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"

by

MOHAMED EZELDIN RASHAD HASSAN

A dissertation submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

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

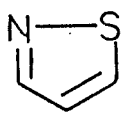
This thesis concerns the syntheses and reactions of a number of compounds containing the isothiazole nucleus, namely the isothiazolium salts, and the isothiazoline-3-, and -5-thiones.

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.

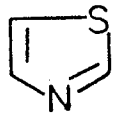
ISOTHIAZOLES

I. DESCRIPTION OF THE MOLECULE

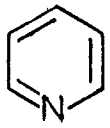
Isothiazole 1 , is an unsaturated five-membered heterocyclic molecule containing two adjacent heteroatoms, namely sulfur and nitrogen. The sulfur atom contributes a free pair of electrons to the mesomeric bond system.



1



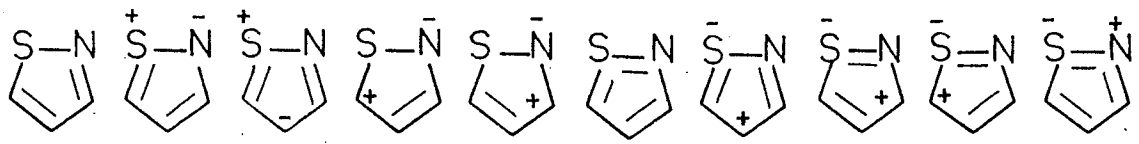
2



3

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.



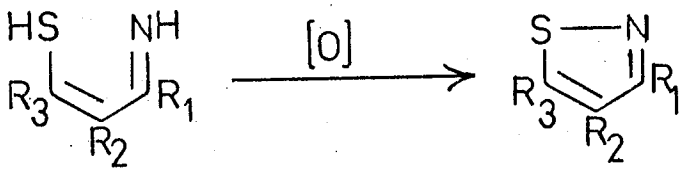
1i 1ii 1iii 1iv 1v 1vi 1vii 1viii 1ix 1x

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:

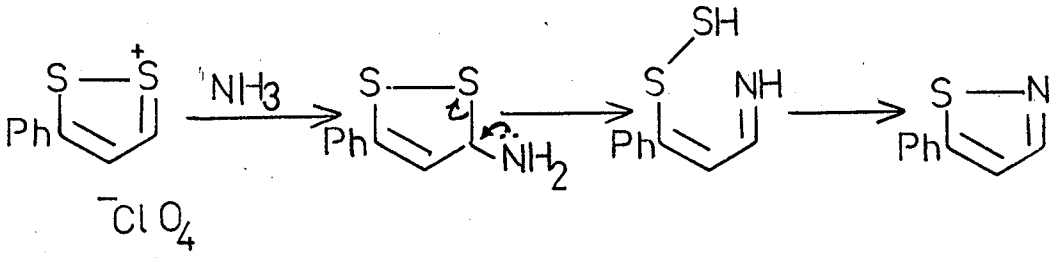
1. Syntheses involving an oxidative N-S bond formation :

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



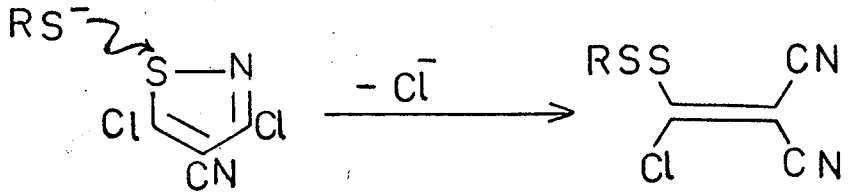
Numerous routes have been devised to these precursors including the addition of hydrogen sulfide to β-iminopropionitriles[4], the addition of isocyanates to primary and secondary enamines[5-7], the thionation of β-iminoketones[8], and the reduction of isoxazole by Raney Nickel, followed by thionation[9]. 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.

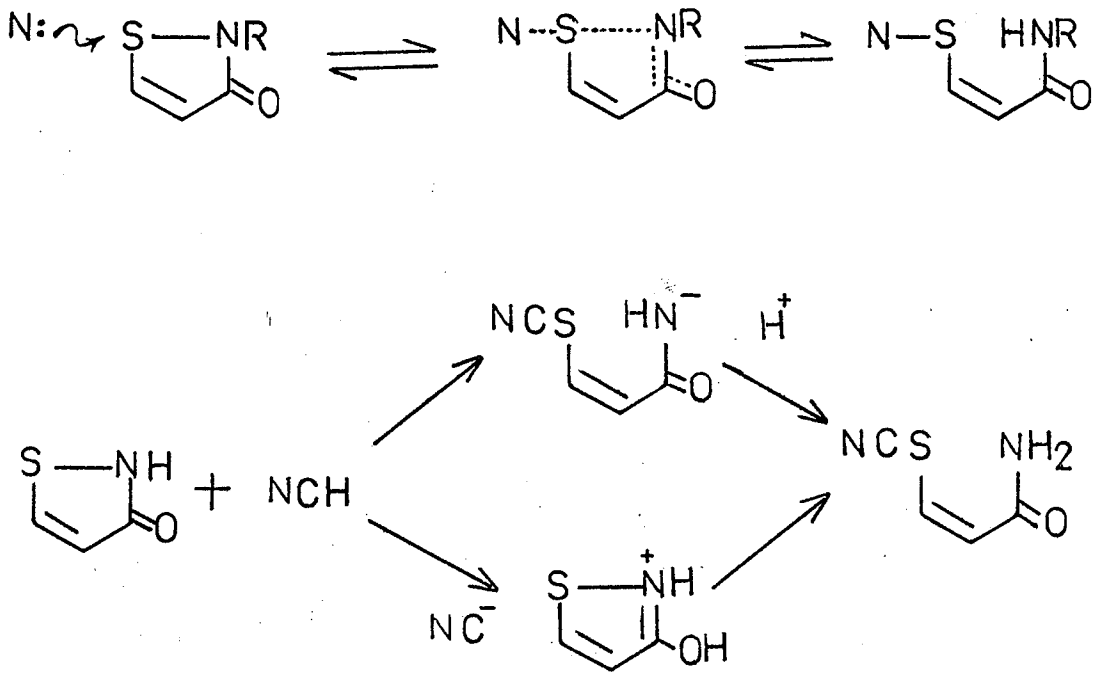


III. THE CHEMICAL PROPERTIES OF ISOTHIAZOLES

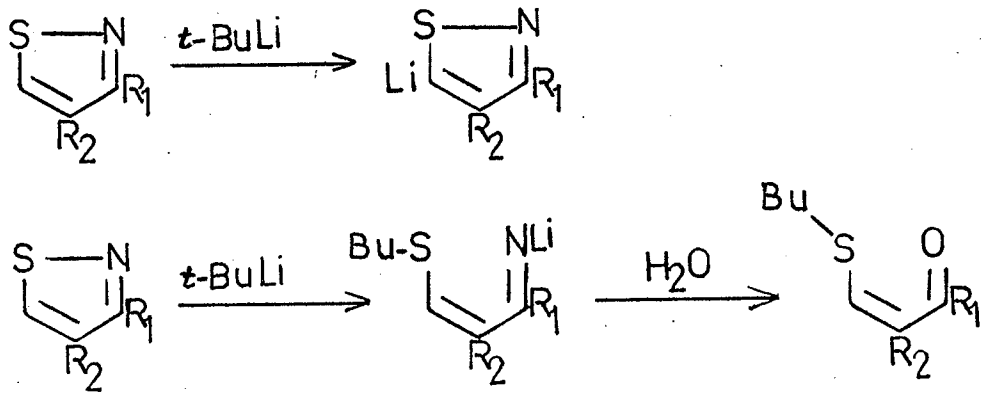
The chemistry of isothiazoles have been discussed in detail in the review by Wooldridge[3] mentioned earlier. Although the ring nitrogen is only weakly basic (pKa = -0.51 ± 0.04 at 25°C)[3], it can be induced to form quaternary derivatives[16]. This observation is of special interest for the preparation 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.



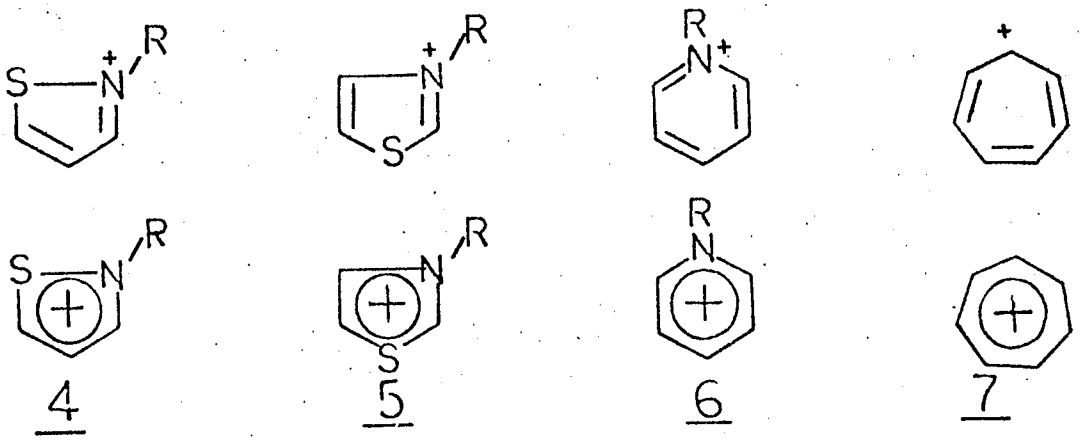
Hydrogen exchange is reported to take place at 5-position very rapidly under basic conditions, and therefore treatment of isothiazoles with butyllithium affords the 5-lithio derivatives[17]. However nucleophilic attack on the ring sulfur also takes place leading to ring cleavage[3].



ISOTHIAZOLIUM SALTS

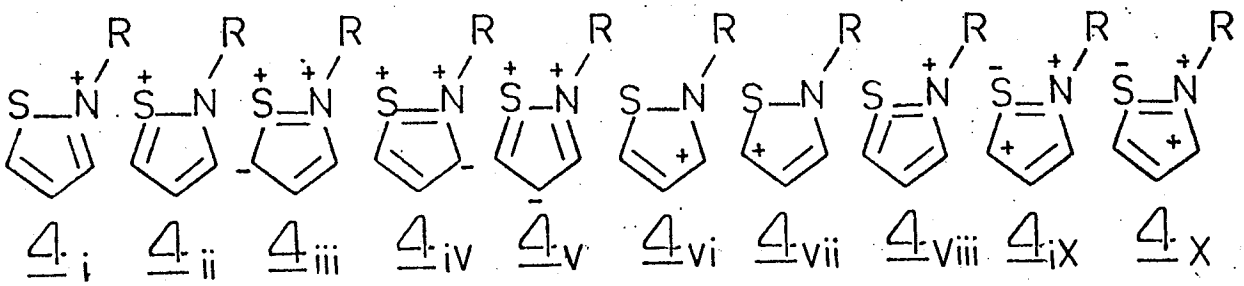
I. DESCRIPTION OF THE MOLECULE

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].

4

8

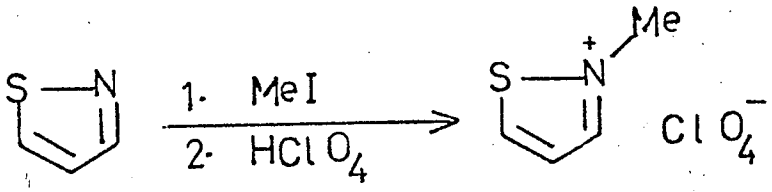
II. SYNTHESIS OF ISOTHIAZOLIUM SALTS

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

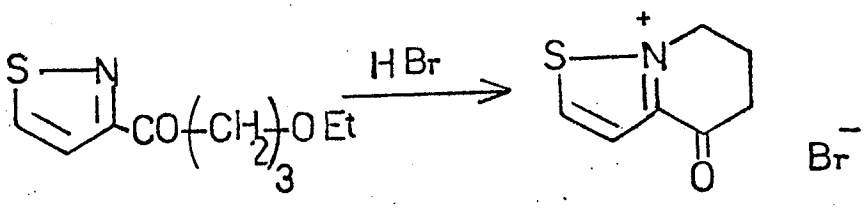
1. The Alkylation of Isothiazoles:

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].



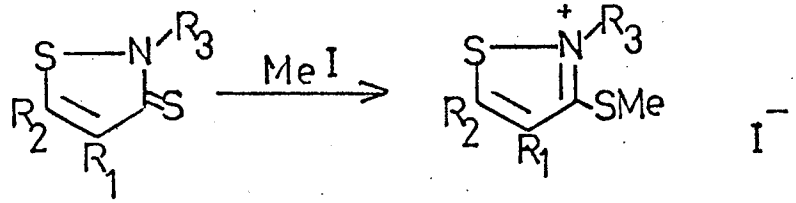
Intramolecular quaternization of isothiazoles afforded a bicyclic system[28].



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.

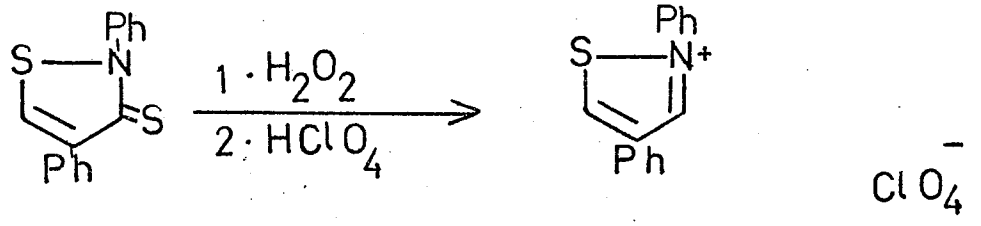
2. The Alkylation of Isothiazolinethiones:

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.



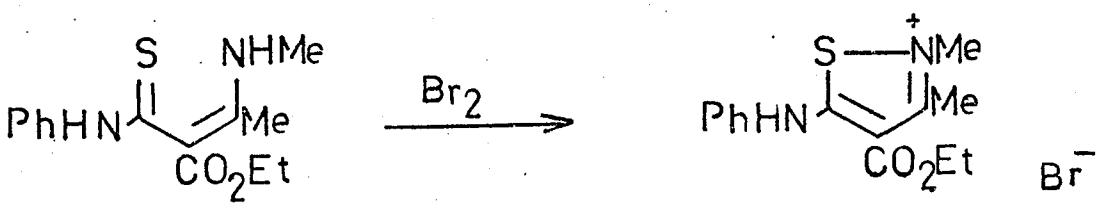
3. Oxidation of Isothiazolinethiones:

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.

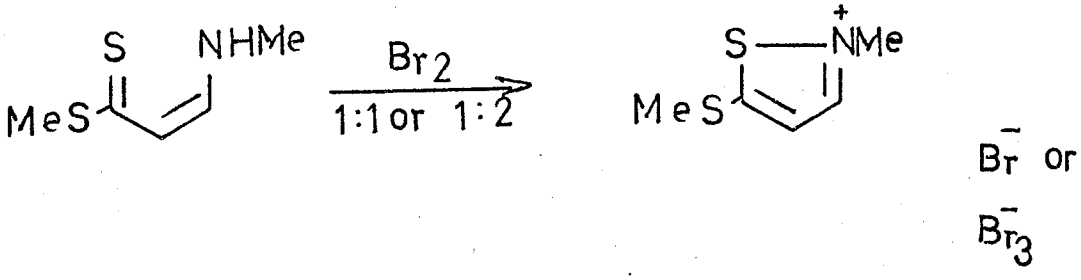


4. Oxidative Formation of the N-S Bond:

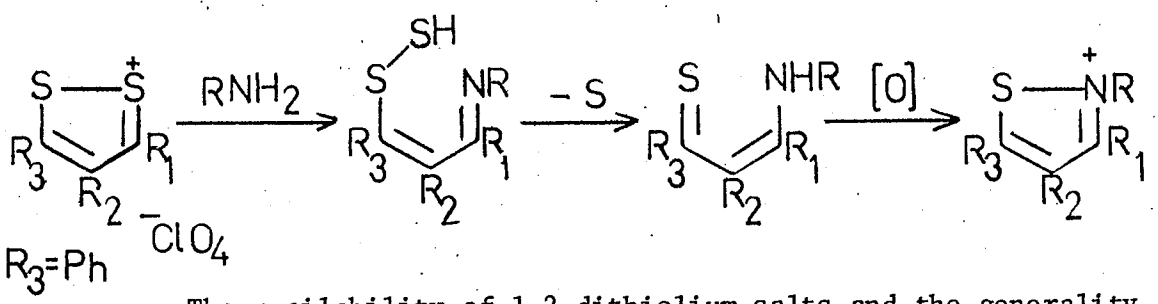
Goerdeler et al.[31], prepared the first isothiazolium cation by dehydrogenation of 3-methylamino-N-phenylbut-2-ene-thioamide derivative with bromine.



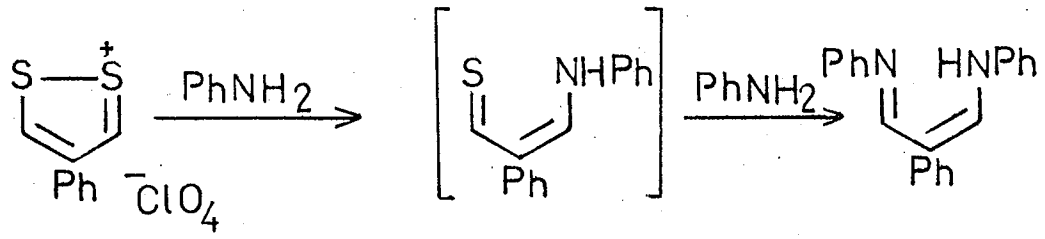
Following the same approach, Faust[32] synthesized the 2-methyl-5-methylthioisothiazolium bromide and the corresponding tribromide.



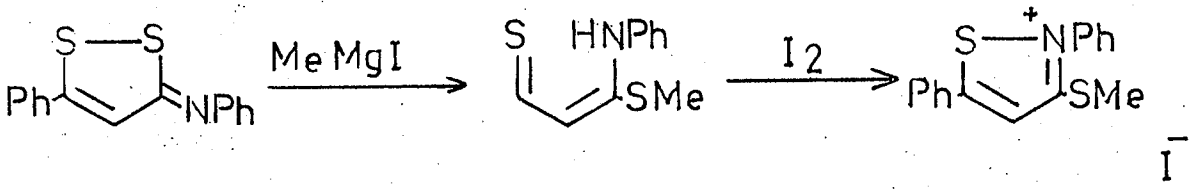
By treating 1,2-dithiolium salts with primary amines, McKinnon and Robak[24] obtained 1-aminopropene-3-thiones. By oxidation with iodine, a variety of isothiazolium triiodides were obtained which were converted into the corresponding perchlorate on treatment with perchloric acid in acetic acid or nitromethane.



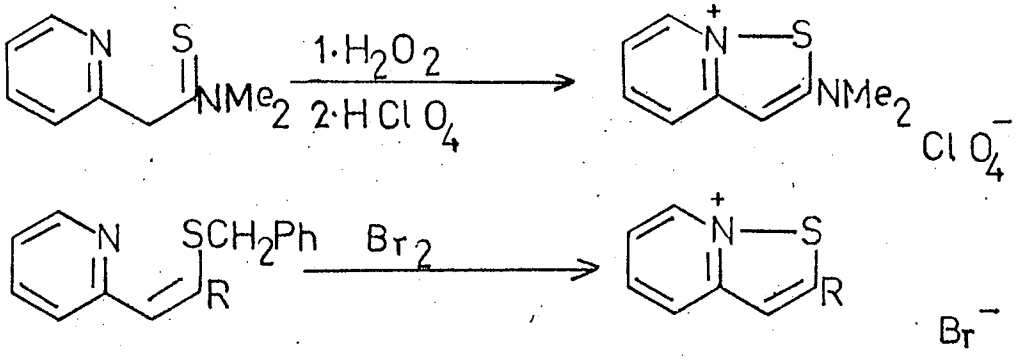
The availability of 1,2-dithiolium salts and the generality of the reaction make this approach a convenient one for the preparation of N-aryl isothiazolium salts. However if R_3 = H , the reactivity of the intermediate thial precludes the synthesis of 5-unsubstituted isothiazolium salts by this method,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



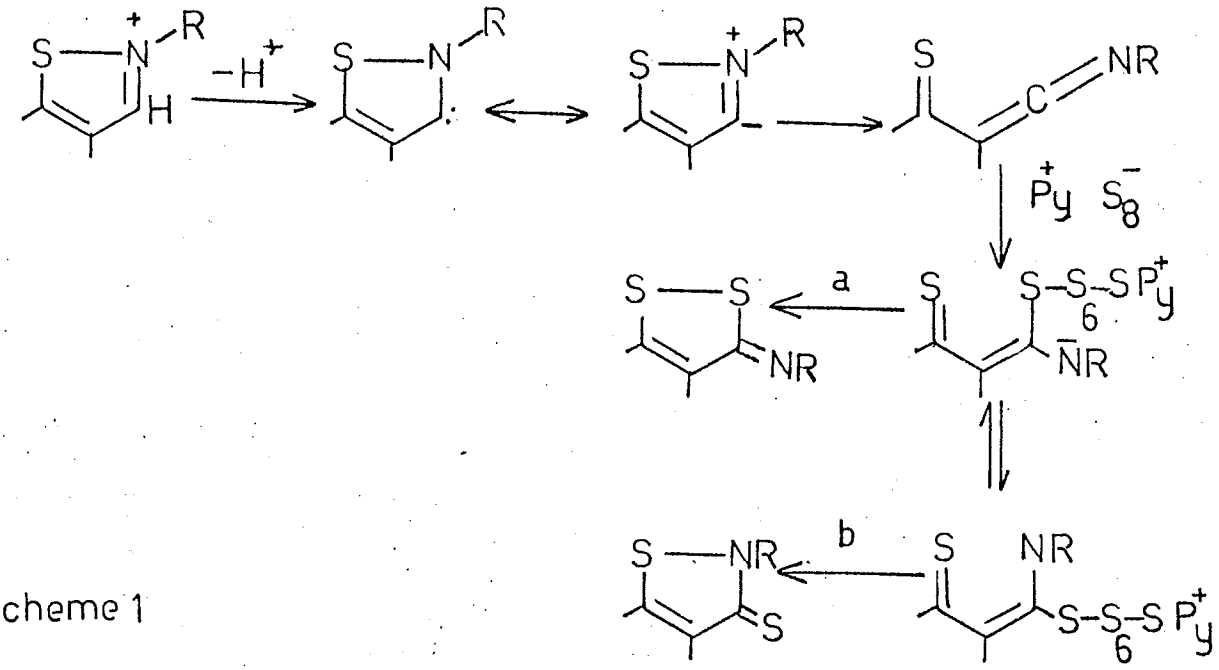
Oxidation of 2-pyridylthioacetamide or 2-(2-benzylthiovinyl) pyridines afforded isothiazolo [2,3-a] pyridinium salts[35], which could be regarded as an isothiazolium cation fused with a pyridine ring.



III. REACTIONS OF ISOTHIAZOLIUM SALTS

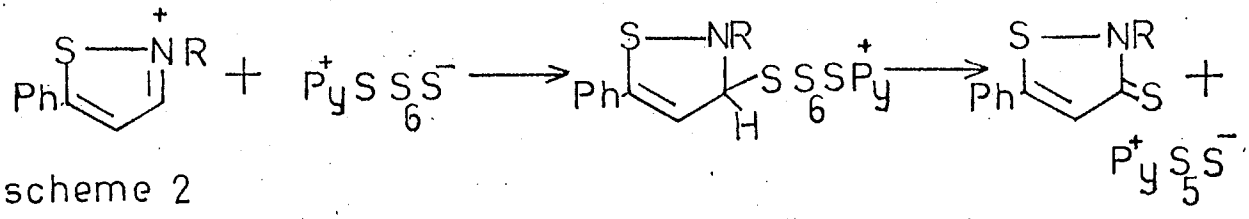
The deprotonation studies mentioned earlier[19] showed that the proton on the 5-position is lost at higher rate than the proton on the 3-position.

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].

