attack of nitrogen nucleophiles on the 3-position of isothiazolium cations, followed by ring opening. (mechanism "C" of Landesberg and Olofson).



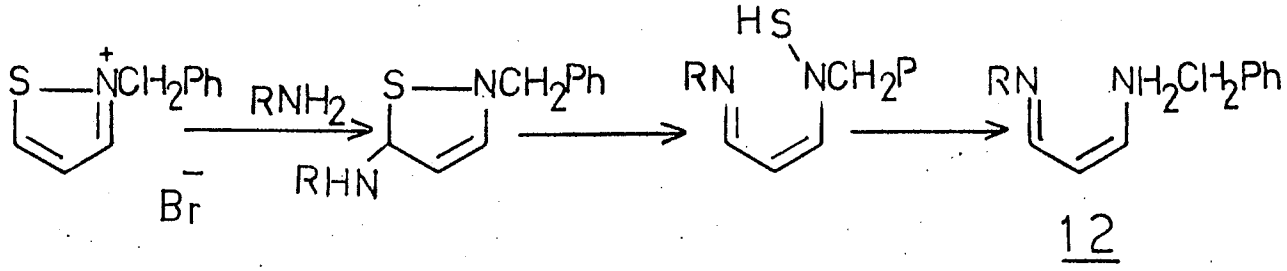
The formation of both 3-, and 5-phenylisoxazole (1:4 mixture) from the reaction of hydroxylamine with 5-phenylisothiazolium salt indicates that the nucleophilic attack on isothiazolium salts does take place on carbon 5 as well as on carbon 3.

Unsubstituted salts under the same conditions, yielded neither isoxazole nor isothiazole N-oxide probably owing to the instability of both potential products under the basic conditions of the reaction.

5-substituted isothiazolium cations react with aniline and benzylamine to yield the corresponding ring opened anilinothiones 11a. , and benzylaminothiones 11b. respectively. Similar results were found for the disubstituted salts with benzylamine but no reaction was observed with aniline.

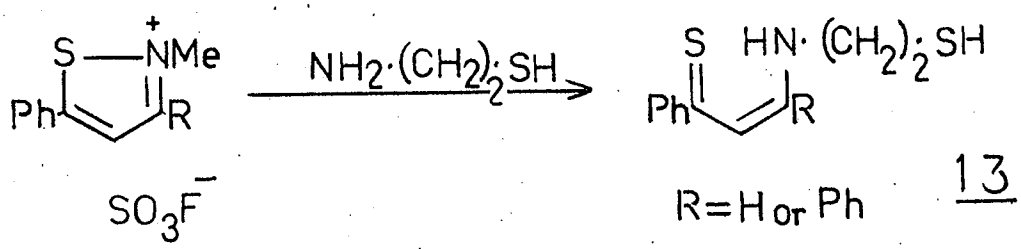


Dianils 12 were obtained from the reaction with the isothiazolium cations lacking 3 or 5-substituents. These must also arise from preferable attack of the initial nucleophilie at C-5 follwed by loss of sulfur.



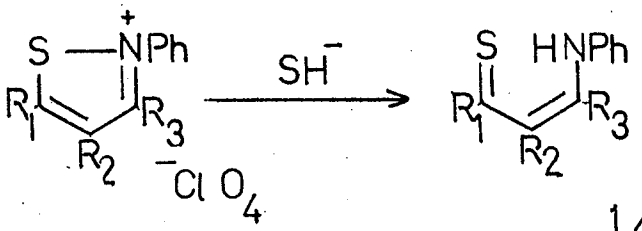
12

An NS-bidentate nucleophile, 2-aminoethanthiol, was employed to investigate whether attack on isothiazolium nucleus occurred preferentially through its nitrogen or its sulfur atom. The attack exclusively took place through the nucleophile's nitrogen to yield the thioethylaminothiones 13 .



13

The reaction of isothiazolium salts with hydrosulfide anion HS^- , was reported by Bachers[33], to yield only the open chain product 1-anilino-3-methylthiopropenethione 14 . It was suggested that formation of 14 might have occurred through nucleophilic attack on ring sulfur or nitrogen.