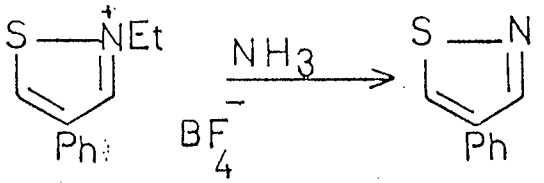


scheme 2

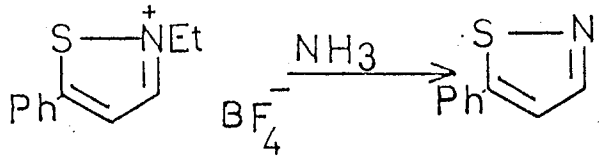
However, an isothiazolium salt with both 3 and 5 positions unsubstituted gave only a product derived from attack at the 5 position. This was taken by the authors as evidence for deprotonation as the first stage in the reaction. Nucleophilic attack on a carbon atom would be favored at the 3-position by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



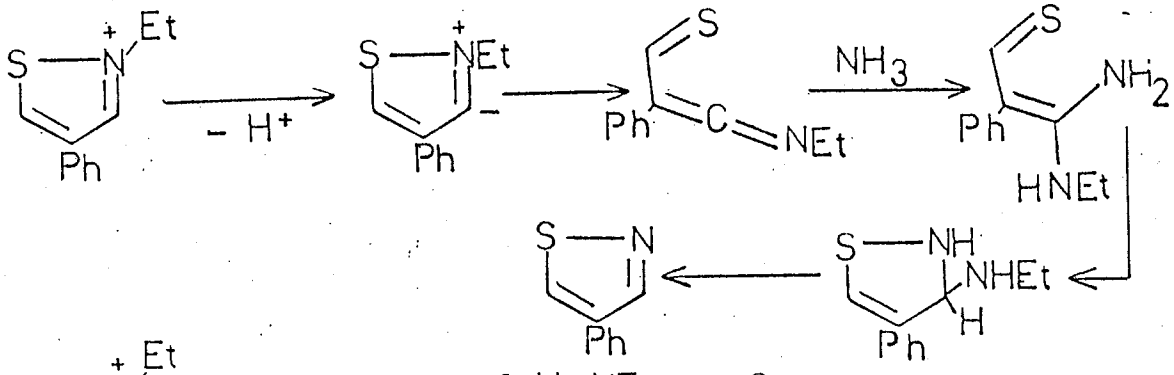
9



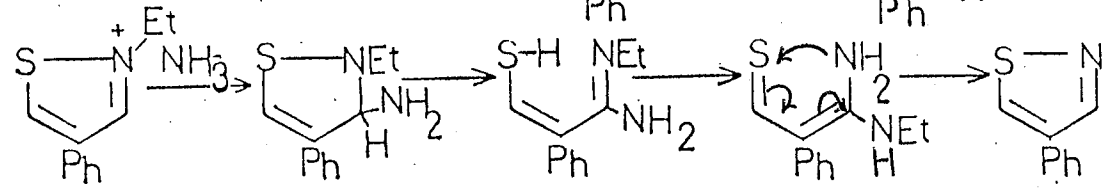
10

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:



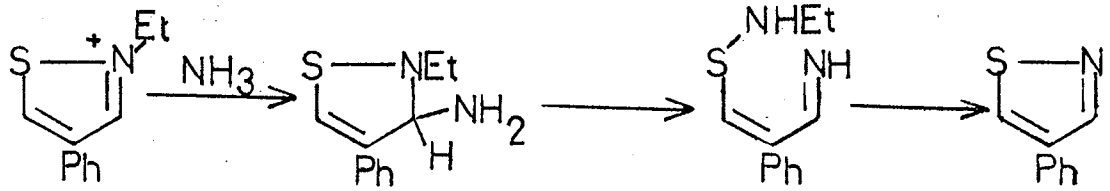
b:



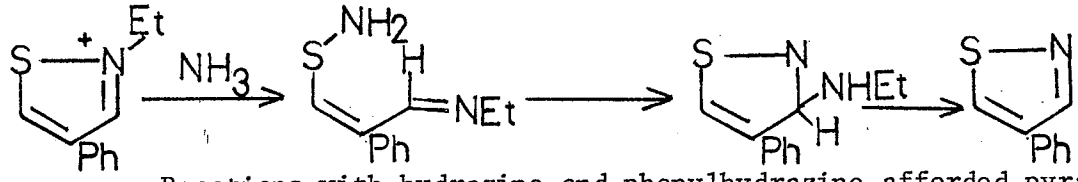
scheme 3

scheme 3 cont.

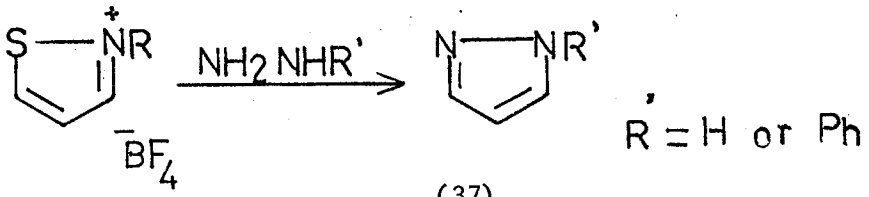
c:



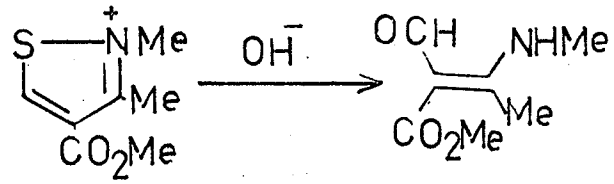
d:



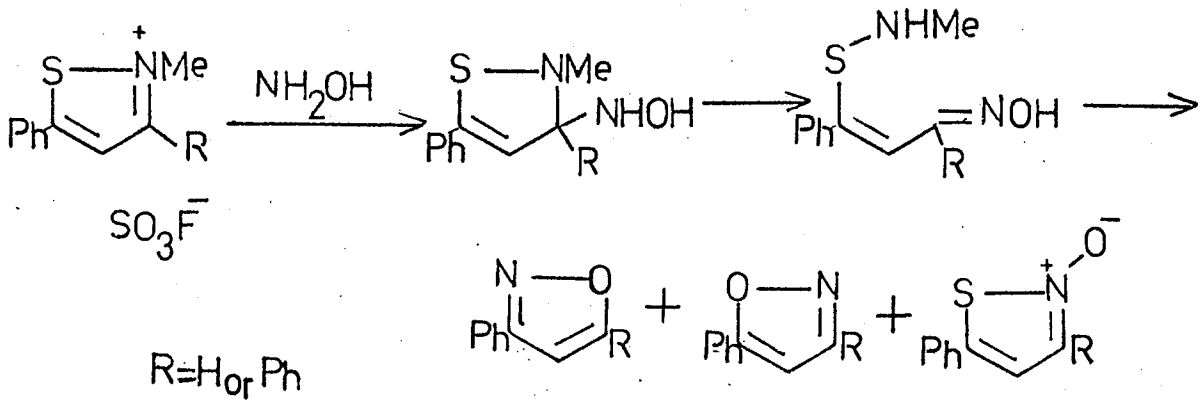
Reactions with hydrazine and phenylhydrazine afforded pyrazoles and phenylpyrazoles respectively[23],[38].



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



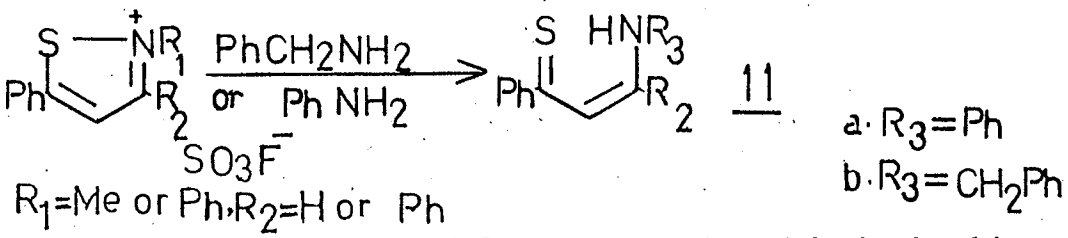
Recently, Sykes and Ullah[38] studied the nucleophilic reactions of hydroxylamine with 5-phenyl or 3,5-diphenyl substituted isothiazolium cations which afforded isoxazole and isothiazole N-oxide. The reaction seems to proceed by initial attack of nitrogen nucleophiles on the 3-position of isothiazolium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



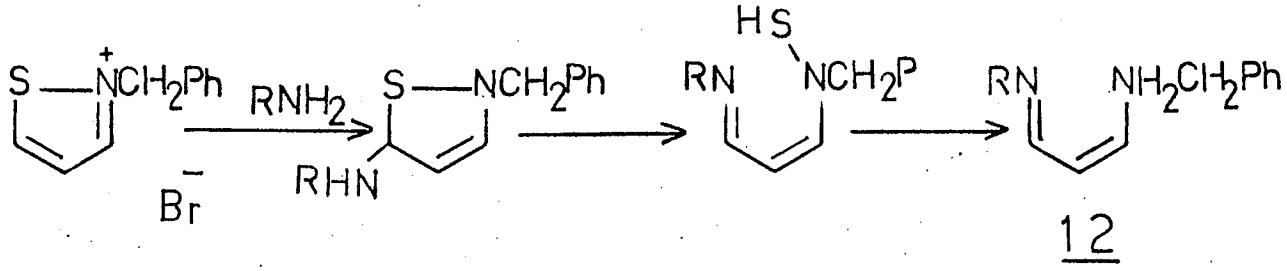
The formation of both 3-, and 5-phenylisoxazole (1:4 mixture) from the reaction of hydroxylamine with 5-phenylisothiazolium salt indicates that the nucleophilic attack on isothiazolium salts does take place on carbon 5 as well as on carbon 3.

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.

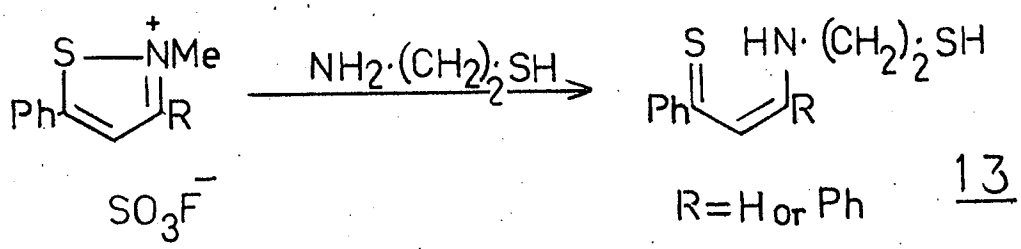


Dianils 12 were obtained from the reaction with the isothiazolium cations lacking 3 or 5-substituents. These must also arise from preferable attack of the initial nucleophilie at C-5 follwed by loss of sulfur.



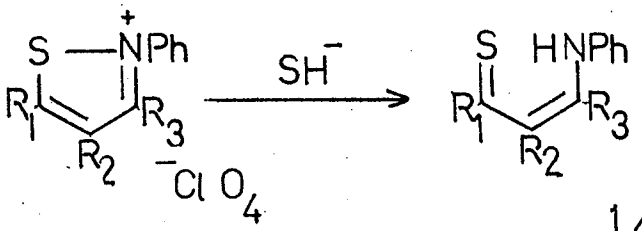
12

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.

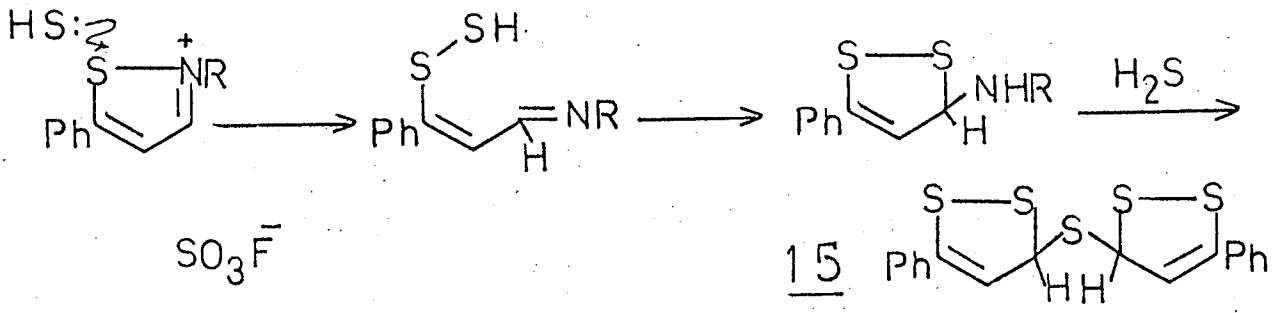


14

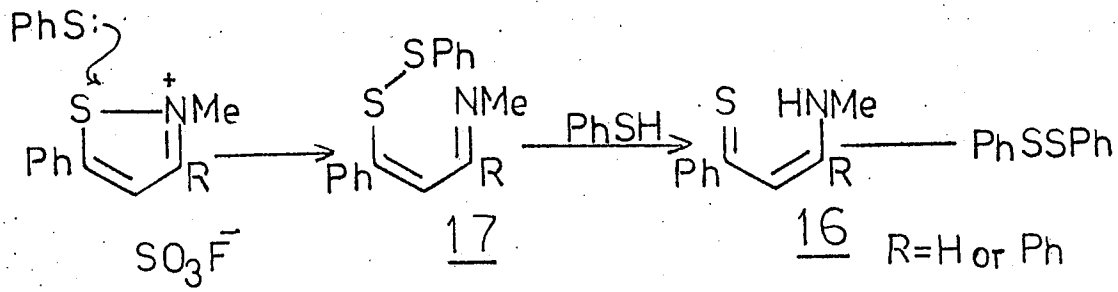
	R_1	R_2	R_3
a -	SMe	ph	H
b -	SEt	H	ph

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

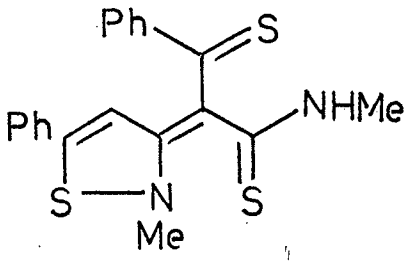
salts lacking a 3-substituent reacted readily to yield the bis-1,2-dithiolyl sulfide 15 , the original 2-substituent being lost as the corresponding amine. The unsubstituted sulfides were extremely unstable. The reaction was explained as taking place by initial nucleophilic attack on the ring sulfur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



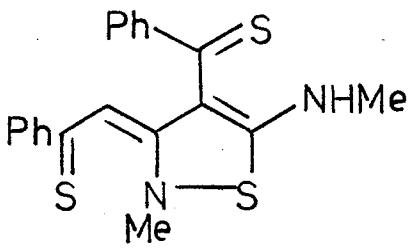
Benzenethiol was found[38] to react with various isothiazolium salts to yield the alkylaminothiones 16 . Its formation was explained in terms of initial attack on sulfur, followed by the reaction of the resultant mixed disulfide 17 with a second molecule of benzenethiol. Significantly, diphenyl disulfide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



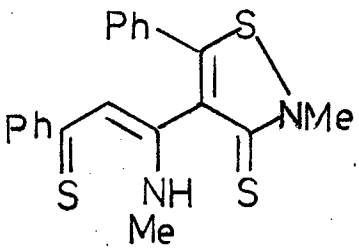
Further investigation of this reaction revealed[39] the existence of another product obtained only when R=H . The product has the molecular formula $C_{20}H_{18}N_2S_3$; the exact structure is not as yet definite but it is expected to be one of at least three possible tautomeric structures 18 , 19 ,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


Ph
S
NHMe
Ph
S
N
S
Me

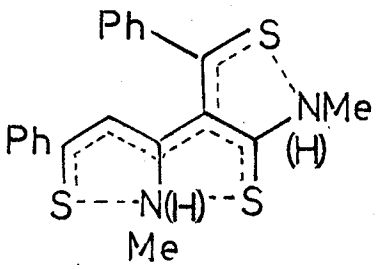
18


Ph
S
NHMe
Ph
S
N
S
Me

19


Ph
S
NMe
Ph
S
NH
S
Me

20

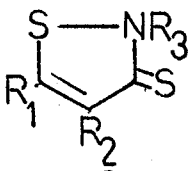

Ph
S
NMe
(H)
Ph
S
N(H)
S
Me

21

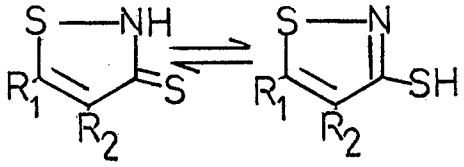
4-ISOTHIAZOLINE-3-THIONES

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.

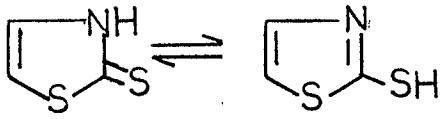


22

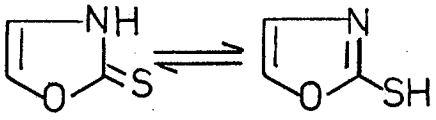


No data are available for the possible tautomerism of 22 , which, when R_3 = H , contains a potential mercapto group. However the isomeric thiazole-2-thiones 23 have been shown by infrared[40] and ultraviolet[41],[42] studies to exist mainly in the thione form. Similar results are also reported for oxazole-2-thiones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



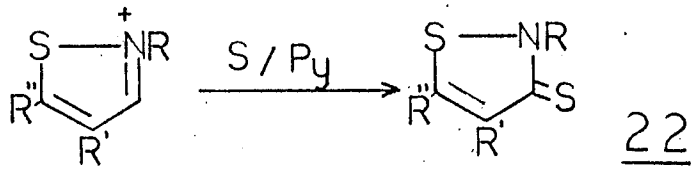
23



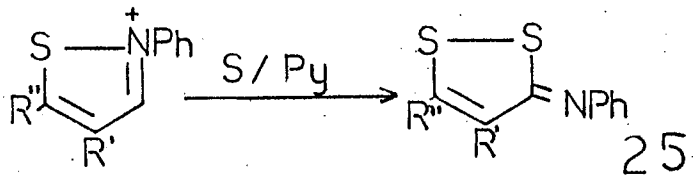
24

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.



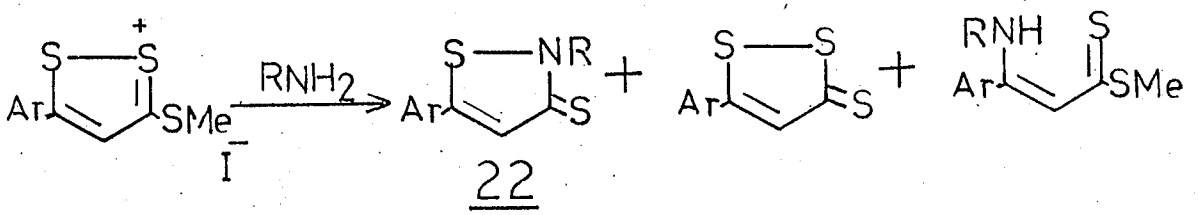
22



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

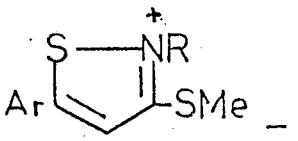
The evidence for structure 22 is:

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

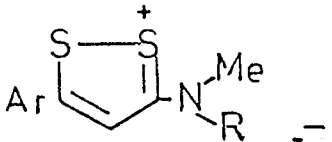
2) The N^{15}-enriched product reacted with methyl iodide giving the salt 26 which showed no N^{15}-methyl coupling which would have been evident in 27 formed from the imino compound and methyl iodide.

---

* P. 12



26 I^-

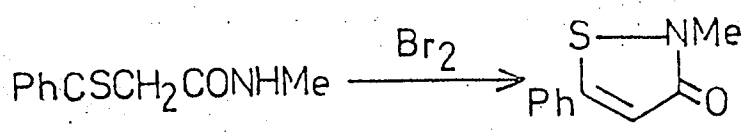


27 I^-

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

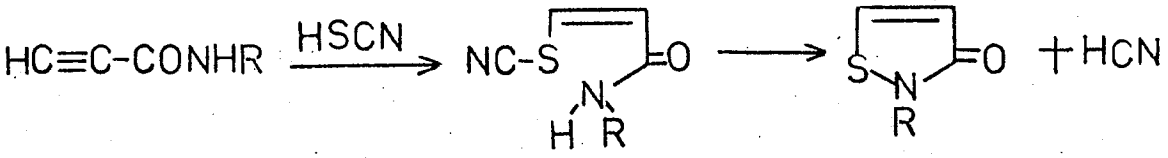
However, it is obvious that these two methods are inapplicable to the synthesis of N-arylisothiazoline-3-thiones, as in this case the 1,2-dithiole-3-imines are obtained instead. As will be discussed later, a suitable precursor for the N-aryl thiones was found to be the N-aryl -3-alkylthioisothiazolium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

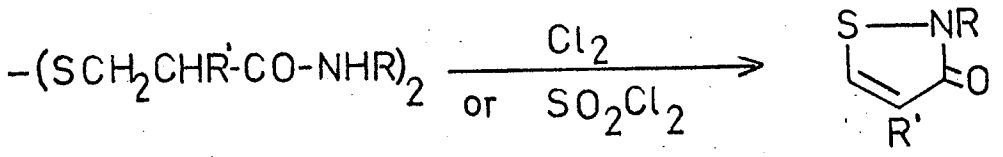


28

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.



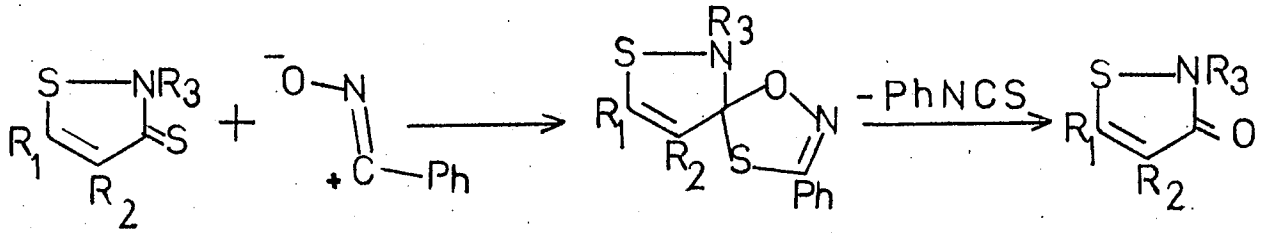
Leonard and Wilson[52] reported the formation of 3-isothiazolone nucleous by ring contraction of the 1,4-thiazepine ring system. Lewis and Miller[53] prepared 4-isothiazoline-3-ones by the chlorine or sulfuryl chloride induced cyclization of 3,3'-dithiodipropionamides. A major advantage of this preparation 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].

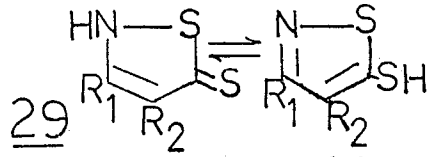


Oxidation with hydrogen peroxide in acetic acid was found to afford the corresponding isothiazolium salts[54], as mentioned earlier.

3-ISOTHIAZOLINE-5-THIONES

I. DESCRIPTION OF THE MOLECULE

3-Isothiazoline-5-thione 29 is isomeric with 4-isothiazoline-3-thione, consisting of an isothiazole nucleus bearing a thione function at the five position, and usually a substituent on the nitrogen atom.

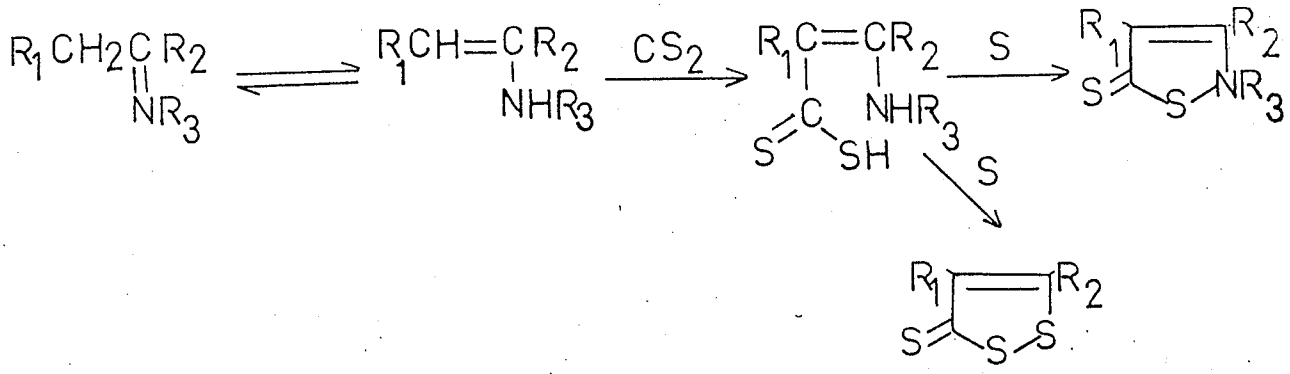


29

Tautomerism to a thiol form when $R_3 = H$ is again possible, although for the same reasons mentioned in the 4-isothiazoline-3-thiones, it is perhaps unlikely and the molecule exists almost entirely in the thione form.

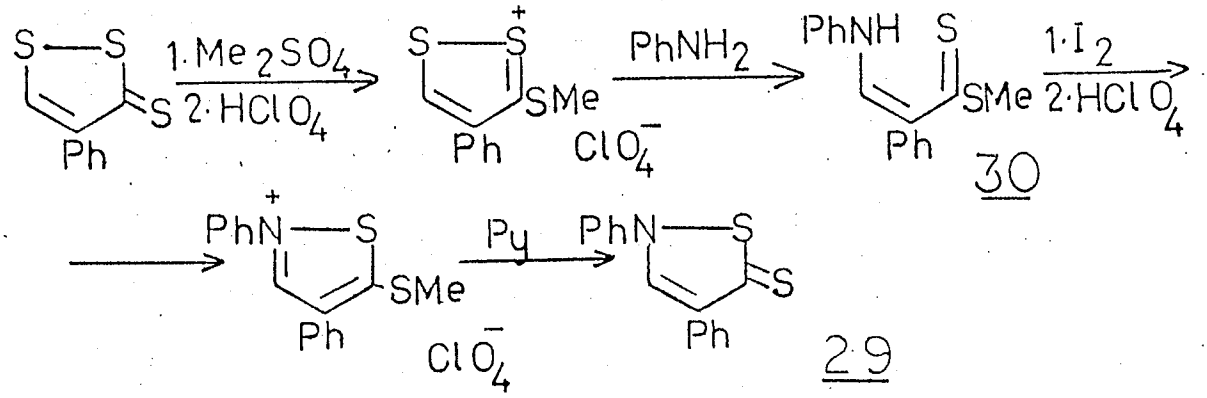
II. SYNTHESES OF 3-ISOTHIAZOLINE-5-THONES

These compounds were first prepared by Mayer and Jentzch[55] from the treatment of ketimines with carbon disulfide and elemental sulfur. The ketimines first react with carbon disulfide to form isolable dithio acids which, in the presence of sulfur, can be either S-thionated into 1,2-dithiole-3-thiones, with elimination of amine, or dehydrogenated into 3-isothiazoline-5-thiones with the elimination of hydrogen sulfide. The reaction product is temperature dependent, isothiazoline-thiones being formed between 15-20°C, and dithiole thiones at higher temperatures.