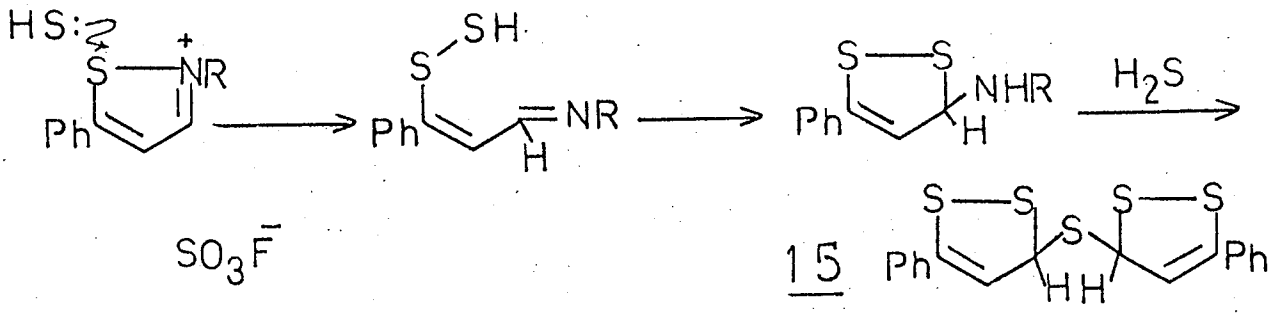


14

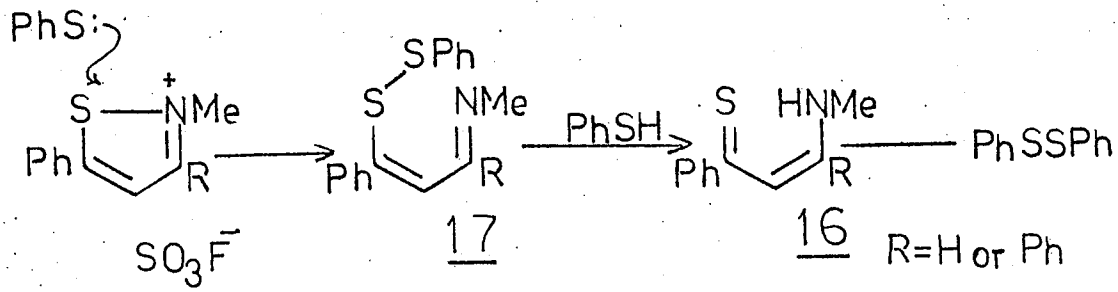
	R_1	R_2	R_3
a -	SMe	ph	H
b -	SEt	H	ph

Sykes and Ullah[38], on the other hand, studied the reaction of hydrogen sulfide in aqueous solutions; they found that isothiazolium

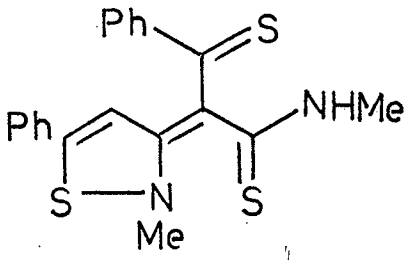
salts lacking a 3-substituent reacted readily to yield the bis-1,2-dithiolyl sulfide 15 , the original 2-substituent being lost as the corresponding amine. The unsubstituted sulfides were extremely unstable. The reaction was explained as taking place by initial nucleophilic attack on the ring sulfur (mechanism "d" of Landesberg and Olofson).



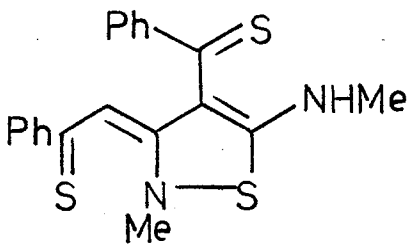
Benzenethiol was found[38] to react with various isothiazolium salts to yield the alkylaminothiones 16 . Its formation was explained in terms of initial attack on sulfur, followed by the reaction of the resultant mixed disulfide 17 with a second molecule of benzenethiol. Significantly, diphenyl disulfide is formed during the reaction.



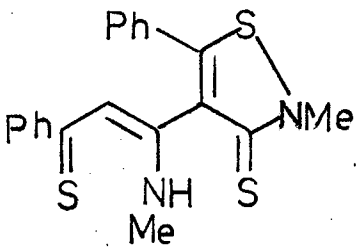
Further investigation of this reaction revealed[39] the existence of another product obtained only when R=H . The product has the molecular formula $C_{20}H_{18}N_2S_3$; the exact structure is not as yet definite but it is expected to be one of at least three possible tautomeric structures 18 , 19 , 20 , which have the general representation 21 .