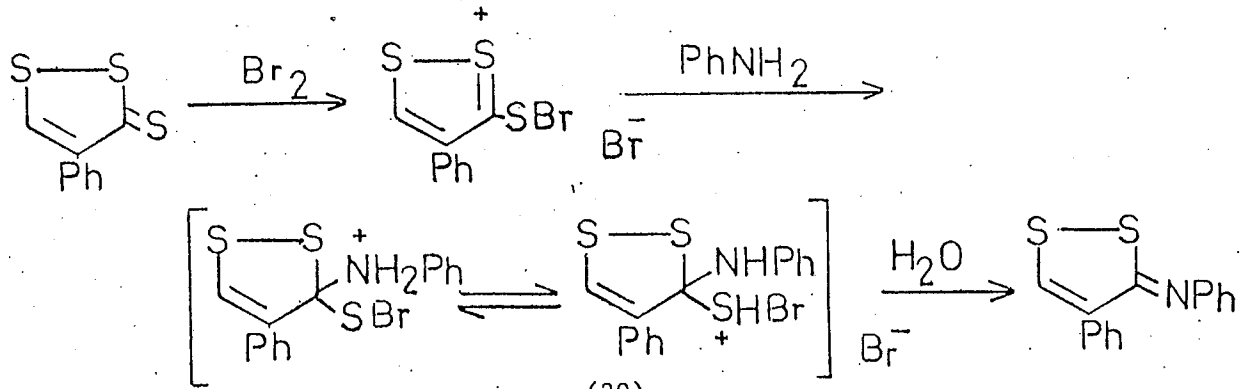


The dehydrogenation can also be brought about by other oxidizing agents such as iodine.

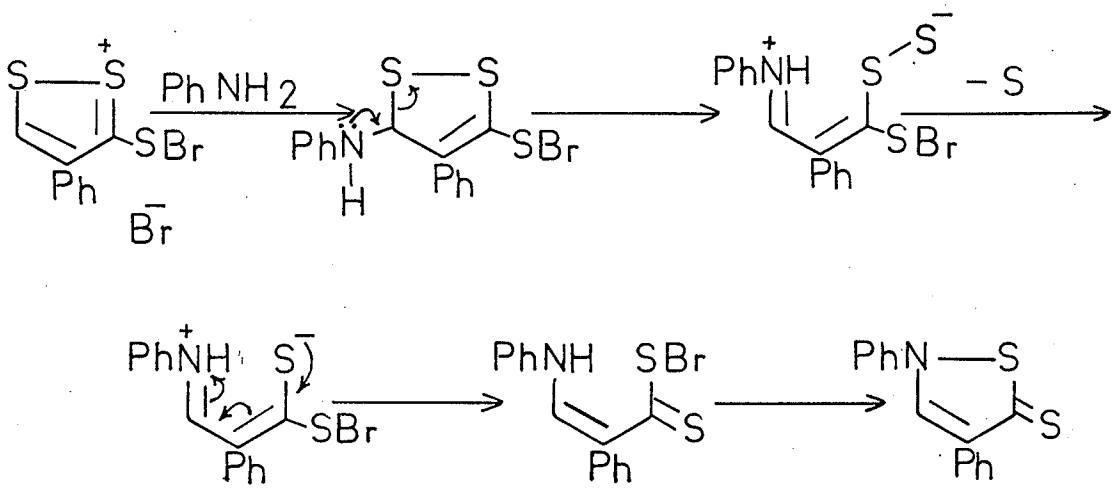
McKinnon and Bachers[33] found that 3-methylthio-4-phenyl-1,2-dithiolium salts, on treatment with aniline, underwent nucleophilic attack at carbon five, followed by ring opening to the dithioester 30, which on iodine oxidation gave 2,4-diphenyl-5-methylthioisothiazolium cation. Demethylation of this cation yielded 2,4-diphenyl-3-isothiazoline-5-thione 29.



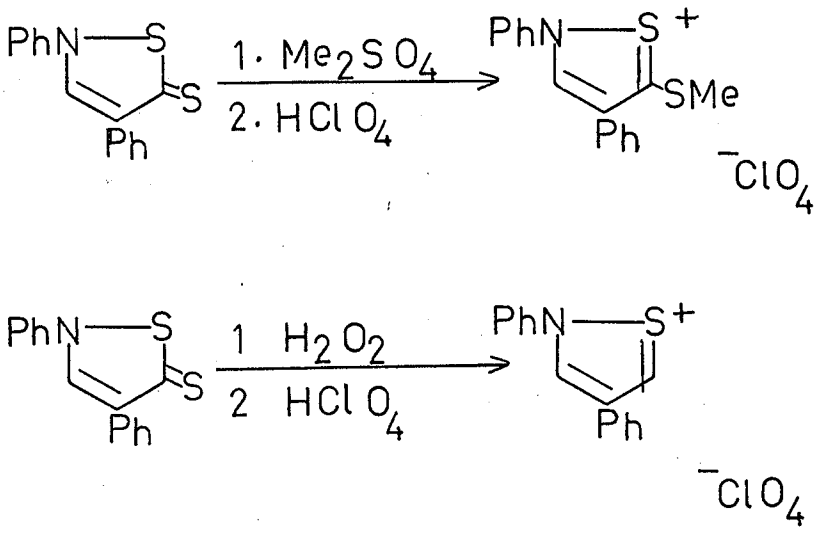
The reaction of 3-bromothio-4-phenyl-1,2-dithiolium salts with aniline was incorrectly reported by Adelfang[56] to give a dithioleimine according to the scheme shown.

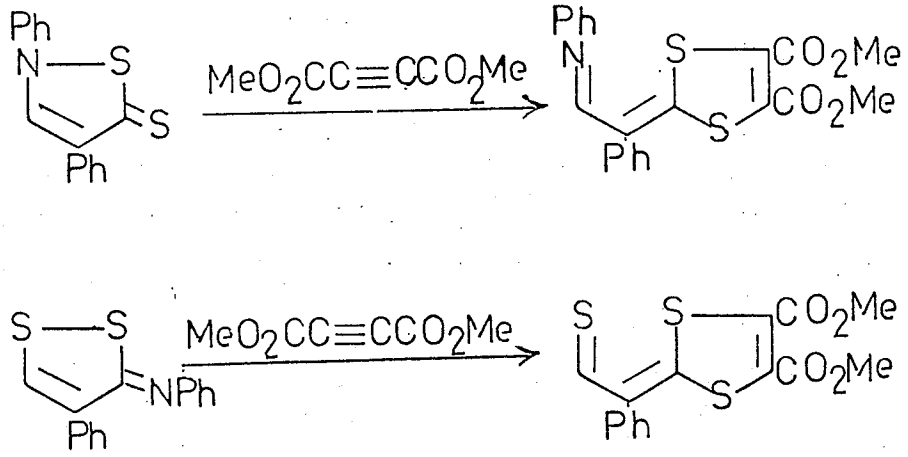


But Bachers and co-workers[29] found this reaction actually follows the same pathway described for the methylthio compound to afford the thione 29, probably according to the following mechanism.

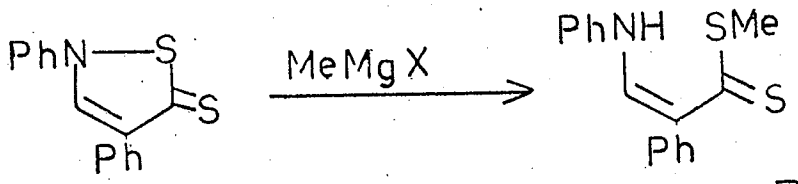


The structure of 29 was proved by the fact that it forms 5-methylthio-2,4-diphenylisothiazolium perchlorate on treatment with dimethyl sulfate followed by perchloric acid, that it is oxidized by hydrogen peroxide to an isothiazolium salt, and also that it formed a monoadduct with dimethyl acetylenedicarboxylate. Had the compound been the 3-imino-1,2-dithiole claimed by Adelfang, the reaction with dimethyl acetylenedicarboxylate would probably have yielded an unstable thial[57].





Furthermore, it was found[58] that on treating the product with Grignard reagents followed by hydrolysis, it afforded the open chain intermediate 1-arylaminopropene-3-thione 30 , proposed to be formed in the reaction route of the 3-alkylthio compounds.



30

III. REACTIONS OF 3-ISOTHIAZOLINE-5-THIONES

As mentioned in the previous section, 3-isothiazoline-5-thiones were found to undergo alkylation into isothiazolium salts[43], oxidation by hydrogen peroxide to form isothiazolium salts[54], adduct formation with dimethyl acetylenedicarboxylate[33], and ring cleavage to acyclic products on treatment with Grignard reagents[58].

1,6,6aS^{IV}-TRITHIAPENTALENES AND AZA ANALOGUES

I. NOMENCLATURE

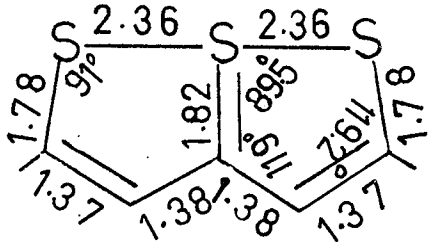
Several names can be found in the literature for this system including [1,2] dithiolo [1,5-b] [1,2] dithiole, thiothiophthene, and thiathiophthene. The latter is the most common name. However it is contrary to IUPAC nomenclature to derive a replacement name from the trivial name of a heterocyclic system, thiophthene[59]. More acceptable is the name 1,6,6aS^{IV}-trithiapentalene based on the pentalene system. It should be understood that the choice of this name, however, based mainly on practical nomenclature considerations, does not define the real electronic structure of the molecule[59], which will be discussed in the following section. In this thesis, for convenience, the name trithiapentalene will be employed.

II. DESCRIPTION OF THE MOLECULE

The electronic structure of the trithiapentalene ring system is one of considerable interest and has been of some controversy. The symmetry of the molecule and the utilization of the central sulfur d-orbitals are two points of major interest. The classical theory of σ and π orbitals does not explain all the properties of these compounds, and various theoretical explanations have been put forward. Several reviews were published on the subject which give a good summary of the problems involved[59-62],[67].

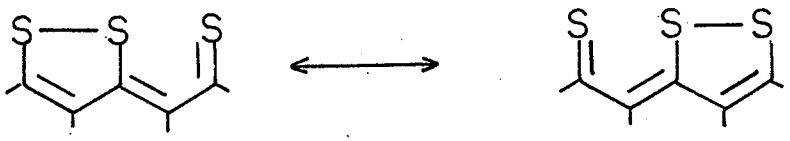
The X-ray investigation[63] indicated that the trithiapentalenes had the structure 31 , with the three sulfur atoms co-linear and equally spaced. The ring carbon atoms are separated by 1.37 to 1.38 A

indicating an aromatic system, and the sulfur-sulfur bond distances are 2.36 A , compared to 2.04 A in an aliphatic disulfide R-SS-R , indicating a bond order of less than unity.



31

From these bond orders and distances it was proposed originally that the molecule should be represented as a resonance hybrid of two contributing Kekulé type structures, where there is a double bond-single bond resonance of carbon-carbon bonds and single bond-no bond resonance in sulfur-sulfur bond.



31a 31b

Recent studies by gaseous electron diffraction at a nozzle-tip temperature of 180°C also suggested a symmetrical structure with sulfur-sulfur atoms equally spaced.[63] On the other hand, X-ray investigations of unsymmetrical trithiapentalenes suggest unsymmetrical structure[65-66]. In a recent investigation by Lozac'h and co-workers[64] it was found that the unsymmetrical structure characterized by different carbon-carbon lengths, different peripheral carbon-sulfur lengths and different sulfur-sulfur bond lengths, appears to be favoured in the case of symmetrically substituted trithiapentalenes.

However Clark and Kilcast[68] found through molecular orbital calculations that the ring system is likely to be susceptible to intermolecular forces, and that factor alone may be sufficient to reconcile apparently conflicting data obtained by different spectroscopic techniques. Sulfur-sulfur bonds involving d-orbitals seem very sensitive to extramolecular influences in the crystal lattice and to intramolecular perturbations such as unsymmetrical substitution. Unequal spacing of the sulfur atoms may perhaps also result from steric interactions between symmetrically placed substituents.

Leaver et al.[69] originally argued that the special properties of trithiapentalenes might be caused by rapid tautomerism instead of single bond-no bond resonance, but these data were later re-evaluated in terms of tetravalent sulfur.

The molecular orbital calculations carried out by Maeda[70-72] has shown that σ bonding between sulfur atoms could result from the participation of the d-orbital in the hybridization of the central sulfur atom. Gleiter and Hoffmann[73] showed that when hybridized p d orbitals are used for the central sulfur atom, the calculated energy curves showed a very flat energy minimum when the central sulfur atom is approximately equidistant from the external sulfur atoms, allowing a displacement of the central atom of approximately ±0.2 A from the symmetrical position. Similar results were also found by Clark[74].

The sulfur 3d-orbital participation have also been suggested by Johnstone and Ward[50] and by Brown, Leaver, and McKinnon[75]. The CNDO/2 calculations showed[68],[76] a relatively higher d-orbital population on S_{6a} as compared with the terminal sulfurs. Clark[68] argued, however, that the absolute values of such calculations cannot be taken

too seriously since CNDO/2 calculations including d-orbitals almost certainly exaggerate their importance.

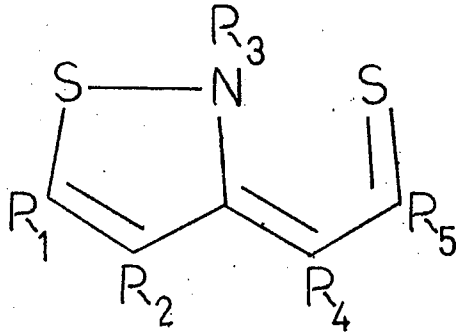
From the previous discussion, one can conclude that the unique characteristics of the trithiapentalenes have been attributed to:

1. Single bond - no bond resonance
2. Rapid tautomerism
3. Utilization of sulfur d-orbitals

Even though no single one of the above hypotheses gives a thorough account of the special properties of 31 , the theories involving d-orbitals appear to provide the most satisfactory explanations. It was of interest to determine to what extent the symmetrical properties of trithiapentalenes could be approached or paralleled by related systems in which the central atom might not be capable of valence shell expansion. Such systems might exhibit single bond - no bond resonance or valence tautomerism.

III. THE AZA ISOSTERES OF TRITHIAPENTALENES

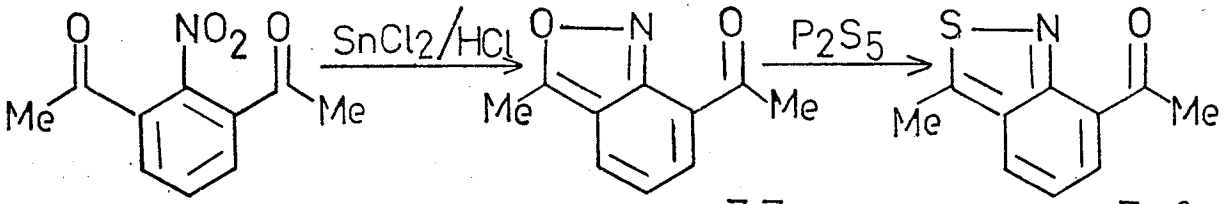
Several attempts were carried out by McKinnon et al. to prepare 3-thioacylmethyleneisothiazoline system 32 , with the nitrogen group at the 6a-position being incapable of valence shell expansion.



32

The reaction of isothiazolium salts with various methyl and methylene carbonyl containing compounds gave no identifiable products[77], although this is a method of producing trithiapentalene precursors. Nucleophilic attack of sodium benzoylacetate on 2,5-diphenylisothiazolium salts was found to yield only decomposition products[33]. This reaction has been re-investigated below.

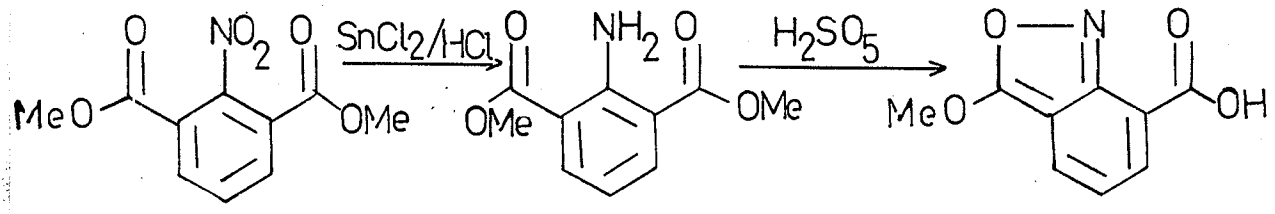
On the other hand, McKinnon and Wong[78] obtained 7-acetyl-3-methyl-2,1-benzisoxazole 33 by reduction of 2,6-diacetylnitrobenzene. Treatment of 33 with phosphorus pentasulfide in pyridine gave the benzisothiazole derivative 34 which has some structural similarities to the compound 32 above.

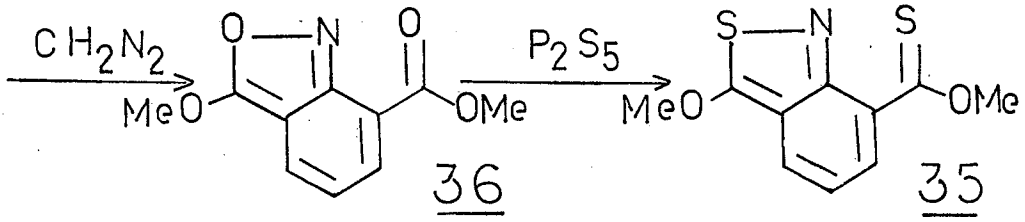


33 34

The NMR spectra of 33 in deuterochloroform showed only one methyl peak at 0-20°C , at other temperatures, however, two peaks were obtained. In hexadeuterobenzene, because of its aromatic solvent effect, wide separation of the two methyl groups was obtained. Under no circumstances was an AB_2 type pattern obtained from the ring protons, only ABX type were evident.

Similarly 7-thioacyl-2,1-benzisothiazole 35 , has been prepared by Chauhan and McKinnon[79].





36 35

The NMR spectrum in dimethyl sulfoxide over the temperature range studied (40-200°C), showed that the methyl groups in 36 were not equivalent although some approach of τ values and line broading was evident. The corresponding 2,1-benzisothiazole 35 , exhibited coalescence at 200°C.

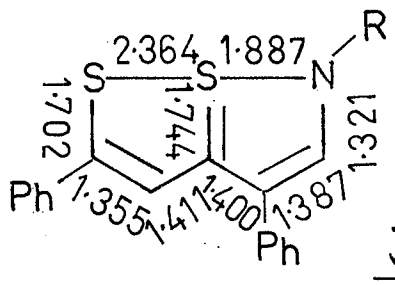
The failure of this system to demonstrate symmetry by suitably rapid tautomerism suggested that valency-tautomerism was inadequate in explaining the special properties of the trithiapentalenes. Likewise, doubt was also cast on the existence of single bond-no bond resonance in this system.

However it could be argued that rapid tautomerism would be less favoured in the above systems than in the case of trithiapentalenes owing to the ring strain arising from fusion onto the benzene ring. Indeed similar effects have been noted between trithiapentalene derivatives[75]. It would, therefore, be highly desirable to synthesize the system 32 and

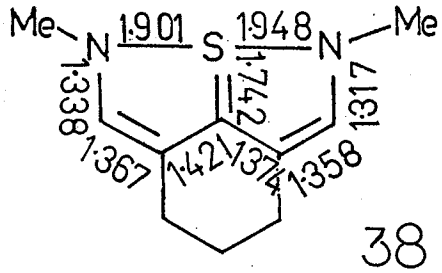
test its properties.

Although no such system has been as yet known, Sykes and Ullah[39] reported obtaining a compound of structural formula $C_{20}H_{18}N_2S_3$. Even though the exact structure of this compound has not as yet been absolutely determined, the proposed structures 18 - 21, mentioned before, contain similar moieties to the 3-thioacylmethylene isothiothiazoles.

Replacement of one or two of the terminal sulfur atoms of trithiapentalene with N-R group, would afford 1,6a S^{IV}-dithia-6-azapentalene 37, or 6a S^{IV}-thia-1,6-diazapentalene 38. Both systems are known[80-82].

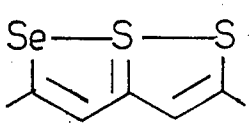


37

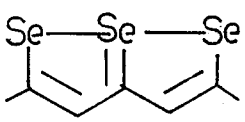


38

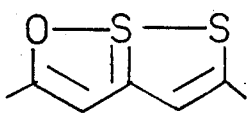
Crystallographic studies of 37[83-84], and 38[21] indicate that their structure and bonding is similar to that of trithiapentalenes. The nitrogen-sulfur bonds are 1.887 A for 37 and average of 1.925 A for 38, about 10% longer than the nitrogen-sulfur single bond. This agrees with the lengthening of sulfur-sulfur bonds in trithiapentalenes 31 which is 12.4%, the selenium-sulfur bond in 39 - 10.4% and the selenium-selenium bond in 40 - 10.3% relative to the respective single bond[21].



39



40



41

NMR studies[85], on 1,6a-dithia-6-azapentalenes 37 , show that the protons are more deshielded than those in the corresponding 1-oxa -6,6a-dithiapentalenes, but much less deshielded than those in the corresponding trithiapentalenes. Thus the ring proton chemical shifts for trithiapentalene 31 , 6-methyl-1,6a-dithia-6-azapentalene 37 , and 1-oxa-6,6a-dithiapentalene 41 are respectively

2-H (5-H in 41) : δ 9.18 , 8.86 , and 7.98

3-H (4-H in 41) : δ 7.96 , 7.45 , and 7.23

4-H (3-H in 41) : δ 7.96 , 7.05 , and 6.86

The chemical shifts of substituents in 1,6a-dithia-6-azapentalines also are intermediate in magnitude between those of 31 and 41 . This phenomenon of progressive increase in deshielding of ring protons and substituents along the series 41 32 31 , was attributed to a corresponding increase in size of the ring current.

SPECIAL PART

Discussion of Results

OBJECT OF RESEARCH

1. To study the effect of nucleophiles on isothiazolium salts, in order to determine the position of nucleophilic attack, the effect of substituents and other factors on the reaction products, and the utility of the reaction as a synthetic route to various heterocyclic systems.

2. To study the dipolar cycloaddition reactions of isothiazoline-thiones with acetylenic reagents to establish the nature of products.

3. To investigate the preparation and properties of certain 3-thioacylmethyleneisothiazoles, which have some similar structural and electronic features to 1,6,6a S^{IV} trithiapentalenes, to determine to what extent their properties approach those of the trithiapentalene system.

Both isothiazolium salts and isothiazolinethiones have high potential as starting materials for this investigation.

STUDIES ON THE NUCLEOPHILIC ATTACK ON ISOTHIAZOLIUM SALTS

While the studies of nucleophilic attack on isothiazoles[3],[86] and isothiazolones[14],[15] indicate the attack takes place at the ring sulfur atom, the situation with isothiazolium salts is by no means as clear.

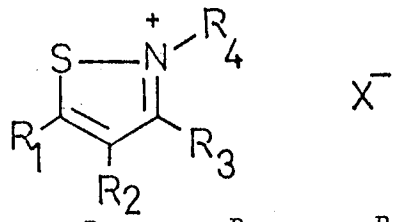
Various reactions of isothiazolium salts with nucleophiles have been interpreted as occurring at carbon 3*[23],[37],[3], (mechanism "c" of Landesberg and Olofson)ø[23], but in these reactions the products obtained could also have been formed by initial attack at sulfur (mechanism "d" of Landesberg and Olofson)[23]. The reaction with sulfur in pyridine is reported[29] to take place through initial deprotonation at carbon 3 or 5 of the isothiazolium cation (mechanism "a" of Landesberg and Olofson)[23]. The reaction of certain 5-methylthioisothiazolium salts with hydrosulfide[29] has been suggested to occur at ring sulfur or nitrogen. Moreover during the progress of this work, a recent publication[38] has demonstrated attack at carbon atoms3 or 5 by nitrogen nucleophiles, and at sulfur by hydrogen sulfide, although some of the products obtained could equally be formed through a different mechanism.

A further investigation was then carried out in order to provide more evidence on the position of nucleophilic attack, and in the light of this evidence, a discussion of the previous reports will be conducted in order to form a general pattern for the site of nucleophilic attack on isothiazolium cations.

A variety of isothiazolium salts 4 a-4k were used in the investigation. Most of these, except 2-methyl-3-phenyl-5-methylthio-

*P. 12-18
øP. 13

isothiazolium perchlorate 4h, and the 3-chloro-2-methyl-5-phenylisothiazolium perchlorate 4l, had been made before.



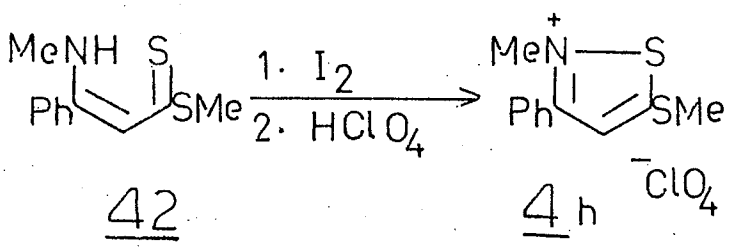
4

	R_1	R_2	R_3	R_4	X
a	H	H	H	Me	ClO_4
b	Ph	H	H	Me	ClO_4
c	Ph	H	H	Ph	ClO_4
d	Ph	Ph	H	Me	ClO_4
e	Ph	H	Ph	Ph	ClO_4
f	Ph	H	SMe	Me	I
g	SMe	Ph	H	Ph	ClO_4
h	SMe	H	Ph	Me	ClO_4
i	H	Ph	H	Ph	ClO_4
j	Ph	Ph	H	Ph	ClO_4
k	H	Ph	H	Me	ClO_4
l	Ph	H	cl	Me	ClO_4

The 2-methylisothiazolium salt 4a had been isolated previously as its iodide[16], either by treatment of the methyltoluene p-sulfonate salt with sodium iodide, or directly when the isothiazole and methyl iodide were allowed to stand at room temperature for 20 days. It is simpler, however, to alkylate the commercially available isothiazole by dimethyl sulfate and isolate the salt as its perchlorate.