Ph
S
NHMe
Ph
S
N
S
Me

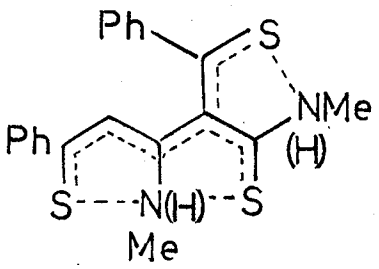
18


Ph
S
NHMe
Ph
S
N
S
Me

19


Ph
S
NMe
Ph
S
NH
S
Me

20

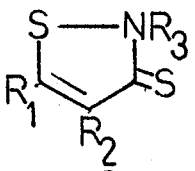

Ph
S
NMe
(H)
Ph
S
N(H)
S
Me

21

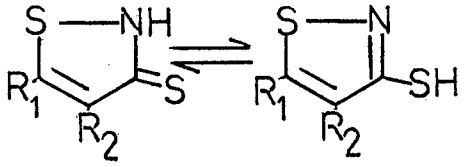
4-ISOTHIAZOLINE-3-THIONES

I. DESCRIPTION OF THE MOLECULE

The 4-isothiazoline-3-thione system 22 , consists of an isothiazole nucleus bearing a thione function at the 3-position and usually a substituent on the nitrogen atom of the isothiazole.

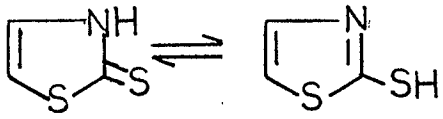


22

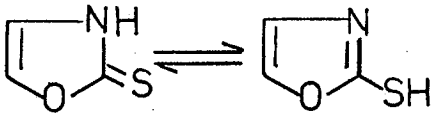


No data are available for the possible tautomerism of 22 , which, when R_3 = H , contains a potential mercapto group. However the isomeric thiazole-2-thiones 23 have been shown by infrared[40] and ultraviolet[41],[42] studies to exist mainly in the thione form. Similar results are also reported for oxazole-2-thiones 24[27].

Therefore it seems more likely that the 4-isothiazoline-3-thione molecule should actually exist as the thione form rather than as the 3-mercapto form.



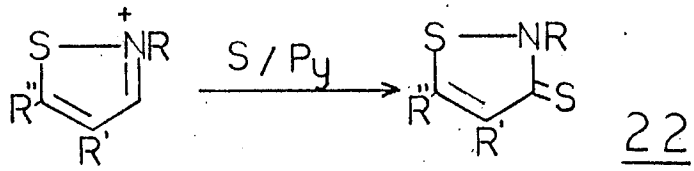
23



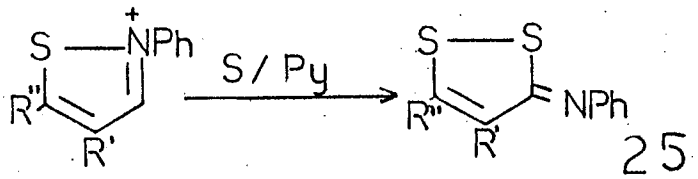
24

II. SYNTHESES OF 4-ISOTHIAZOLINE-3-THIONES

The preparation of 4-isothiazoline-3-thiones was first reported by McKinnon and Robak[24], from the reaction of isothiazolium salts with sulfur in boiling pyridine.



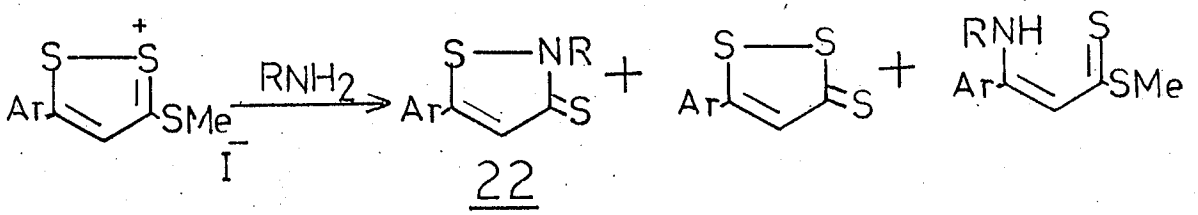
22



25

In case of N-aryl compounds, the isomeric system 1,2-dithiole-3-imine 25 is obtained instead by a mechanism indicated earlier*.