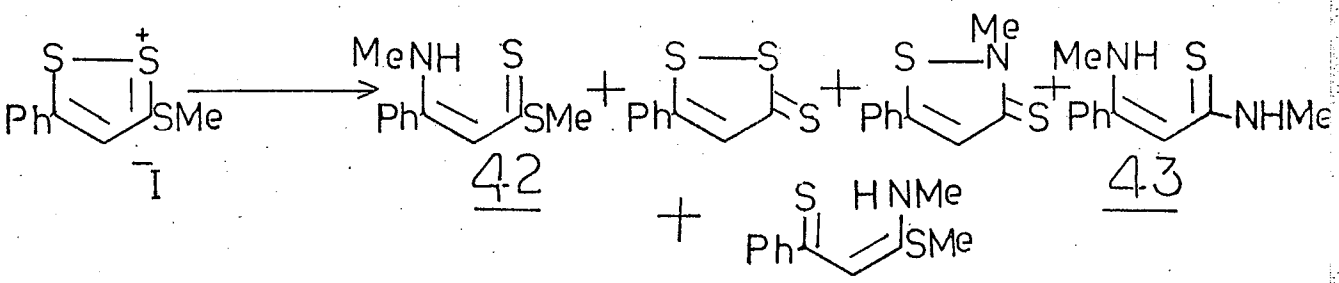
The 2,4-diphenyl-5-methylthioisothiazolium perchlorate 4g was smoothly prepared by alkylation of 2,4-diphenylisothiazoline-3-thione, the reverse of a reaction previously described[29].

The 2-methyl-4-phenyl-5-methylthioisothiazolium perchlorate 4h which was new, was prepared by iodine oxidation of methyl-3-methylaminodithiocinnamate 42 , similar to the known method by McKinnon and Robak[24].



42 4h

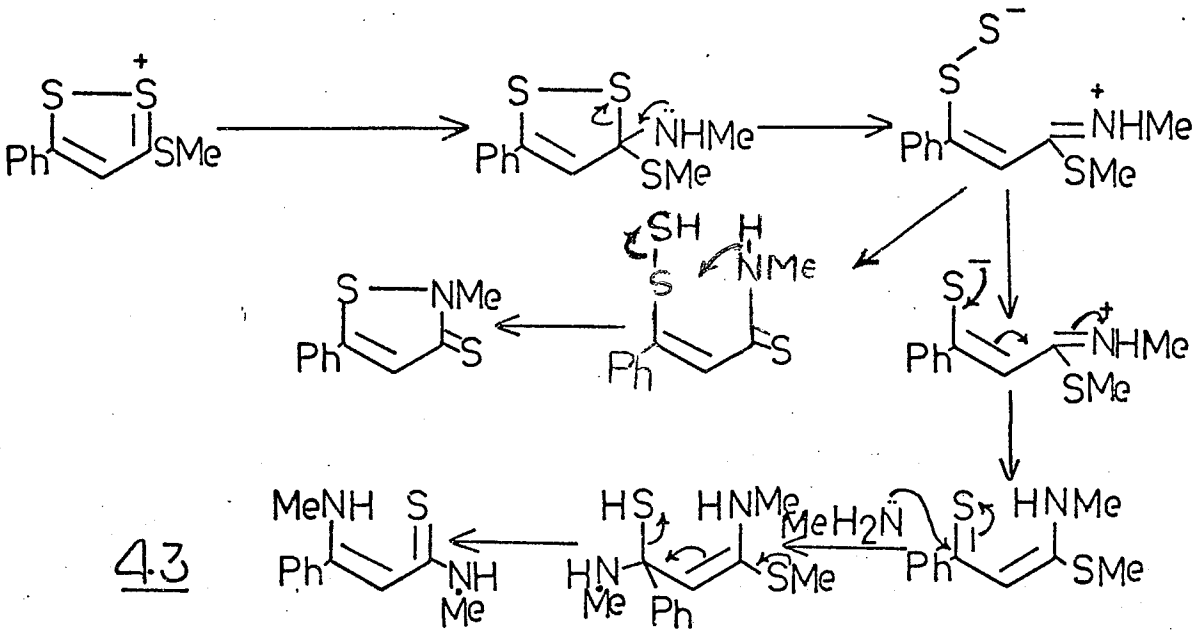
The dithioester 42 was prepared by treatment of 3-methylthio-5-phenyl-1,2-dithiolium iodide with methylamine according to the method of Le Coustumer and Mollier*[27]. It is reported to be accompanied by 2-methyl-5-phenylisothiazoline-3-thione and 5-phenyl-1,2-dithiole-3-thione. Re-investigating the reaction, it was found that the former compound was accompanied by greater or lesser amounts of N-methyl-3-methylaminothiocinnamate 43 , depending on the quantity of methylamine used, and in fact, when a large excess of methylamine was used, the isothiazolinethione was not found and the amide was obtained instead.



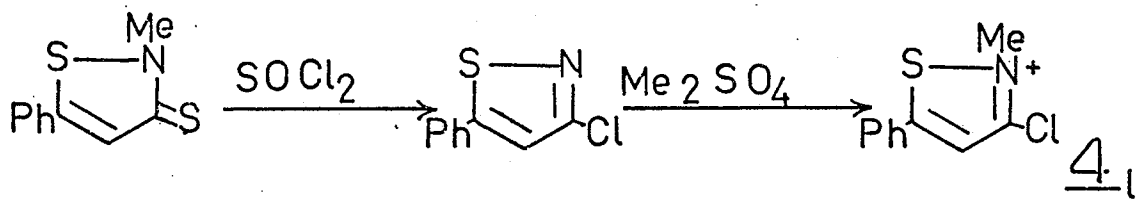
Treatment of the isothiazolinethione with methylamine gave no reaction, suggesting that the thione is not a precursor of the thioamide, and that the latter arises instead through some mechanistic change in the reaction of the dithiolium salt with the amine as shown

* P. 20

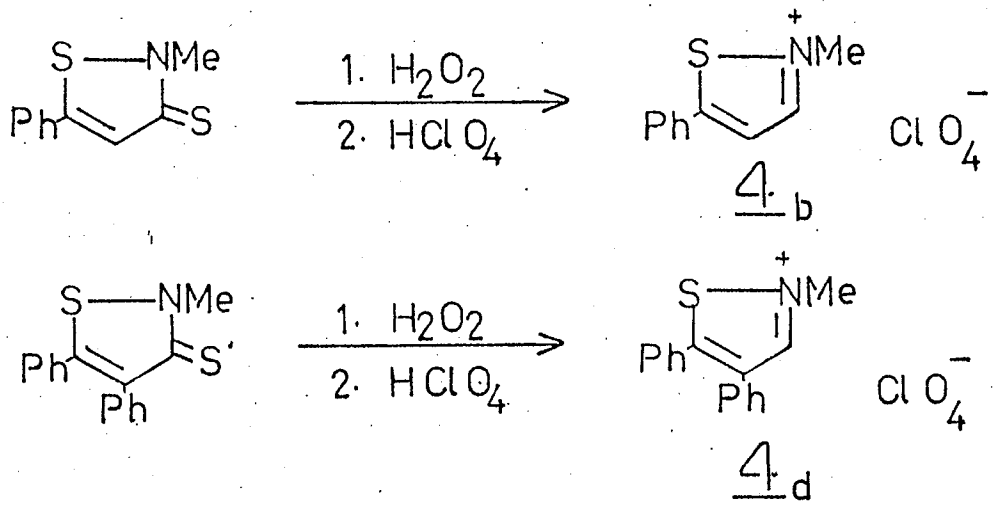
in the following scheme.



The isothiazoline-3-thione from the above reaction was smoothly converted by thionyl chloride into 3-chloro-5-phenyl-isothiazole, which was treated with dimethyl sulfate to afford the isothiazolium cation $\underline{4}_1$, obtained as the perchlorate.

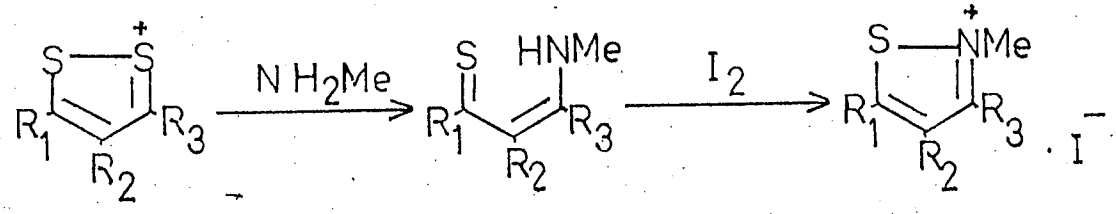


Treatment of the isothiazoline-3-thione obtained above with hydrogen peroxide in acetic acid afforded the 2-methyl-5-phenyl-isothiazolium cation, isolated as its perchlorate $\underline{4}$b. Likewise, 2-methyl-4,5-diphenylisothiazoline-3-thione, prepared by reaction of 3-methylthio-4,5-diphenyl-1,2-dithiolium iodide with methylamine was converted to 2-methyl-4,5-diphenylisothiazolium perchlorate.



These oxidations by hydrogen peroxide in acetic acid are related to reactions of isothiazoline-5-thiones[29], and dithiolethiones[87-90]. Since N-alkylisothiazolium salts can be de-alkylated to isothiszoles[48], the reaction would represent another synthesis of these from dithiolium salts, although this was not studied here.

The salts obtained by the above method were identical to ones prepared by methylation of isothiazoles*[29], and by another method through the treatment of 1,2-dithiolium salts with methylamine to form β-methylaminopropenthiones[91]. Iodine oxidation was then carried out to obtain the N-methylisothiazolium salts 4b , 4d isolated as perchlorate.



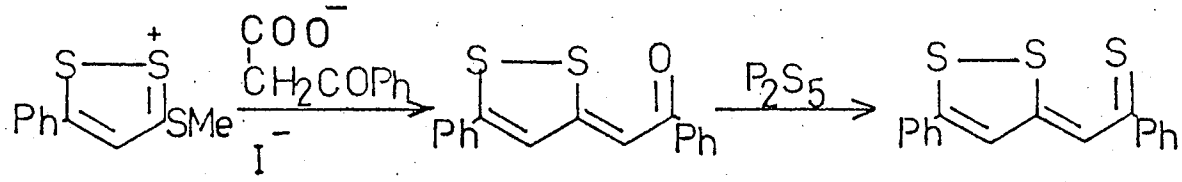
Yields by this last method were rather poor, comparable to one such

* P. F

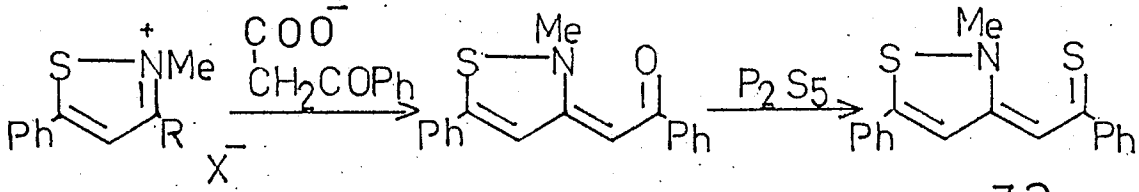
reaction previously studied by McKinnon and Robak[24], but it does at least represent a quick synthesis of N-alkylisothiazolium salts from the readily accessible 1,2-dithiolium salts.

REACTION OF ISOTHIAZOLIUM SALTS WITH SODIUM BENZOYLACETATE

Trithiapentalene precursors (3-acylmethylene-1,2-dithioles) have been prepared[92] via the nucleophilic attack of sodium benzoylacetate on 3-methylthio-5-phenyl-1,2-dithiolium iodide.



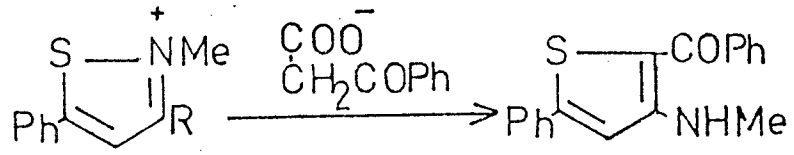
Isothiazolium salts with good leaving groups at the 3-carbon atom were initially expected to undergo the same reaction to afford compound 32.



32

R = good leaving group

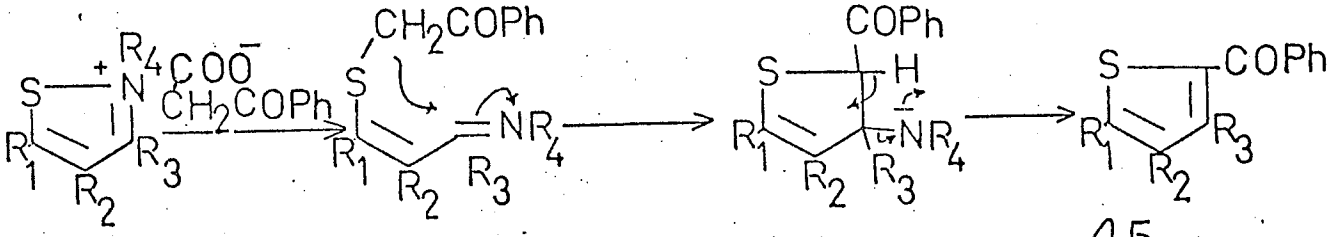
Both 3-methylthio- and 3-chloro-5-phenylisothiazolium perchlorate were allowed to react with sodium benzoylacetate in boiling ethanol. Methyl mercaptan and carbon dioxide were evolved, and in both cases the solution, on evaporation, yielded mainly 3-methylamino-2-benzo[illegible]phenes 44, as proved by NMR spectra and elemental analysis



R=Cl or SMe

44

In fact treatment of all the other isothiazolium salts 4 with sodium benzoylacetate yielded 2-benzoylthiophenes 45 in all cases. The formation of these can be explained by nucleophilic attack of a phenacyl ion (actual or potential) derived from the sodium benzoylacetate on ring sulfur, to give ring opening. This is followed by attack of the activated methylene group on the imine function to give recyclization to thiophenes.



45

The fact that isothiazolium salts 4e , 4f , and 4h underwent this reaction excluded the possibility of an initial deprotonation as a proper mechanism for this reaction, since, in these three cations, both the 3 and 5 positions carry substituents.

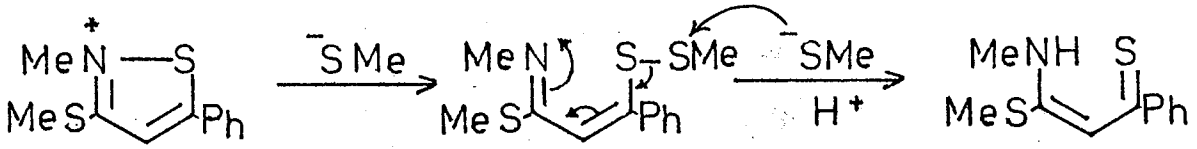
The results from the 3-chloro and 3- or 5-alkylthioisothiazolium cations, 4e , 4f , 4g , and 4h*, are especially striking. By analogy with other related heterocyclic systems, had nucleophilic attack occurred at carbon 3 or 5 , acylmethyleneisothiazoles would have been expected, as shown earlier.

In all cases, except where carbon 3 carries chloro or alkylthio

* P. 38

substituent, cyclization occurs by loss of amine, but in these two cases, 4e and 4f , the better leaving group chloride or methylthiolate anion is lost instead, with formation of a 3-amino-2-benzoylthiophene 44 . The retention of the amino function in this position indicates clearly the inability of the nucleophilic attack on carbon to explain this reaction.

In case of the 3-alkylthioisothiazolium salt 4f , an acyclic reduction product 46 was obtained in (15%) yield.
This could have arisen by reaction of eliminated methanethiolate ion with another molecule of starting isothiazolium cation, either by reduction, or by nucleophilic attack. Similar products have been obtained for the attack of benzenethiol[38] or benzenethiolate anion on isothiazolium salts as will be discussed below.



46

It was obvious from these studies that direct attack of a phenacylidene group precursor on isothiazolium salts would take place at the sulfur atom and therefore be of no use in the preparation of 3-thioacylmethyleneisothiazole system 32 . However, as will be seen later, it was possible to make use of steric and reactivity factors to obtain suitable precursors from isothiazolium salts.

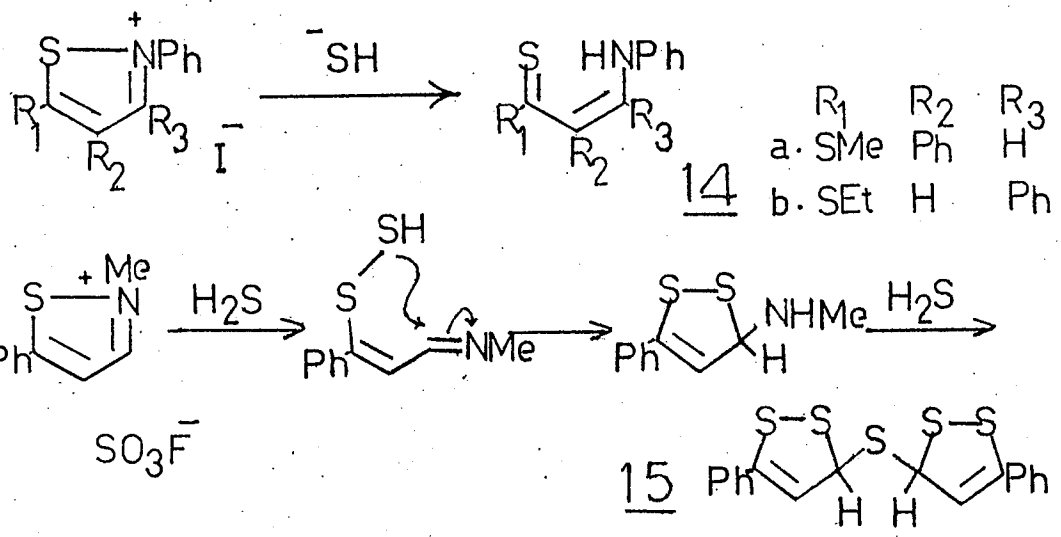
REACTION OF ISOTHIAZOLIUM SALTS WITH HYDROGEN SULFIDE AND HYDROSULFIDE ION

The attack of hydrosulfide ion on two alkylthioisothiazolium salts in ethanol was reported*[29] to afford the reduction product 14 .

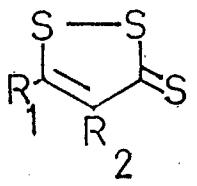
*P. 16

This could be rationalized as occurring by a route similar to that leading to 46 above.

Sykes and Ullah*(38), however, found that attack of hydrogen sulfide on the isothiazolium system in aqueous solution gave bis-1,2-dithiol-3-yl sulfide 15 instead of the reduction products 14 .



Accordingly, a number of isothiazolium salts were treated with hydrosulfide ion in ethanol or hydrogen sulfide in water, and the products examined. Little if any difference was found in the reaction products derived from either method (see table 2) , and the course of the reaction appears to depend mainly on whether the original isothiazolium cation is N-aryl or N-alkyl substituted. The former give mainly reduction products, β-aminopropenethione or derivative 14 , while the latter give reduction, bis-1,2-dithiol-3-yl sulfides 15 , or the dithiole-3-thione 47 .

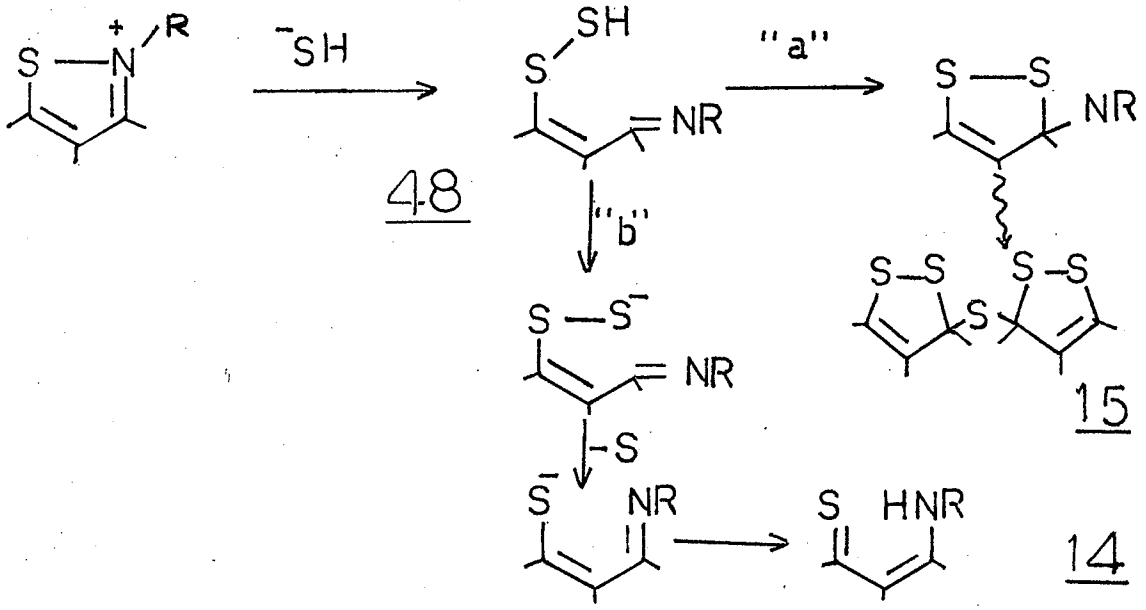


47

a. R_1= H , R_2= Ph
b. R_1= Ph, R_2= H

The differences in the products obtained probably arise from changes in the mechanism shown in the following scheme.

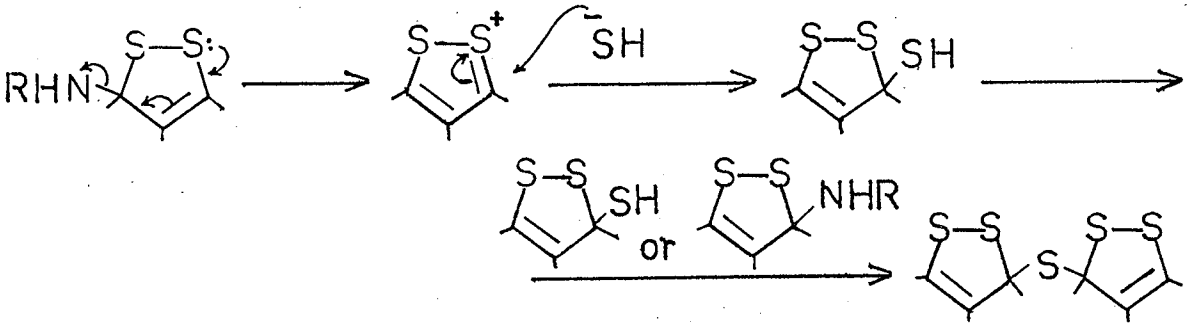
*P. 17



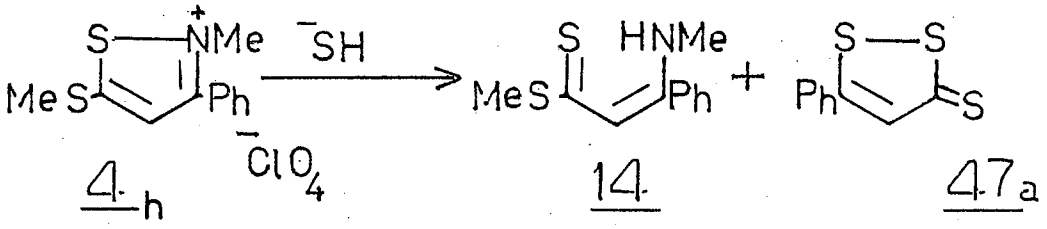
The intermediate disulfide imine 48 could either add to the imine group (path "a") to give an aminodithiole with eventual formation of a bis-dithiolyl sulfide, or extrude sulfur (path "b") to give a β-aminothione derivative.

For aliphatic imines 48 , the former would be the preferred route, but where the imine is stabilized by conjugation with an aromatic ring, the latter would be preferred leading to an acyclic reduction product. Path "a" is analogous to a step in the formation of 1,2-dithiolium salts from 1,3-diketones with hydrogen disulfide in acidic media[90], while path "b" is analogous to steps in the known reactions of 1,2-dithiolium salts with bases, particularly with primary aromatic amines[11].

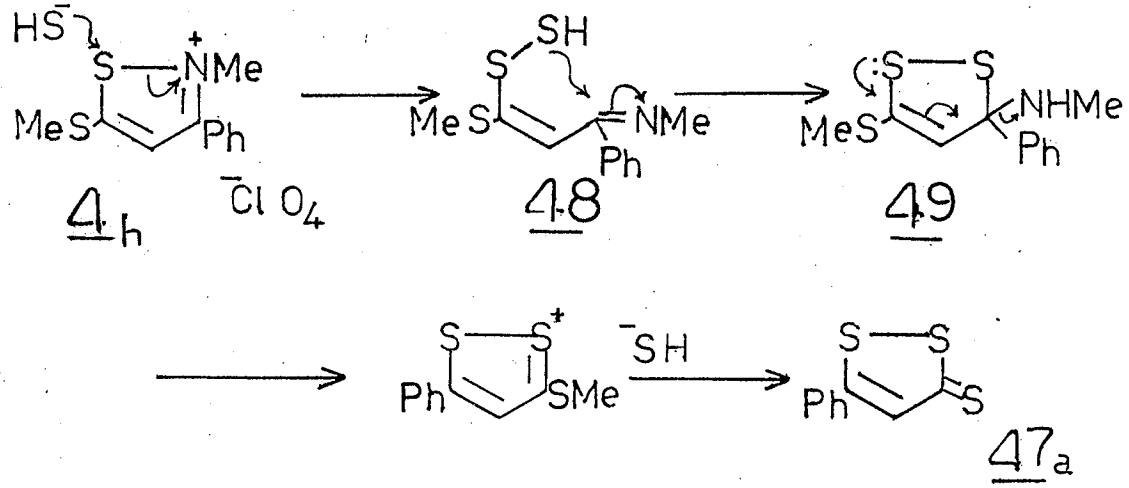
In path "a" , the conversion of the aminodithiole to the sulfide could be accomplished by nucleophilic exchange between the aminodithiole and hydrogen sulfide, as has been suggested[11] for reactions of 1,2-dithioles. Intermediate formation of a 1,2-dithiolium cation[38] may be involved.



With the salt 2-methyl-5-methylthio-3-phenylisothiazolium perchlorate 4h , the acyclic product 14 was obtained. The other product isolated was not a bis-ditholyl sulfide 15 , but was 5-phenyl-1,2-dithiole-3-thione 47a .

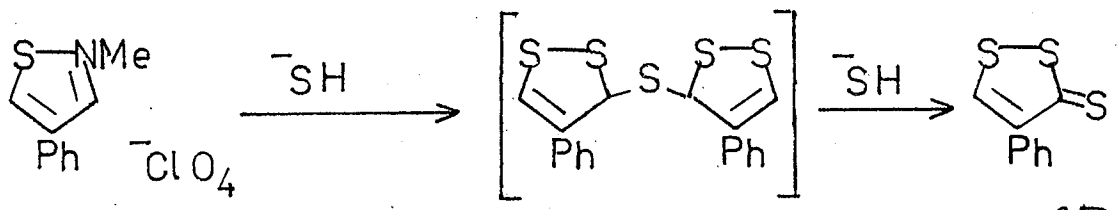


While the exact mechanism leading to this is unknown, it is not unreasonable that it could be derived from a compound of the type 49 formed by cyclization of the intermediate disulfide 48 suggested in the scheme above.

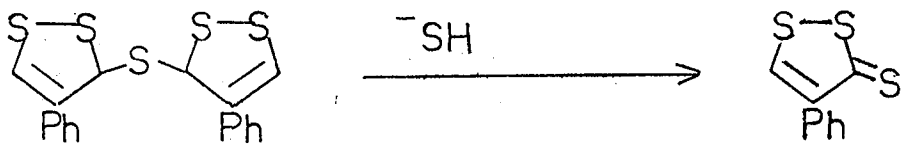


The reactions leading to the formation of 47b and 47a from 2-methyl-3-methylthio-5-phenylisothiazolium iodide 4f , and 2,4-diphenyl-5-methylthioisothiazolium perchlorate 4g , likely follow a similar scheme.

The isolation of only the thione 47a from the reaction of 2-methyl-4-phenylisothiazolium cation 4k , instead of a disulfide 15b , presents some difficulty. However, the thione does appear to be derived from the sulfide. To verify this, the sulfide was prepared from the reaction of 4-phenyldithiolium salt with hydrogen sulfide[94]. It was separated from the thione obtained as a co-product during its preparation, and was subjected to prolonged treatment with hydrogen sulfide or sodium hydrosulfide to give the thione 47a .



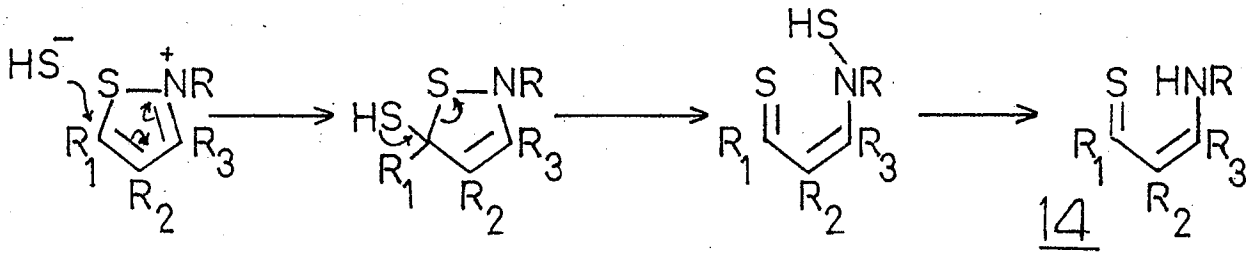
47a



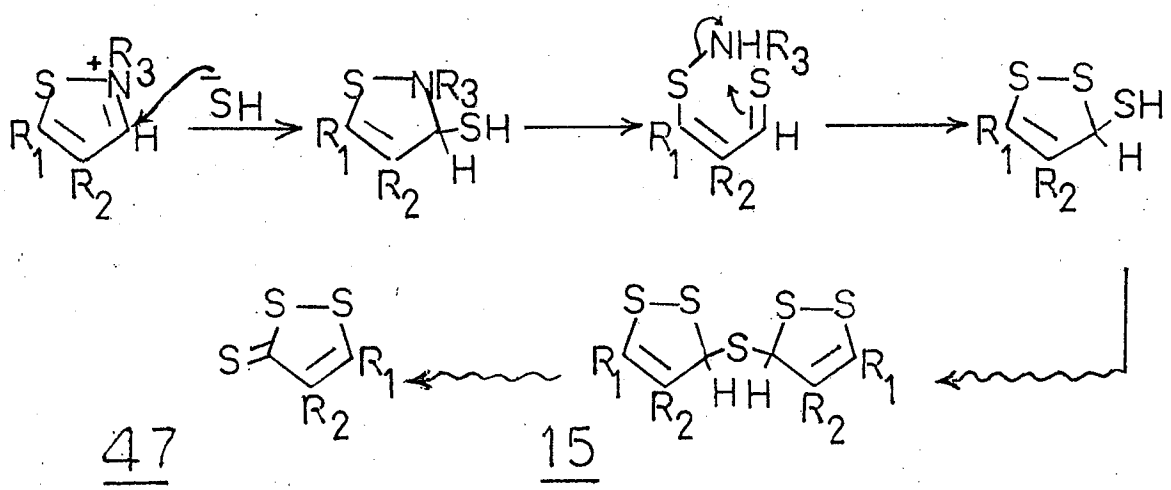
47a

During the discussion of nucleophilic attack of hydrogen sulfide or hydrosulfide ion on the isothiazolium cations, only the possibility of nucleophilic attack on the ring sulfur was mentioned, and that was also the case in the study carried out by Sykes and Ullah[38]. Although that proved satisfactory to explain all the products, a discussion

of the other possible mechanisms is due. The initial deprotonation mechanism (mechanism "a" in Landesberg and Olofson)[23] could not be in operation since cations lacking both 3 and 5 protons were found to be as reactive as those carrying such protons and give comparative yields. On the other hand, nucleophilic attack on carbon 5 , has been suggested by Bachers[33] as a possible mechanism to explain the formation of the acyclic product 14 .



Nucleophilic attack on carbon 3 could also be used to explain the formation of the sulfide 15 and subsequently the thione 47 .



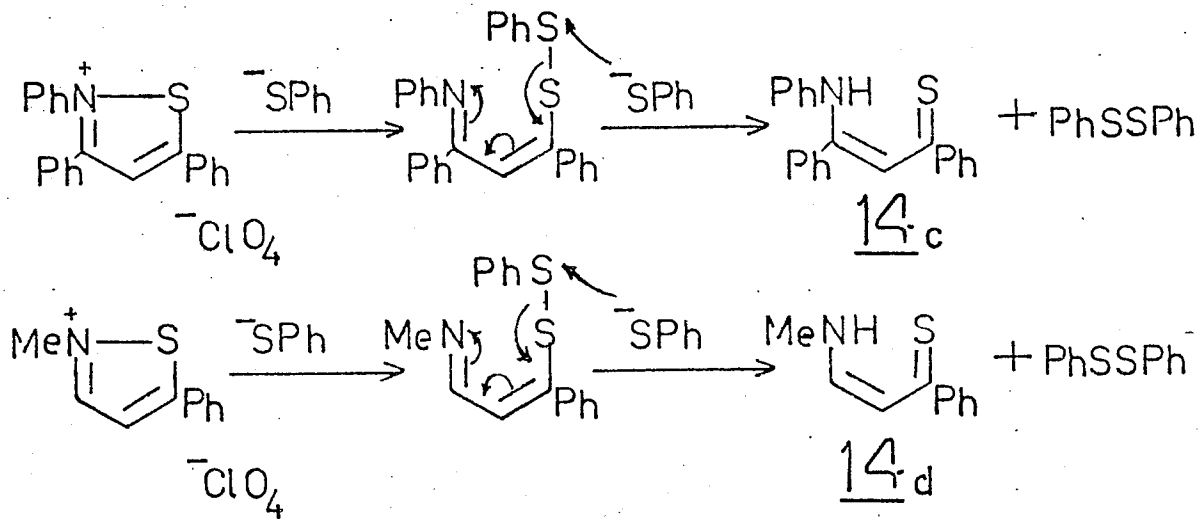
Whether the isothiazolium cation would react by nucleophilic attack at carbon 3 or 5 would depend on a combination of steric and electronic factors. Coulombic factors would indicate attack at carbon 3

next to nitrogen, but undoubtedly, steric factors must also be important. N-aryl compounds would then undergo nucleophilic attack at carbon 5 (less steric interference by sulfur) more than N-alkyl groups except possibly N-tertiary butyl.

Although it seems possible to explain the formation of the reaction products equally by nucleophilic attack on sulfur as on carbon, the only reason for this ambiguous situation remaining is the difficulty in differentiating the products between the sulfur derived from the original isothiazolium ring and that from the attacking hydrogen sulfide.

REACTION OF ISOTHIAZOLIUM SALTS WITH SODIUM BENZENETHIOLATE

Treatment of 2, 3, 5-triphenylisothiazolium perchlorate 4e , and 2-methyl-5-phenylisothiazolium perchlorate 4b with sodium benzenethiolate in ethanol gave the acyclic reduction products 14 , and diphenyl disulfide. These results are comparable to other such studies made by Sykes and Ullah*(38). Compound 14 seems to be formed either by nucleophilic attack on the ring sulfur or alternatively through a redox type (electron transfer) mechanism.



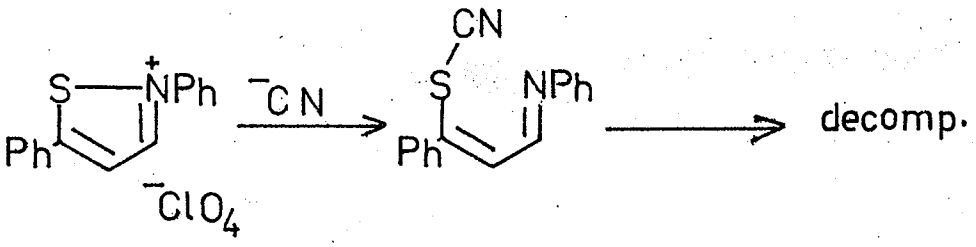
* P. 17

The reaction of the first cation demonstrates clearly that initial deprotonation mechanism is not involved. While the second cation shows that nucleophilic attack at carbon need not necessarily be involved in this reaction (and similarly in the reaction with hydrogen sulfide or hydrosulfide) since in this case nucleophilic attack would be favoured at carbon 3, and in such case the compound 14d would not be the right product.

It was now desired to study the effect of other commonly available nucleophiles on isothiazolium salts to determine their synthetic utility.

REACTION WITH SODIUM CYANIDE

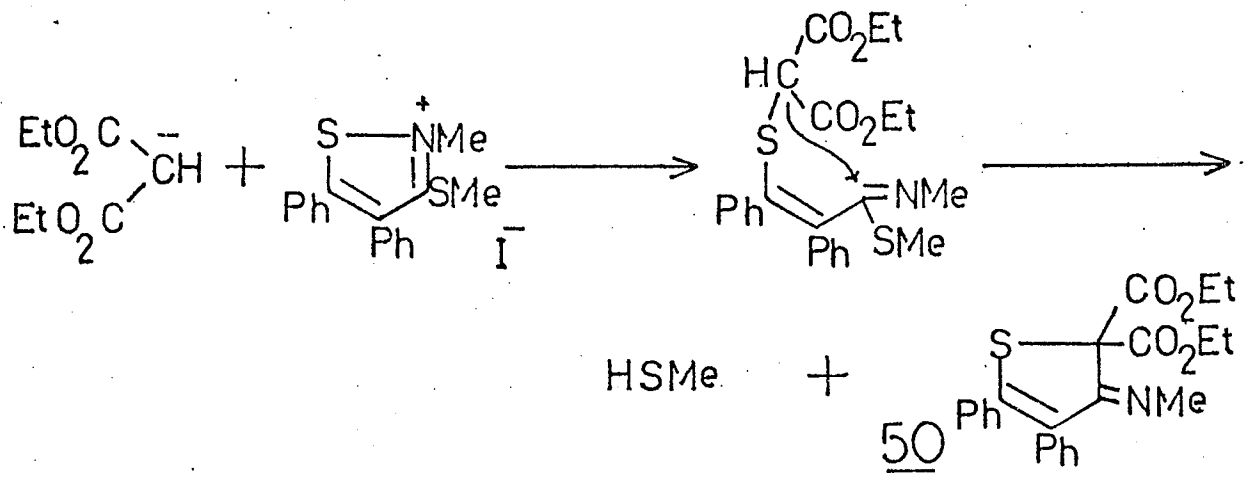
Treatment of 2,5-diphenylisothiazolium perchlorate with sodium cyanide in ethanol afforded several bands of unidentified decomposition products.



This did not appear to be very promising and the approach was abandoned.

REACTION WITH SODIODIETHYLMALONATE

The 2-methyl-3-methylthio-4,5-diphenylisothiazolium iodide, on treatment with sodiodiethylmalonate in ethanol, afforded the 3-iminothiophene derivative 50.

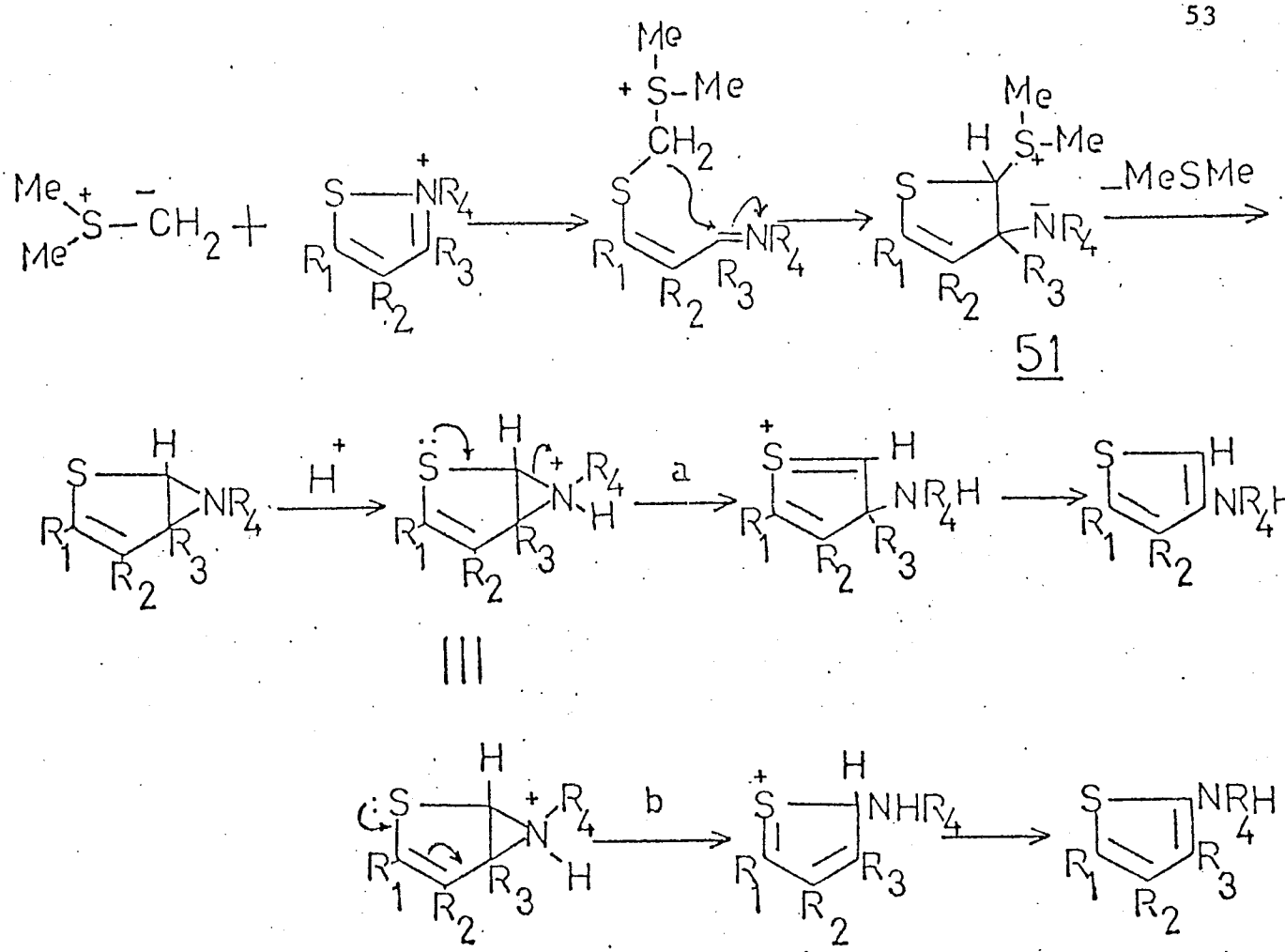


The reaction seems to follow a route similar to that of the reaction of isothiazolium salts with sodium benzoylacetate, nucleophilic attack of diethyl malonate anion on the ring sulfur to give ring opening, followed by attack of the activated methylene group on the imine function to give recyclization to the thiophene, with the elimination of methanethiolate ion.

Neither nucleophilic attack on carbon, nor initial deprotonation mechanisms could explain the formation of 50 . Compound 50 could be of some synthetic potential . However, the fact that this reaction requires a good leaving group at carbon 3 limits the synthetic utility of the reaction. The importance of the reaction lies in the fact that it is another demonstration that the nucleophilic attack of carbon nucleophiles takes place at the ring sulfur.

REACTION WITH SULFONIUM YLIDS

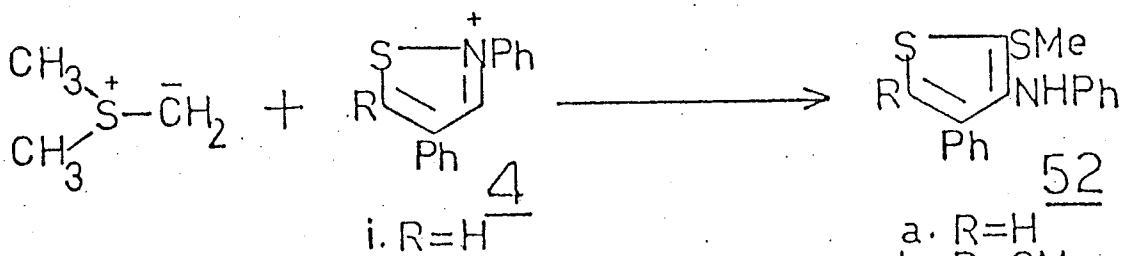
Dimethylmethylenesulfurane was initially expected to react with isothiazolium cations according to the following scheme to afford 3-amino, or 2-aminothiophenes depending on the substituent R_3 . If it is hydrogen the reaction may take path "a" to afford a 3-aminothiophene, otherwise path "b" would be preferred leading to a 2-aminothiophene.



51

III

However it was of interest to find that the reaction does not exactly follow the above scheme. 3-Unsubstituted isothiazolium salts indeed afforded 3 aminothiophenes as expected. However these were found to carry methylthio groups on carbon2, as proved by NMR and mass spectra. Thus 2-methylthio-4-phenyl-3-anilinothiophene, 52a , and 2,5-dimethylthio-4-phenyl-3-anilinothiophene, 52b , were obtained from the reaction of 2,4-diphenylisothiazolium salt 4i , and 5-methylthio-2,4-diphenylisothiazolium salt 4g , respectively.



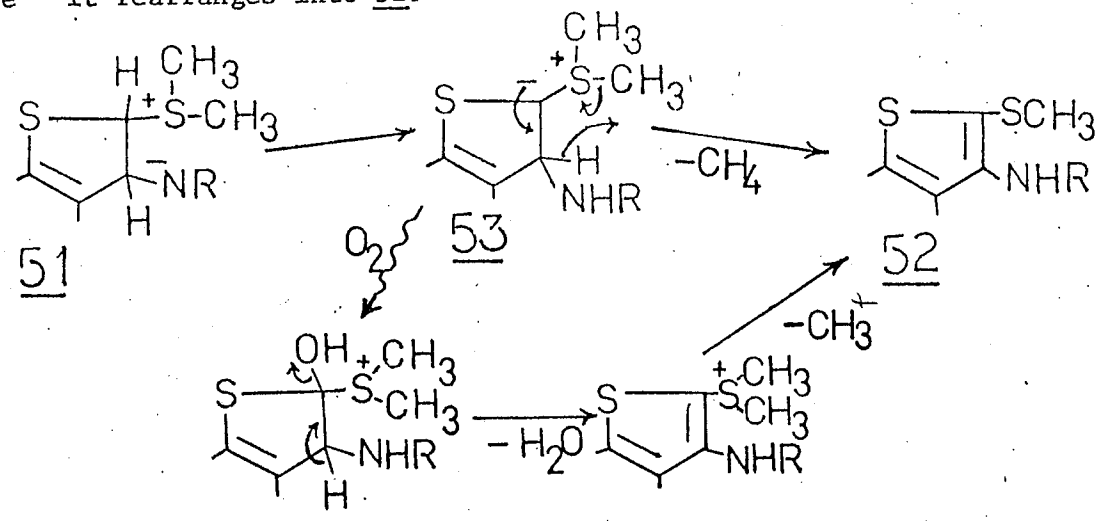
4

i. R=H
g. R=SMe

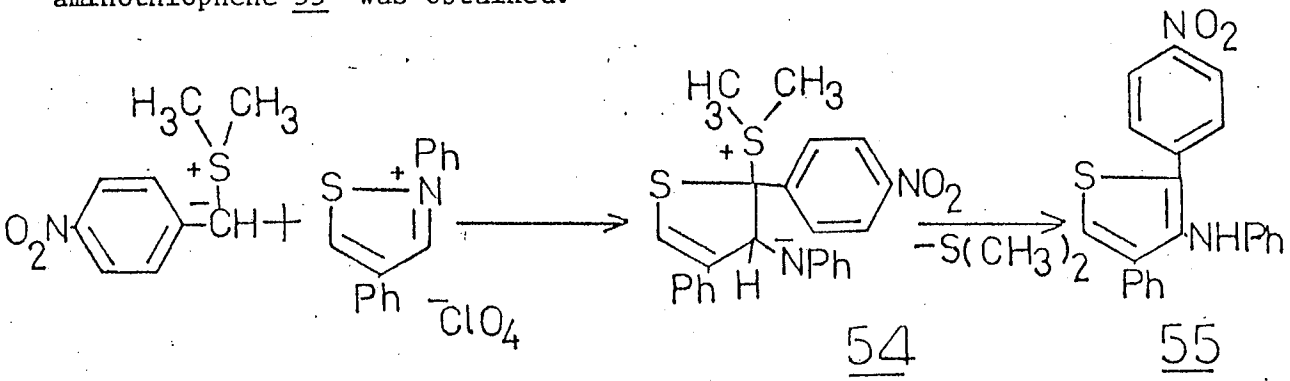
52

a. R=H
b. R=SMe

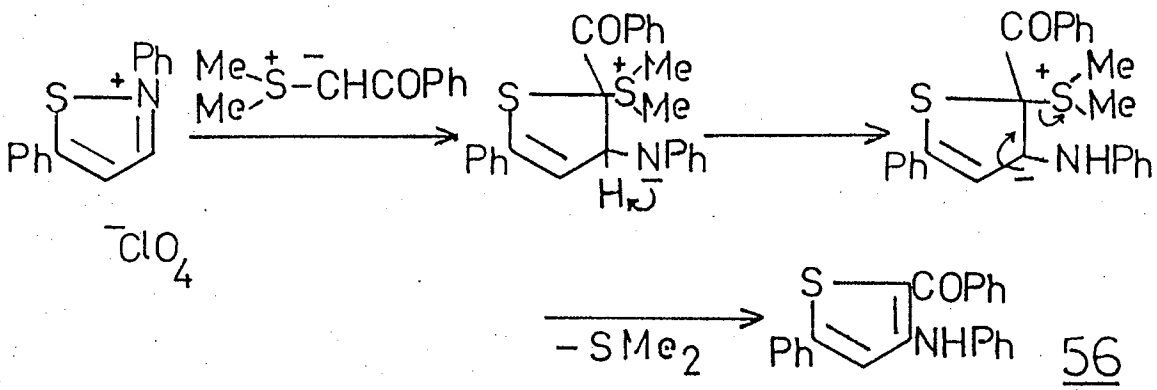
A possible mechanism for the formation of 52 would involve the intermediate 51 , which, instead of extruding dimethyl sulfide, actually undergoes deprotonation to form a second sulfonium ylid 53 , which undergoes rearrangement, and loss of methane, into 2-methylthio-3-aminothiophenes 52. Alternatively, the intermediate 53, may undergo oxidation before it rearranges into 52.



When substituted sulfonium ylids such as p-nitrobenzylidenedimethylsulfurane, were allowed to react with 2,4-diphenylisothiazolium salt 4i , an intermediate 54 equivalent to the intermediate 51 probably was formed. However in this case, because of lack of hydrogen at carbon 2 , no second ylid could be formed and the correspondingly substituted 3-aminothiophene 55 was obtained.

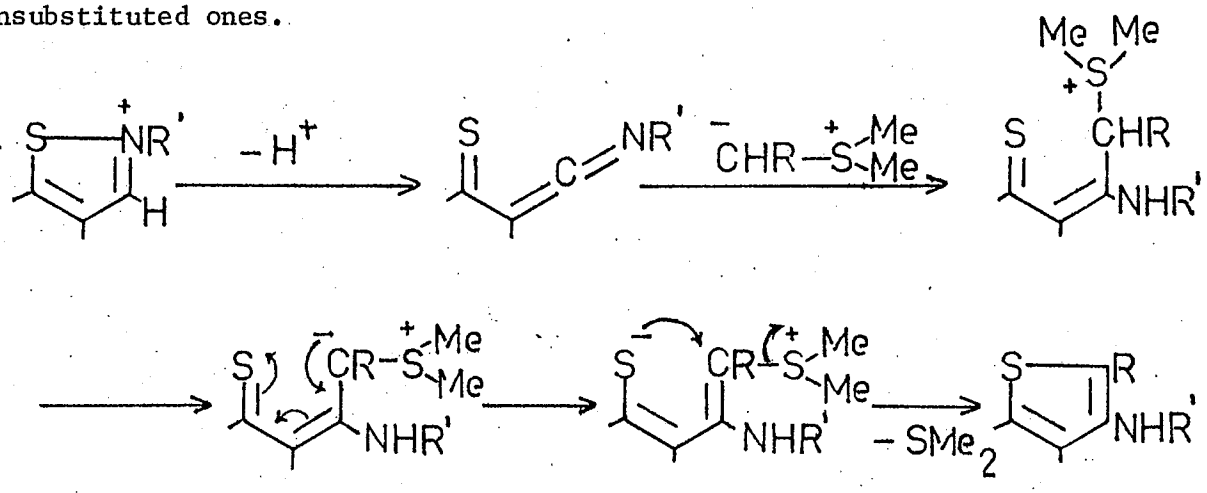


It was also found that α-keto substituted sulfonium ylids reacted similarly to afford the 2-ketosubstituted-3-aminothiophenes.