Le Coustumer and Mollier[27],[44] in their studies of the reaction of 5-aryl-3-thiomethyl-1,2-dithiolium salts with primary aliphatic amines expected, in analogy to the reaction with aromatic amines[45], to obtain 5-aryl-3-arylimino-1,2-dithioles 25[46]. However, on the basis of evidence described below, the main product was confirmed as having the thione structure 22 .



22

The evidence for structure 22 is:

1) The product reacted with benzonitrile oxide to give the corresponding 4-isothiazoline-3-thione.

2) The N^{15}-enriched product reacted with methyl iodide giving the salt 26 which showed no N^{15}-methyl coupling which would have been evident in 27 formed from the imino compound and methyl iodide.

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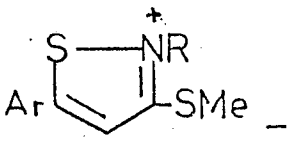
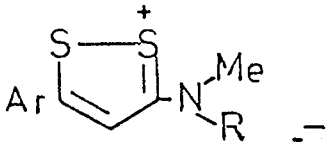
* P. 12



26 I^-

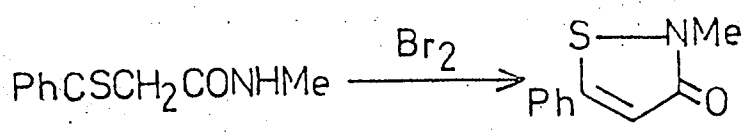


27 I^-

3) The compound was comparable to the one obtained alternatively by the reaction of isothiazolium salts with sulfur in pyridine.

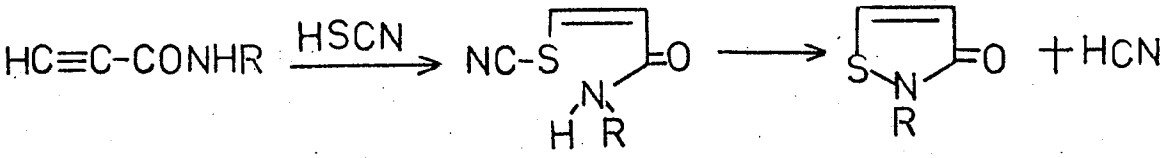
However, it is obvious that these two methods are inapplicable to the synthesis of N-arylisothiazoline-3-thiones, as in this case the 1,2-dithiole-3-imines are obtained instead. As will be discussed later, a suitable precursor for the N-aryl thiones was found to be the N-aryl -3-alkylthioisothiazolium salts prepared by Boberg[34].

4-Isothiazoline-3-thiones should also be available by the thionation of the corresponding 4-isothiazoline-3-one 28 . Such ketones are accessible by the oxidation of the appropriate N-substituted thioacylacetamide[47],[48].

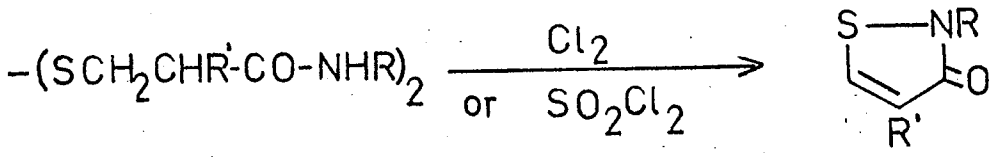


28

Crow and Leonard[49],[50] developed another method along lines suggested by the isothiazole synthesis of Wille, Capeller and Steiner[51]. cis-3-Thiocyanoarylamides were obtained by the addition of hydrogen thiocyanate to the propiolamides. Conversion to the corresponding substituted-3-isothiazolones was then effected readily by treatment with acid.



Leonard and Wilson[52] reported the formation of 3-isothiazolone nucleous by ring contraction of the 1,4-thiazepine ring system. Lewis and Miller[53] prepared 4-isothiazoline-3-ones by the chlorine or sulfuryl chloride induced cyclization of 3,3'-dithiodipropionamides. A major advantage of this preparation route is the ready availability of the 3,3'-dithiodipropionamide intermediates, conveniently prepared by amidation via the acid chloride of the corresponding diacids.



III. REACTIONS OF 4-ISOTHIAZOLINE-3-THIONES

4-Isothiazoline-3-thiones undergo alkylation reactions with methyl iodide to yield 3-alkylthioisothiazolium salts[24],[44].

Reaction with benzonitrile oxide leads to the formation of unstable adduct which decomposes to form the corresponding ketone[44].