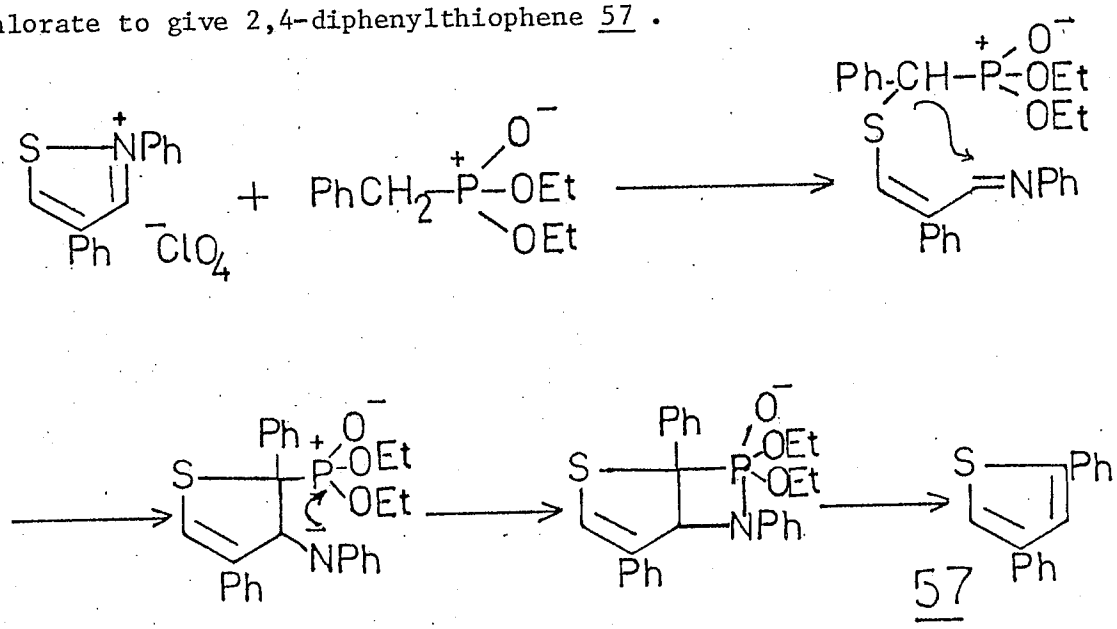
The 2-benzoylthio-3-aminothiophene 56 , obtained from this reaction, was identical to the ones obtained from the reaction of sodium benzoylacetate with certain isothiazolium salts discussed earlier. It is thus a method of making 2-acyl-3-aminothiophenes without the necessity of preparation of 3-alkylthioisothiazolium salts, for which methods of syntheses are unsatisfactory. Compounds 56 were found to be of interesting synthetic utility as will be discussed later in the preparation of thienoisothiazolium salts.

As was the case in the reaction with sodium benzoylacetate the retention of the amino group in the product eliminates the possibility of nucleophilic attack on carbon 3 as a probable mechanism. The mechanism of initial deprotonation could be used to explain the formation of the products obtained from the reactions of substituted ylids as shown in the mechanism below, but is not valid for the reaction of the unsubstituted ones.

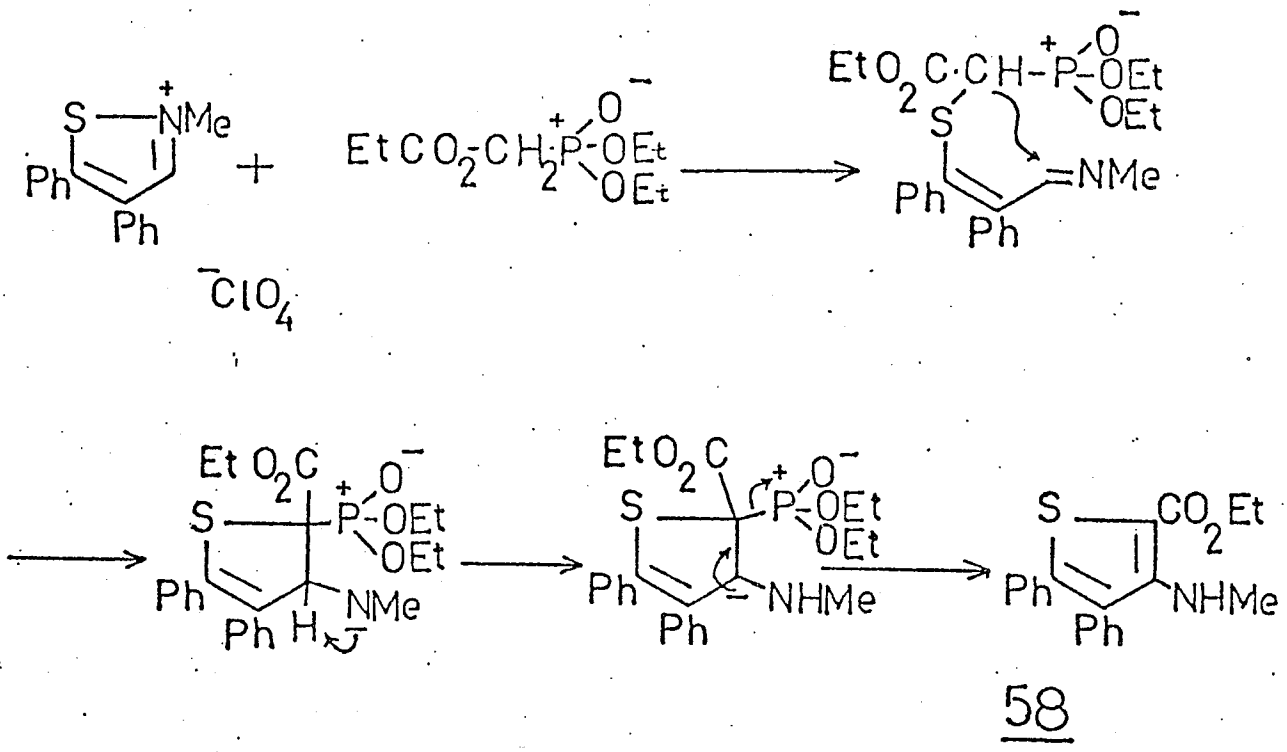


REACTION WITH WITTIG REAGENTS

As expected, the reaction followed the same pattern for most reactions described so far, i.e. nucleophilic attack on the ring sulfur followed by ring opening. Attack of the activated methylene group on the imine function then leads to recyclization into thiophenes. Thus diethyl benzylphosphonate reacted with 2,4-diphenylisothiazolium perchlorate to give 2,4-diphenylthiophene 57 .



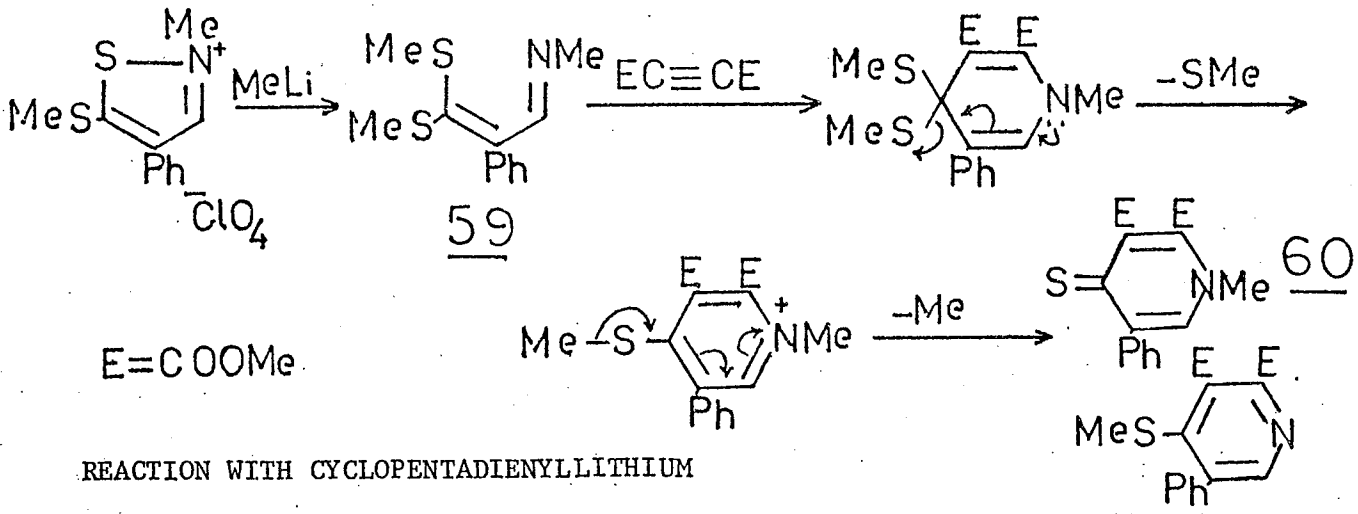
However, use of ethoxycarbonylmethyldiethyl phosphonate on 2-methyl-4,5-diphenylisothiazolium perchlorate, gave a 3-aminothiophene ester. The elimination thus appears to proceed via an alternative mechanism. The reason for this is not clear but may represent the difference in stability in the different possible aminophosphorus species.



While it is possible to explain the formation of diphenylthiophene 57 , through nucleophilic attack at carbon 3 , this is not the case with the aminothiophene derivative 58 .

REACTION WITH METHYLLITHIUM

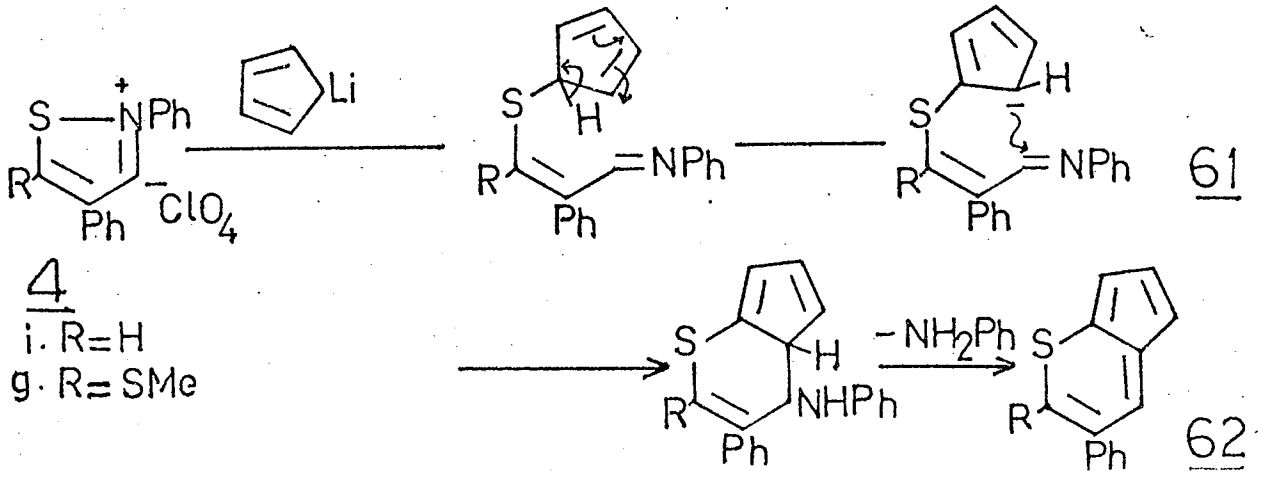
The nucleophilic attack of methyllithium on 2-methyl-4-phenyl-5-methylthioisothiazolium salt in anhydrous ether appears to take place on the ring sulfur leading to the acyclic propene derivative 59 . This was unstable and attempted isolation led to hydrolysis and decomposition. However performing the reaction under nitrogen and treating 59 in situ with dimethyl acetylenedicarboxylate gave a small amount of material whose mass spectrum corresponds to the adduct 60 or its isomer. The reaction proceeds with too low a yield to be of any synthetic value.



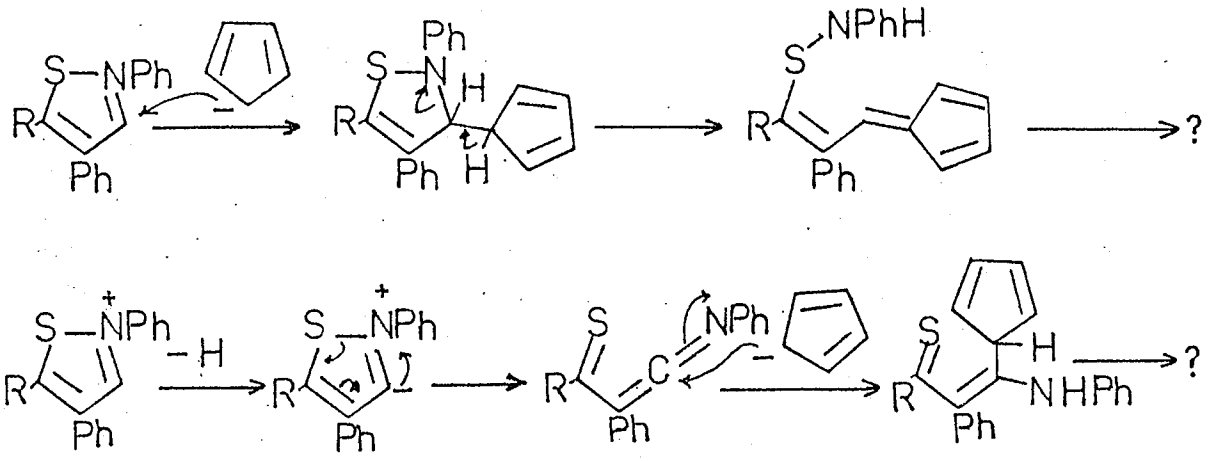
REACTION WITH CYCLOPENTADIENYLLITHIUM

Treatment of 2,4-diphenyl isothiazolium cation 4i , or 5-methylthio-2,4-diphenyl isothiazolium cation 4h , with cyclopentadienyllithium afforded pseudoazulene derivatives 62 , as deep blue-black crystalline material. The structure of these was proved by its NMR spectra which was comparable to that of azulenes , (for more details see the experimental section) , by its mass spectra and elemental analysis.

The formation of pseudoazulenes can be explained by initial nucleophilic attack on the ring sulfur which led to ring opening. Loss of a proton from the cyclopentadiene ring and rearrangement affords the intermediate 61 . Attack of the cyclopentadienyl moiety on the imine function leads to recyclization, aromatization is then gained by loss of aminogroup and adjacent hydrogen atom to afford the pseudoazulene 62 as shown in the scheme below.

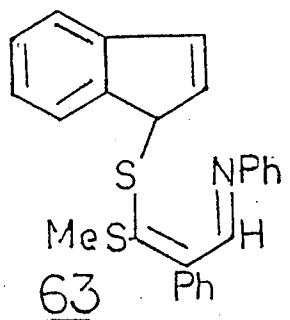


It is worth noting that formation of 62 , could neither be explained through nucleophilic attack on carbon 3, nor through an initial deprotonation mechanism, since in both cases an acyclic product would be formed which will not likely recyclize to pseudoazulene.

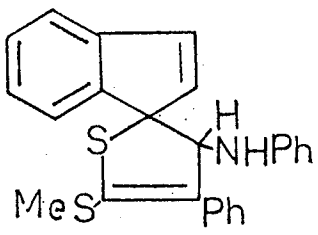


REACTION WITH THE INDENYL ANION

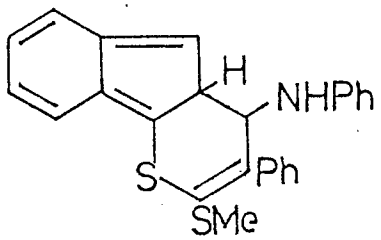
The reaction of 2,4-diphenyl-5-methylthioisothiazolium perchlorate with the indenyl anion, carried out in anhydrous ether under nitrogen, afforded a compound of molecular weight 399 . Three structures could be assigned to such compound, supposing that it is formed through nucleophilic attack on the ring sulfur similar to the reaction with cyclopentadiene anion. These structures are: the open chain structure 63 , the spiro compound 64 , and the aminopseudoazulene structure 65 .



63

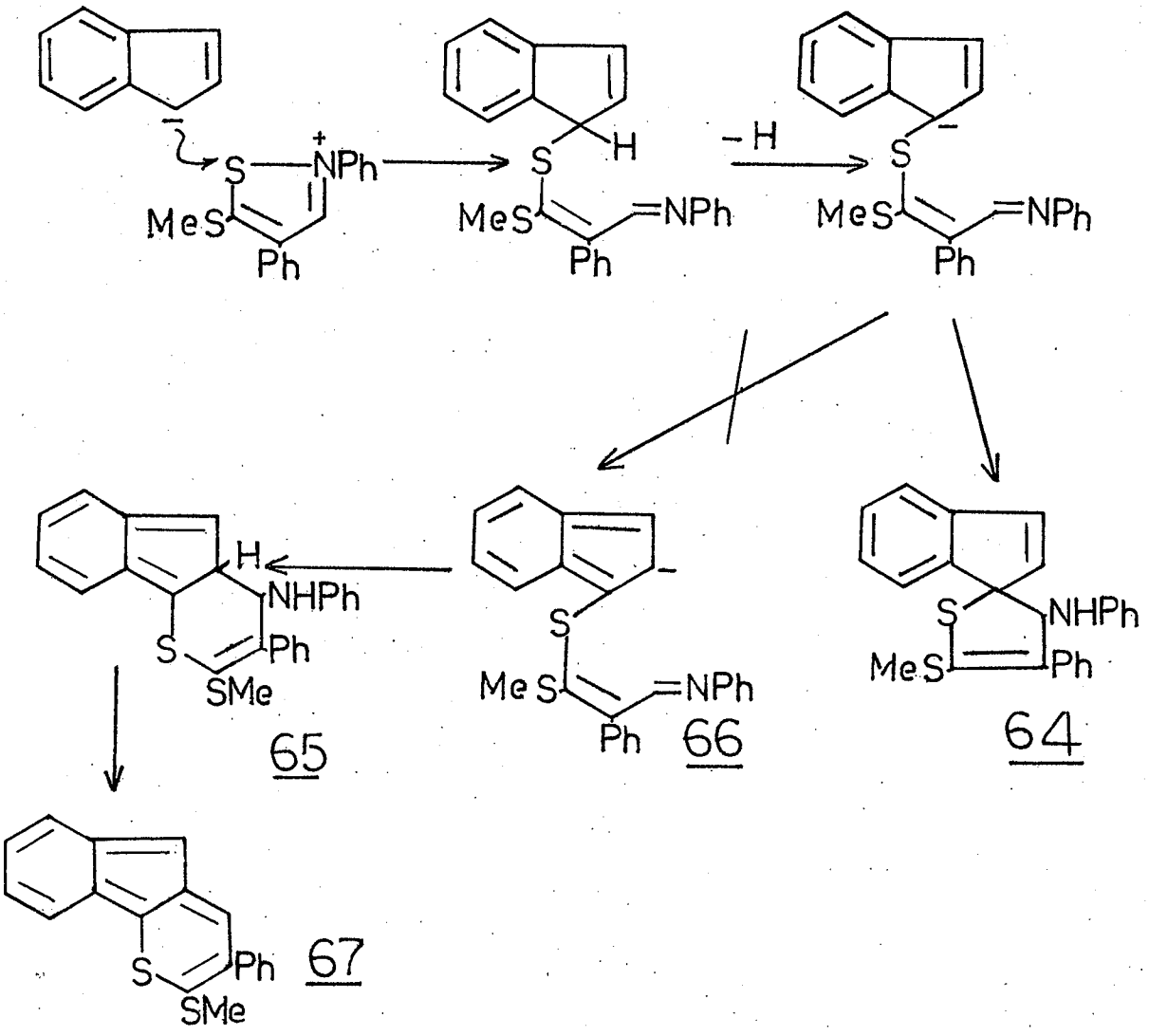


64



65

The first structure 63 was excluded on the basis that the second peak in the mass spectrum was 367 , corresponding to a loss of sulfur atom; such a loss could not be afforded by structure 63 without breaking into parts. The presence of N-H peak in the I.R. Spectrum (frequency 3500 cm^{-1}) also helps to exclude structure 63 . On the other hand, structure 65 is less favored than 64 since an o-quinonoid intermediate 66 would be necessary in its formation, and even if it is formed, it would be expected to lose the amino group and adjacent hydrogen to form the aromatic structure 67 , similar to 62 obtained in the reaction with cyclopentadiene anion. However the relatively low yield of the reaction discouraged further investigations.

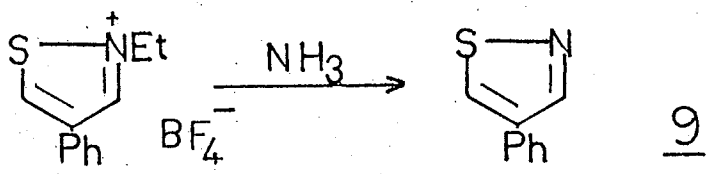


GENERAL DISCUSSION ON NUCLEOPHILIC ATTACK ON ISOTHIAZOLIUM SALTS

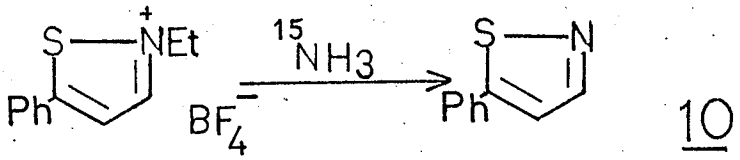
The previous results demonstrate clearly that the nucleophilic attack of sulfur nucleophiles and carbon nucleophiles do take place at the ring sulfur atom (mechanism "d" of Landesberg and Olofson)[23].

Nitrogen nucleophiles has not been included in this study, however the two reports[23],[38] about the subject agree that it takes place at carbon 3, and to a lesser extent, at carbon 5. A few points in these reports need to be discussed briefly in the following.

The nucleophilic attack of ammonia on isothiazolium salts[23] gave a higher yield of isothiazole 10 rather than 9 .



9

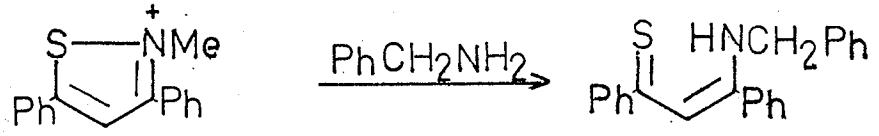


10

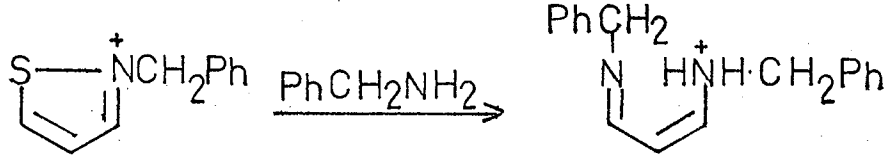
The authors argue that nucleophilic attack at carbon may be preferred to nucleophilic attack at sulfur, Assuming steric factors are the most important in determining the relative rates of these reactions, the sulfur atom in the second reaction is more sterically hindered and therefore was expected to give a lower yield of 10 if the attack takes place at sulfur. However, the lower yield of 9 may as well be a result of the

steric effect of the phenyl group at the carbon 4 on the nucleophilic attack at carbon 3. Moreover the absence of a substituent on carbon 5 would increase the probability of the less favoured nucleophilic attack at carbon 5, which tends to reduce the yield of 9 . This effect is more noticeable with increasing the size of the substituent on the nitrogen.

Sykes and Ullah[38] reported that while 2-methyl-3,5-diphenylisothiazolium cation reacted with benzylamine to form benzylaminothiones 68 resulting from nucleophilic attack on carbon 3, the 4,5 unsubstituted 2-benzylisothiazolium cation, on the other hand, afforded the dianil salts 69 obtained from preferential attack at carbon 5. No explanation was given for this alteration of the reaction mechanism. However it seems that the large substituent on the nitrogen in the second case allowed the less favoured attack on carbon 5 to become the predominant reaction.

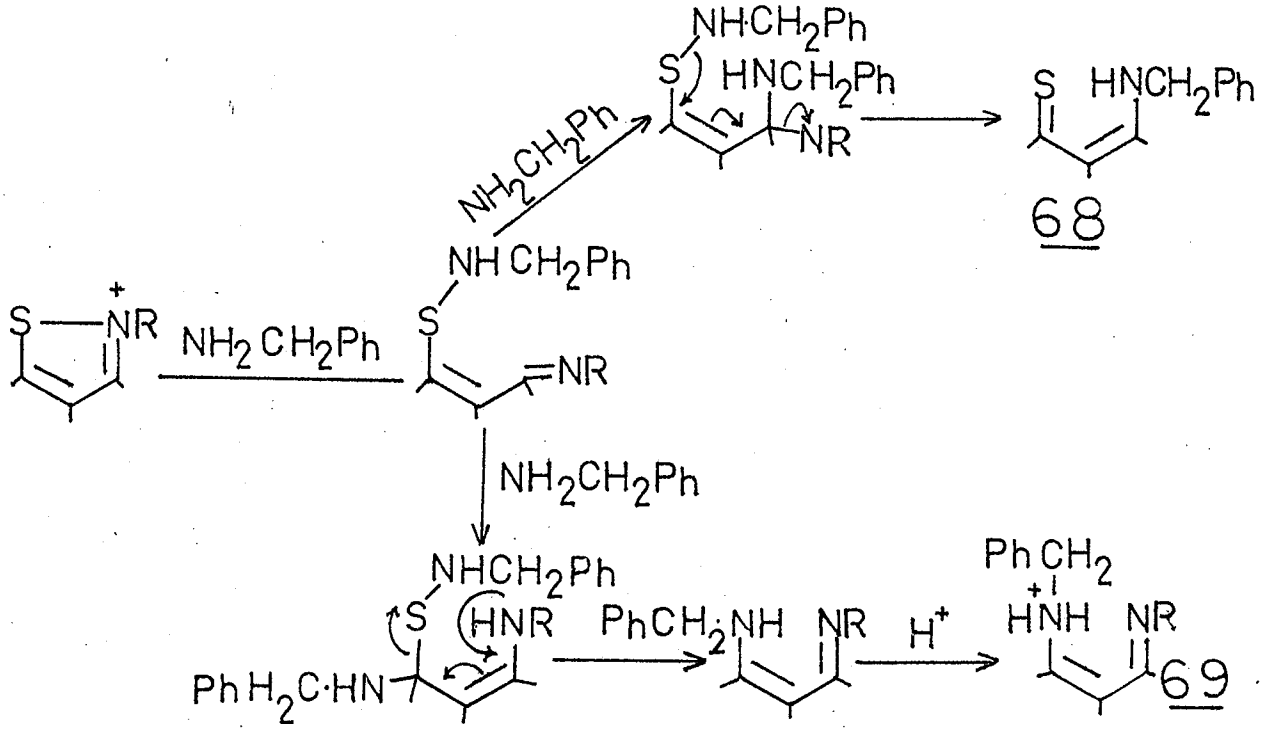


68

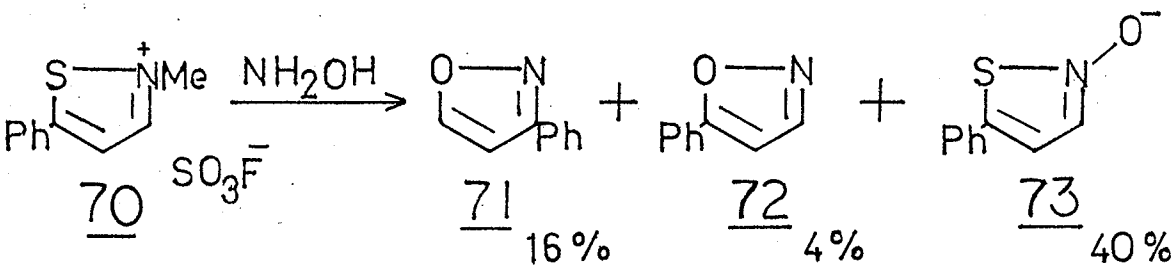


69

A mechanism including nucleophilic attack on the ring sulfur could be invoked to explain the formation of 68 and 69 . However nucleophilic attack at carbon seems to be more consistent with the other results.

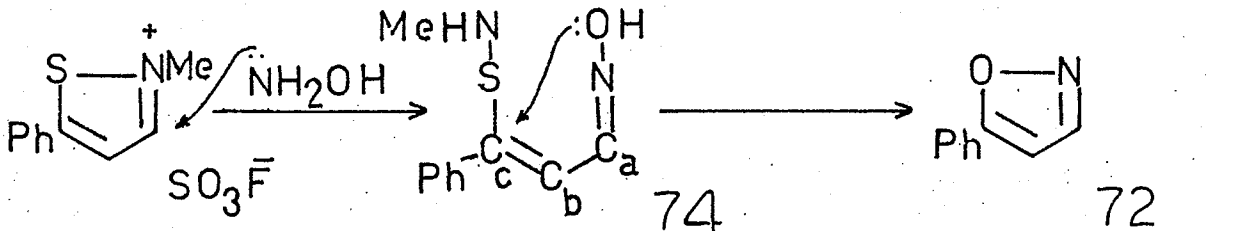


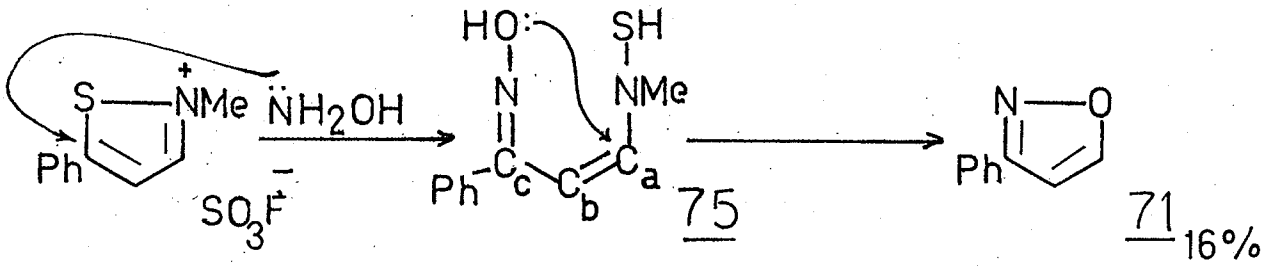
Sykes and Ullah[38] also reported that the attack of hydroxylamine on the unsymetrically 5-substituted cation 70 , afforded the products 71 , 72 , and 73 in 16% , 4% , and 40% yield respectively.



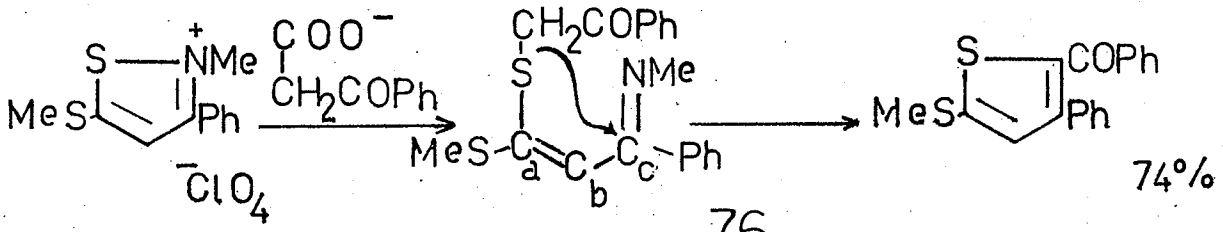
Compound 71 which must be formed by initial attack on the sterically hindered carbon 5 , is surprisingly obtained in a higher yield relative to 72 formed from attack on the sterically free carbon 3. The authors argue that the product ratio is controlled by the greater difficulty of

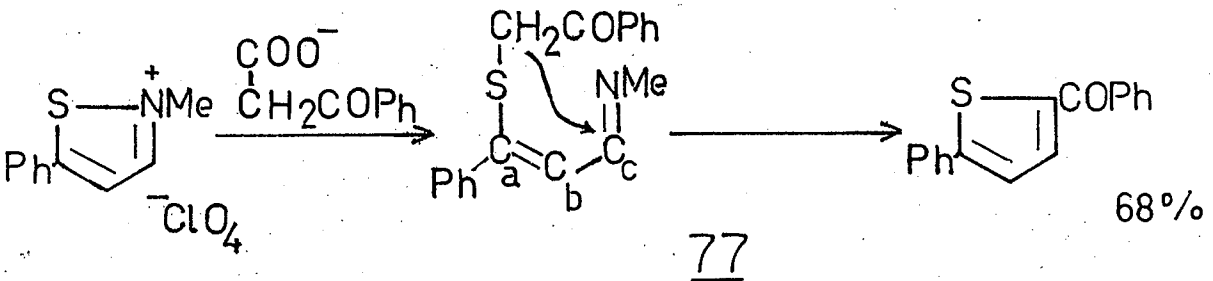
lone pair attack on C_c in the intermediate 74 (formed from attack on carbon 5), than on C_a in 75 (formed from attack on carbon 3) rather than by the relative ease of initial nucleophilic attack on carbon 3 versus on carbon 5.



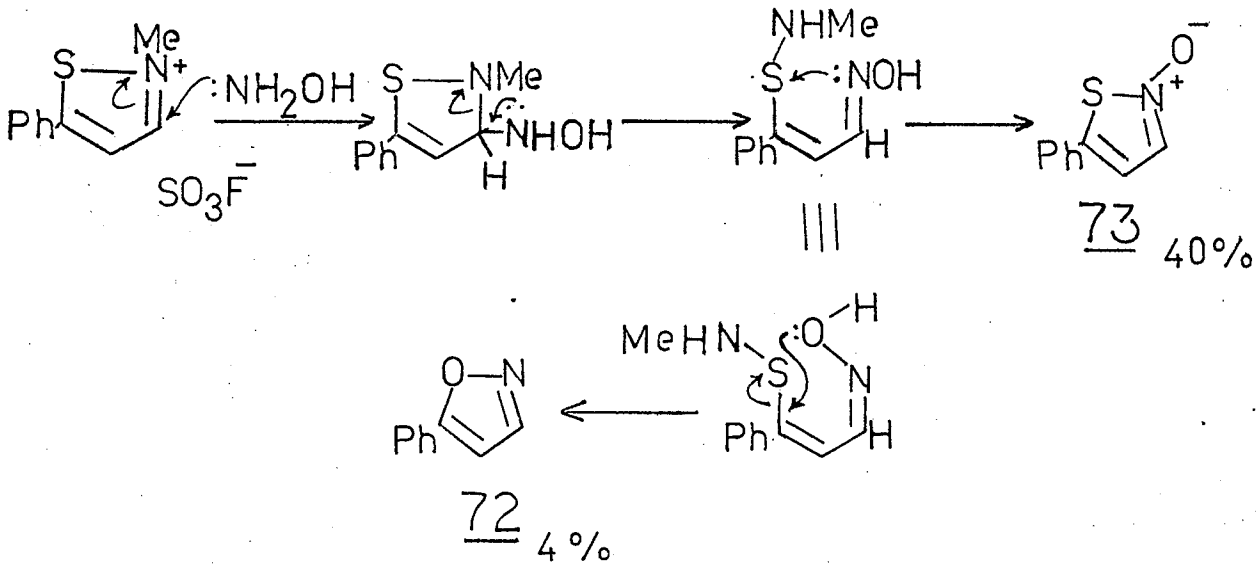


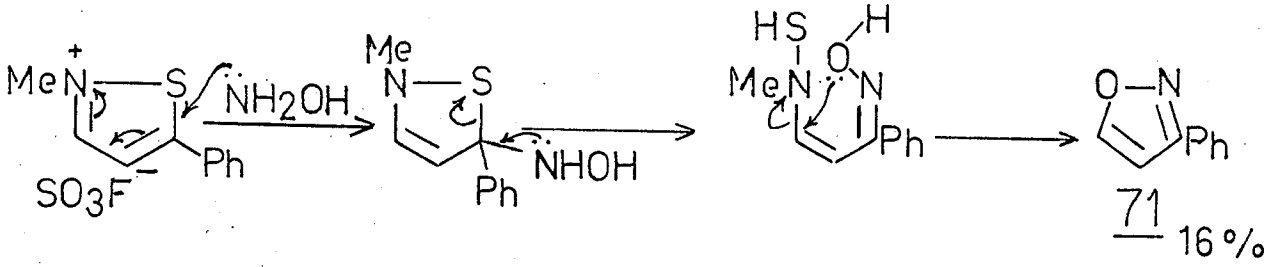
This argument does not fit very well with some of the results mentioned above. For example, from the reaction of isothiazolium salts with sodium benzoylacetate, the intermediates 76 and 77 are comparable to 74 and 75 respectively, and here no effect of such greater difficulty of lone pair attack on C_c in 76 as compared with 77 was noticed as yields were comparable.



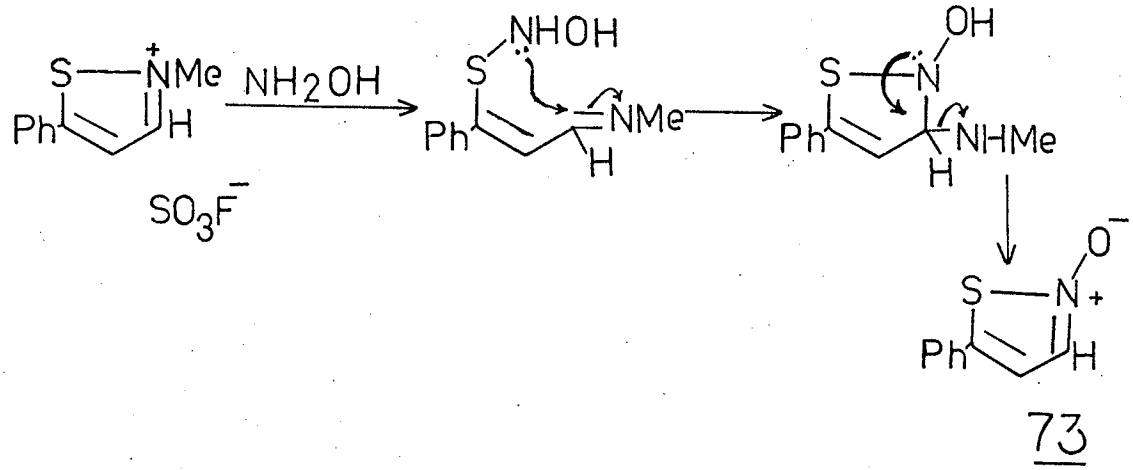


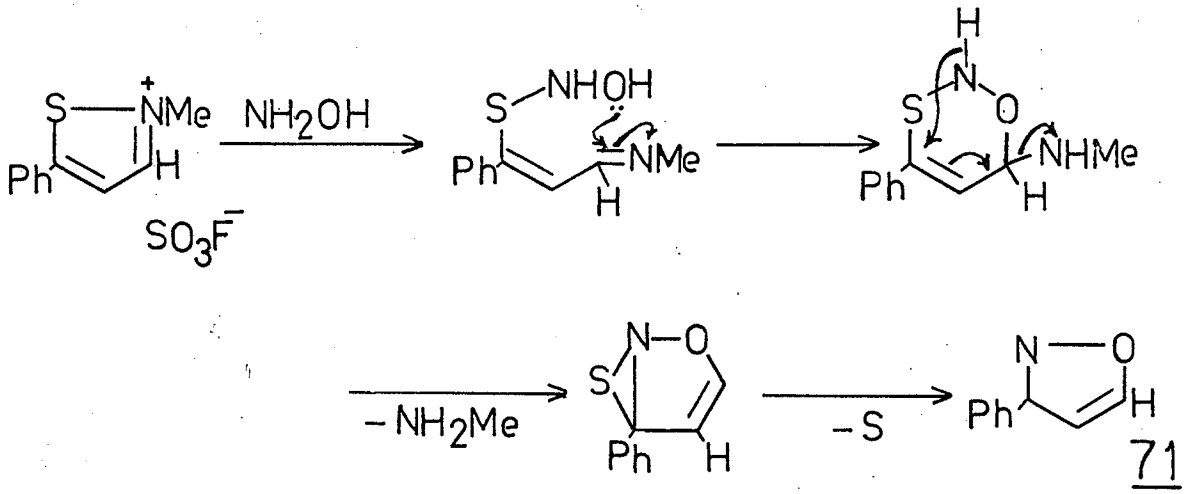
The results of Sykes and Ullah[38] could simply be explained by two competing reactions at carbon 3 and carbon 5 . The first leads to formation of compound 72 as well as 73 for a total yield of 44%, While the attack at carbon 5 affords 71 which accounts for only a 16% yield.





However formation of 71 and 73 could also be explained as taking place through initial nucleophilic attack on the ring sulfur.





Nucleophilic attack of hydroxylamine on 1,2-benzoisothiazolium salts seems to take place also at the ring sulfur[93],[95]. The 2,1-benzoisothiazolium system, on the other hand, is reported[96] to undergo nucleophilic attack by amines on carbon rather than on the ring sulfur. Nucleophilic attack of sulfur nucleophiles on 1,2-benzoisothiazolium salts is reported[97] to take place at the ring sulfur. However the comparison with benzoisothiazolium salts should be taken with great caution, due to the effect of the fused benzene ring on the reactivity of the isothiazolium nucleus.

One may conclude, therefore, that nucleophilic attack of sulfur nucleophiles as well as carbon nucleophiles on isothiazolium salts seems to take place at the ring sulfur. The nucleophilic attack of nitrogen nucleophiles, on the other hand, seems to take place at carbon 3, and to a lesser extent, at carbon 5. Steric factors might, however, cause the nucleophilic attack at carbon 5 to become predominant.

PREPARATION AND CYCLOADDITION REACTIONS OF ISOTHIAZOLINETHIONES

Although cycloaddition reactions of 1,2-dithiole-3-thiones with various acetylenic and other reagents have been widely studied[57],[98-100], much less has been reported on these reactions applied to the isoelectronic and structurally related isothiazoline -3- and -5-thiones, 22 and 29 respectively.

Reactions* of two N-alkylisothiazoline-5-thiones and one 5-iminoisothiazoline with dimethyl acetylenedicarboxylate are reported[43] to give 1,3-dithiol and thiazole derivatives respectively, 2,4-diphenylisothiazoline-5-thione reacted similarly with dimethyl acetylenedicarboxylate[29].

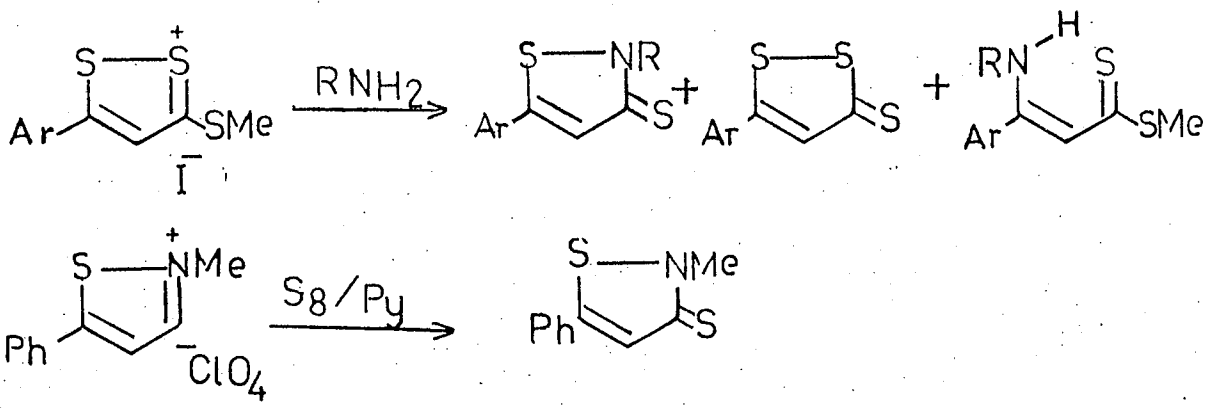
Only one such reaction is reported for the isomeric isothiazoline-3-thiones. The 2-methyl-5-phenyl compound reacted with benzonitrile oxide to form an unstable adduct which decomposed to form 2-methyl-5-phenylisothiazoline-3-one and phenylisothiocyanate[ø 27].

It seemed desirable to study in more detail the cycloaddition reactions of these compounds to determine to what extent these paralleled those of the 1,2-dithiole-3-thiones, in particular with respect to the effect of the ring nitrogen, and the effect, if any, of substituents on reactivity and products.

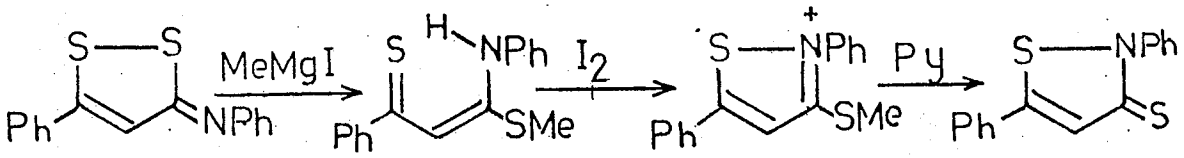
Within recent years, certain isothiazoline-3- and -5-thiones have become available through a variety of syntheses. N-Alkyl-3-thiones are prepared[44] by reaction of 3-alkylthio-1,2-dithiolium

*P. 27
øP. 22

salts with aliphatic amines or by sulfurization of N-alkylisothiazolium salts[29].



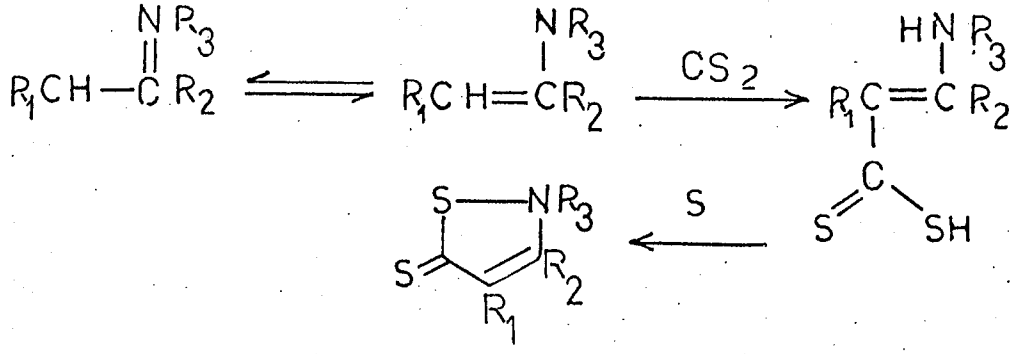
These methods are inapplicable to the synthesis of N-aryl-isothiazoline-3-thiones, as 1,2-dithiole-3-imines are obtained instead[29],[101]. Recently, however, a synthesis of a 2,5-diphenyl-3-methylthioisothiazolium salt by oxidation of a β-aminothione was reported[34] Dealkylation of this in pyridine was then carried out to get the desired 2,5-diphenyl isothiazoline-3-thione 22b.

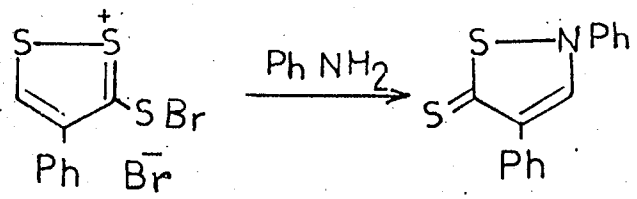


22b

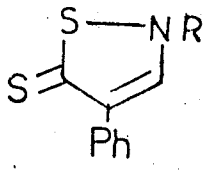
N-Alkylisothiazoline-5-thiones are obtained* by treatment of certain imines with carbon disulfide[55], but this method is inapplicable to the N-aryl compounds. These may be prepared[29] by dealkylation of the corresponding 5-alkylthioisothiazolium salts, or in one case, by treatment of 3-bromothio-4-phenyl-1,2-dithiolium bromide with aniline.

*P.24-27





In fact, further studies of this last reaction demonstrated that it is also applicable to other aromatic amines and to aliphatic amines as well. The bromide salt reacted vigorously with alcoholic solutions of primary amines to form the new thiones 29b - 29i, conveniently and in good yield.

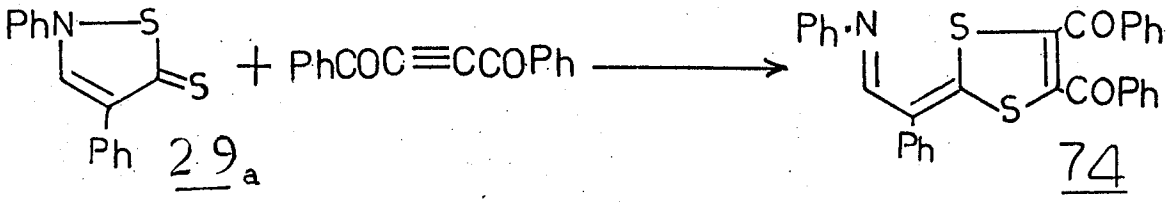


29

a- R = Ph
b- R = Me
c- R = $PhCH_2$
d- R = $(CH_3)_2CH$
e- R = CH_2- $(CH_2)_4$-CH -
f- R = C_6H_4 p · CH_3
g- R = C_6H_4 m · CH_3
h- R = C_6H_4 O · CH_3
i- R = C_6H_4 p · OCH_3

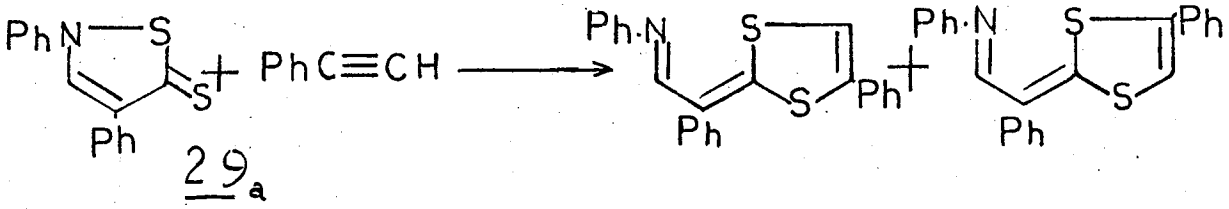
REACTIONS OF ISOTHIAZOLINE-5-THIONES

2,4-Diphenylisothiazoline-5-thione 29a reacted rapidly with dibenzoylacetylene to give a dibenzoyl-1,3-dithiole derivative 74 , similarly to known reactions of dithiolethiones[102].



29a 74

It also reacted with phenylacetylene but the product formed could not be crystallized. In this case, reaction of the thione with the unsymmetrically substituted acetylene could give two geometrically isomeric products[103]. These probably mutually interfere with crystallization.

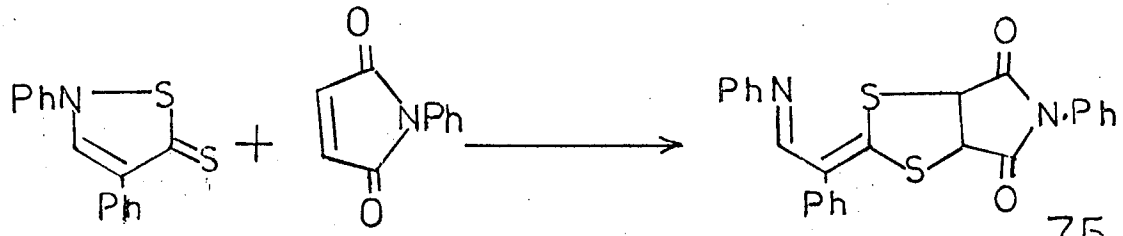


29a

The adducts also appear to be unstable and revert to starting material, for although a satisfactory mass spectrum indicating the parent ions were obtained, starting thione was always detectable on chromatography, even after repeated attempts at purification. Reaction with diphenylacetylene was similar. Chromatography indicated the formation of a red compound but attempted crystallization gave only starting material.

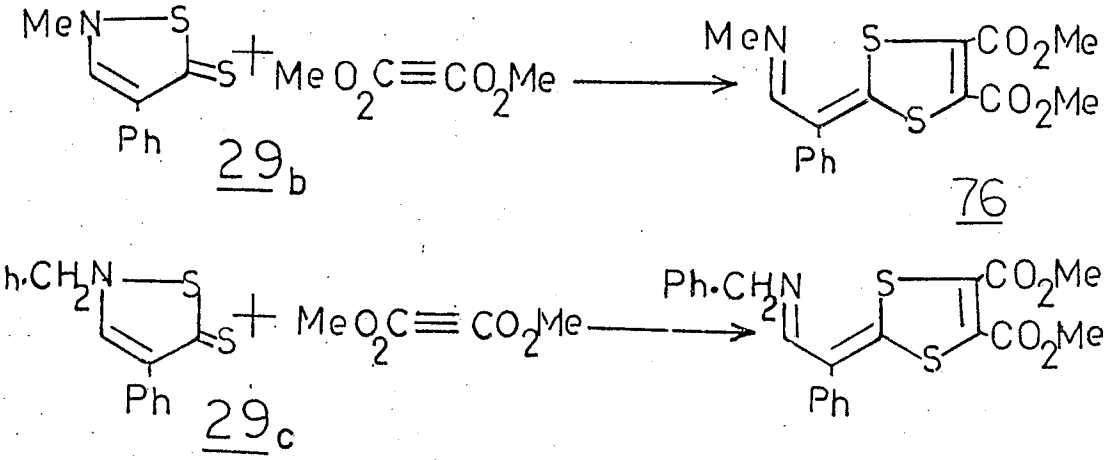
Reaction of the thione with N-phenylmaleimide gave an adduct

which appears to be the 1,3-dithiolanedicarboximide 75 , but reaction with diethyl azodicarboxylate gave only decomposition products.



75

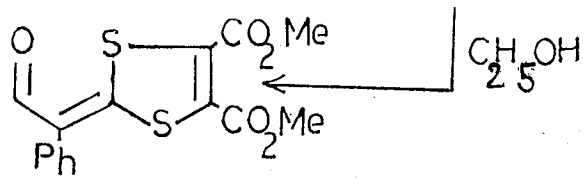
Reaction of N-alkylisothiazoline-5-thiones with dimethyl acetylenedicarboxylate also proceeded rapidly. The N-methylthione 29b gave a crystalline aldimine adduct 76 in good yield, but from the reaction of the N-benzyl compound 29c , an oil was obtained. Trituration of this with ethanol gave only the aldehyde 77 , presumably by hydrolysis of the initially formed aldimine. This aldehyde had been previously reported as a product from the reaction of 4-phenyl-1,2-dithiole-3-thione with dimethyl acetylenedicarboxylate[104].



29b

76

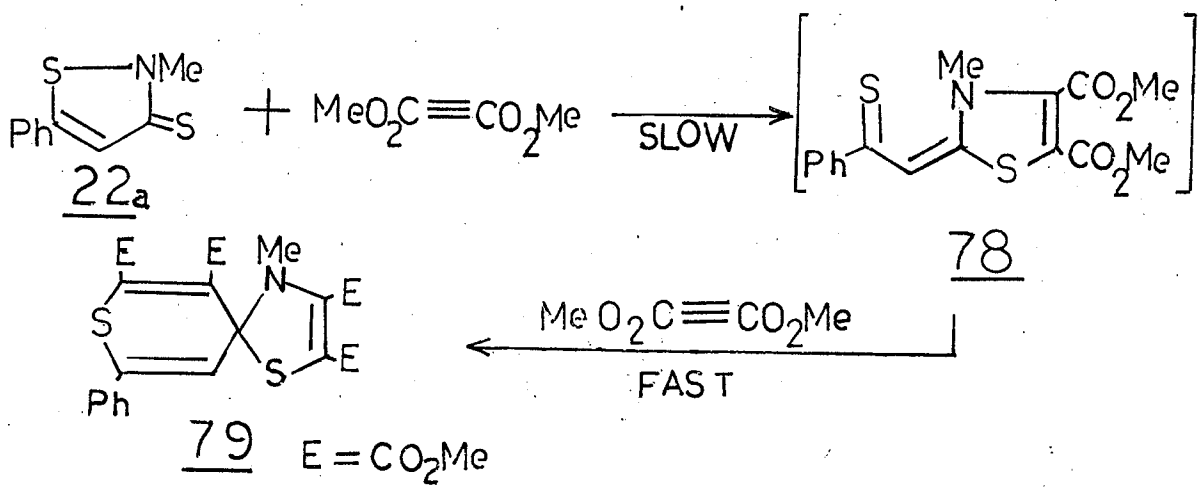
29c



77

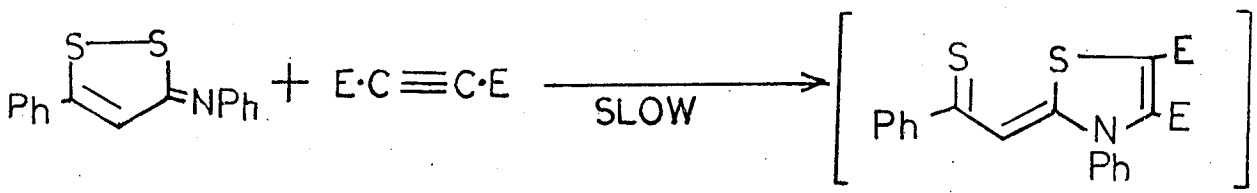
REACTIONS OF ISOTHIAZOLINE-3-THIONES

In contrast to the above rapid reactions of the 5-thiones, the 3-thiones 22 reacted much more slowly with dimethyl acetylenedicarboxylate. Treatment of 2-methyl-5-phenylisothiazoline-3-thione 22a with the ester in boiling benzene for 24 hours gave a mixture of products from which were obtained starting thione and an orange oil, formed by combination of thione with two moles of ester. This is probably the spiran diadduct 79 .

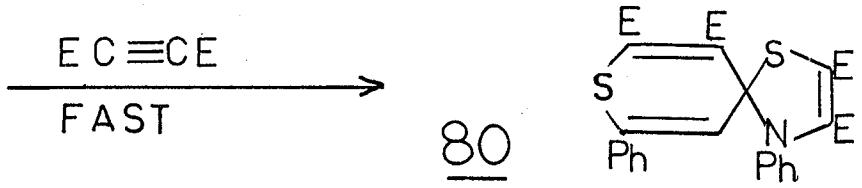


22a 78 79 E = CO_2Me

No monoadduct 78 could be isolated, suggesting that the rate of the second reaction is greater than that of the first. These reactions correspond to reactions of the dithiole series[101], and it is interesting that reactions of 3-phenylimino-1,2-dithioles with dimethyl acetylenedicarboxylate give only diadducts of type 79 . None of the intermediate monoadducts of type 78 was obtained there either.



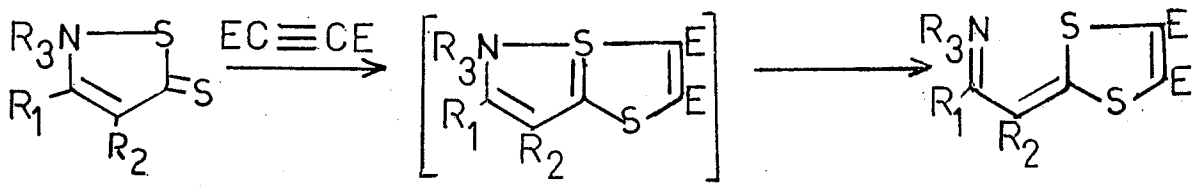
E = CO_2Me



80

One possibility is that the 2-methyl-5-phenylisothiazoline -3-thione could undergo thermal rearrangement to 2-methylimino-5-phenyl-1,2-dithiole, as has been found for the benzo-compound[104], and that the iminodithiole underwent the subsequent reactions. However, the isothiazolinethione was unchanged in boiling benzene indicating that it is a direct precursor of the mono- and diadducts.

The marked difference in reactivity of the two isoelectronic thione systems 22 and 29 , with dimethyl acetylenedicarboxylate, is interesting. It could be explained as a result of the steric effect exerted by the substituent on the nitrogen on the course of the reaction in 22 . The sulfur atom in 29 does not suffer from such effect. Alternatively, that difference in reactivity may actually be due to the fact that structures such as 81 , involving sulfur d-orbital participation might be involved as intermediate in the reactions of the isothiazoline-5-thiones 29 .

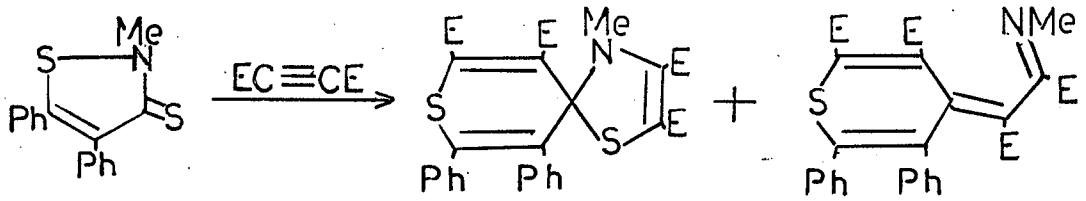


E=CO2Me

81

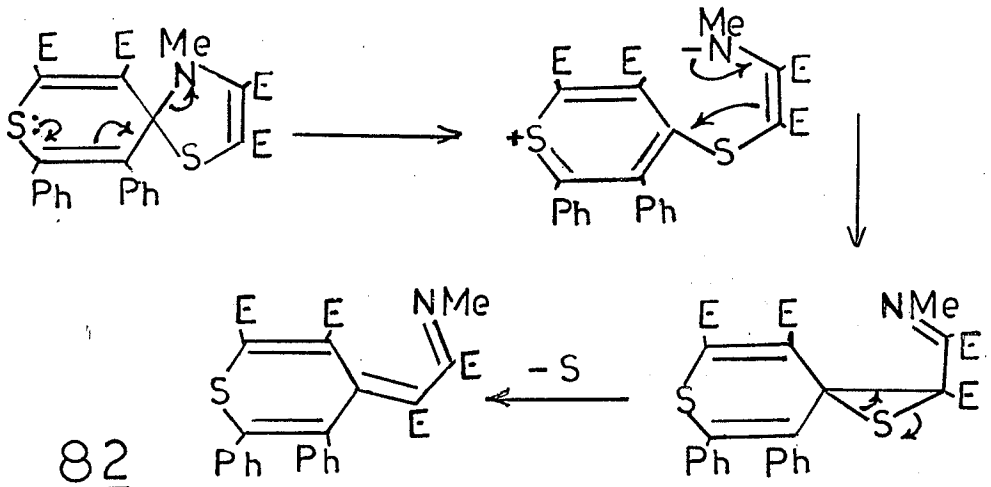
The intermediate 81 , corresponds to contributing structures of 2-thioacylmethylene-1,3-dithioles, or intermediates in their formation from 1,2-dithiole-3-thiones[59]. Since no such intermediates are possible in the reactions of the isothiazoline-3-thiones 22 , the reaction may proceed with greater difficulty, however once the monoadduct in this case is formed, it rapidly underwent further reaction to form the diadduct.

2-Methyl-4,5-diphenylisothiazoline-3-thione 22c also reacted with the ester. A crystalline diadduct was obtained, along with a small amount of deep red material. The mass spectrum and analysis indicated that it contains one sulfur atom less than the spiran diadduct. On this basis and because of its deep color, it was tentatively assigned the conjugated thiopyran structure 82 .

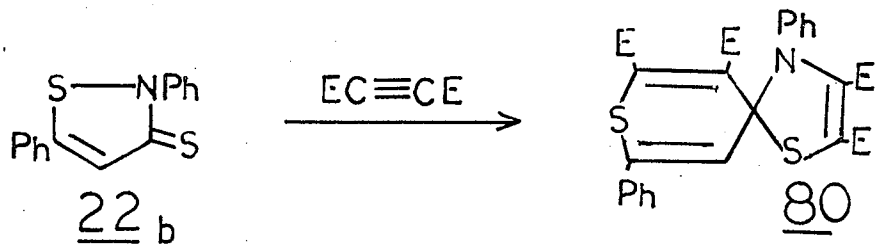


22c 82

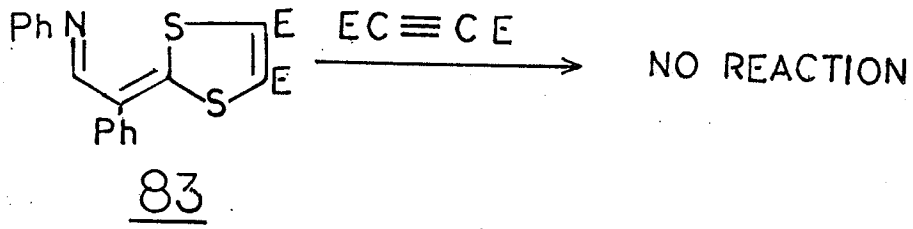
Compound 82 could have arisen from the diadduct by extrusion of sulfur by a mechanism analogous to a step in the sulfur catalyzed rearrangements of 2-thiophenacylidene-1,3-dithioles to 3-thiophenacylidene-1,2-dithioles (trithiapentalenes)[105].



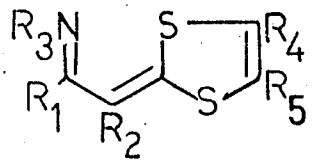
2,5-Diphenylisothiazoline-3-thione 22b also reacted with dimethyl acetylenedicarboxylate. The product here was the known diadduct 80 . Once more, no monoadduct was obtained.



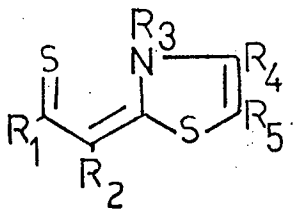
Attempts to synthesize the diadduct from the imine adducts formed from the isothiazoline-5-thiones were unsuccessful. Thus compound 83 , was recovered from further treatment with dimethyl acetylenedicarboxylate. Compound 76 gave the aldehyde 77 by hydrolysis during the work-up.



These results are comparable to those of Behringer et al.[43], and may reflect the different electronic effects of the nitrogen and sulfur containing side chains in the isomeric systems 84 and 85 . The steric effect of the nitrogen substituent may also play a role in this reaction.



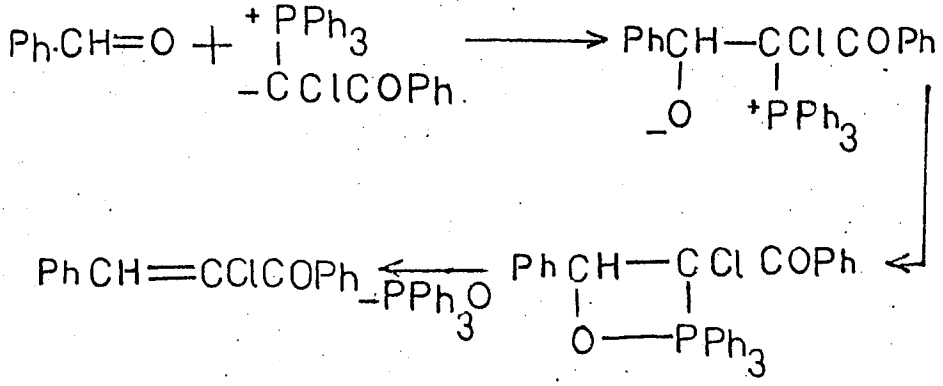
84



85

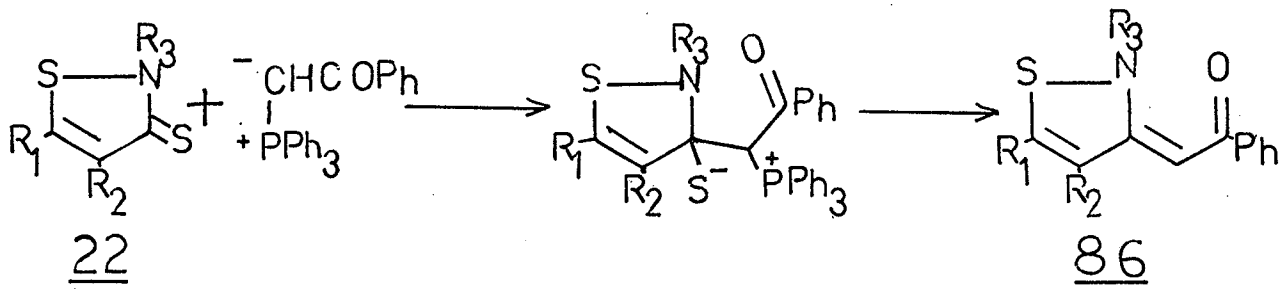
REACTION WITH PHOSPHORUS YLIDS

The reaction of ketostabilized phosphorus ylids with aldehydes and ketones is reported to take place through a Wittig type of reaction to afford olefine derivatives[106].



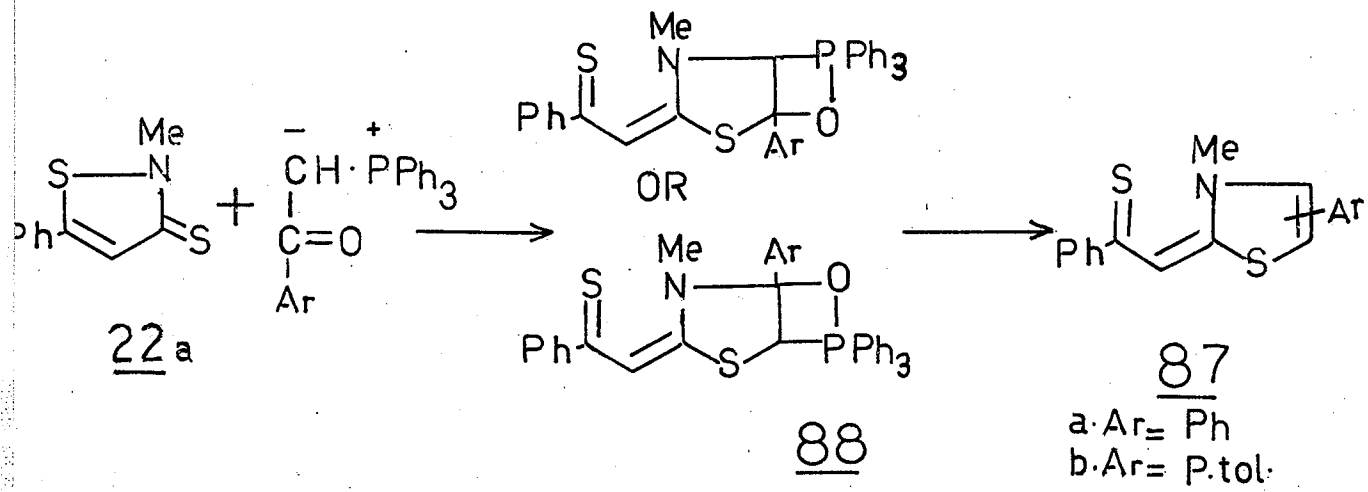
On a similar basis, one would expect the thione group in the isothiazoline-3-thiones 22 , on treatment with phenacylidenetriphenylphosphorane, to afford 3-phenacylidene substituted isothiazoles 86 , which would be precursors of the 3-thioacylmethyleneisothiazole system 32 *.

* P. 31



22 86

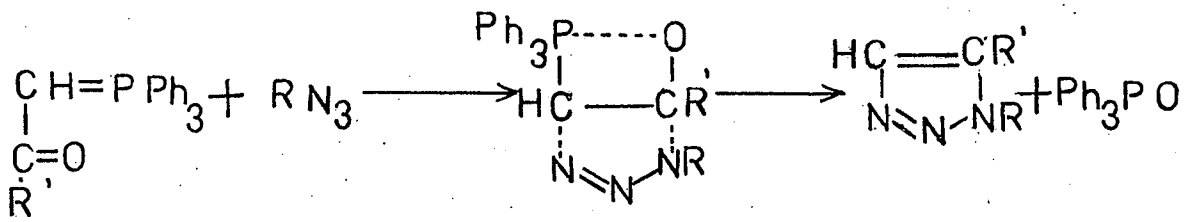
Treatment of 2-methyl-5-phenylisothiazoline-3-thione 22a , with phenacylidenetriphenylphosphorane or p-methylphenacylidenetriphenylphosphorane, did not, in fact, afford substituted isothiazoles of structure 86 . Instead it gave the 1,3-thiazole adducts 87a , and 87b . The reaction probably proceeds via intermediate of structure 88 , formed through a 1,3-dipolar cycloaddition reaction.



22a 88 87

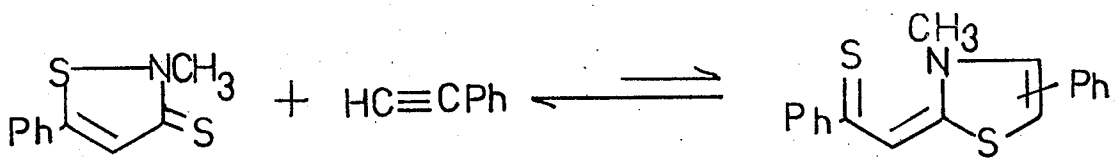
a·Ar= Ph
b·Ar= P.tol·

Although these reaction products are not what would be expected on the bases of similarity to the reactions of phosphoranes with ketones described above, there is evidence that some reactions of the phosphoranes with azides does take a similar reaction pathway[107].



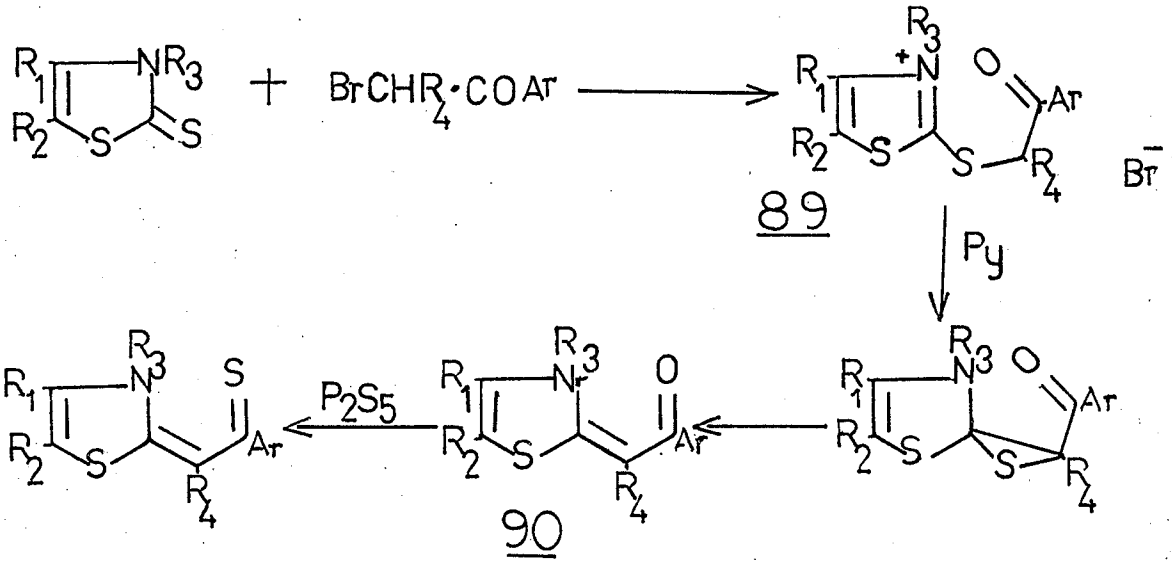
Steric factors seem to play an important role in this reaction, since while the reaction of the phosphoranes with 22a gave the thiazole derivatives 87a and 87b in reasonable yields (36% and 41% respectively), the reaction with 2,5-diphenylisothiazoline-3-thione 22b proceeds only with very low yield (>10%) and in case of 2-methyl -4,5-diphenylisothiazoline-3-thione 22c there was almost no reaction and the starting thione was recovered unchanged.

In order to prove the thioacylmethylenethiazole structure 87 and determine the direction of addition and the orientation of the aryl group in 87 , an alternative synthesis was necessary. The first attempt in this direction was the condensation of the isothiazoline-3-thione 22a with phenylacetylene. The reaction, however, proceeds very slowly, with extremely low yield.



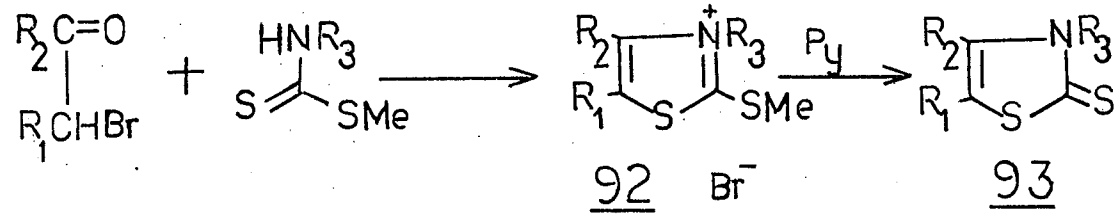
22a

The following approach was found to be more fruitful. Heterocyclic thiones are reported by Knott[108], to undergo condensation reactions with ∝-bromoketones to afford the salt 89 , which on treatment with pyridine or triethylamine extruded sulfur via intramolecular nucleophilic attack to give the ketone 90 . This ketone could then be easily treated with phosphorus pentasulfide to give the desired thione.

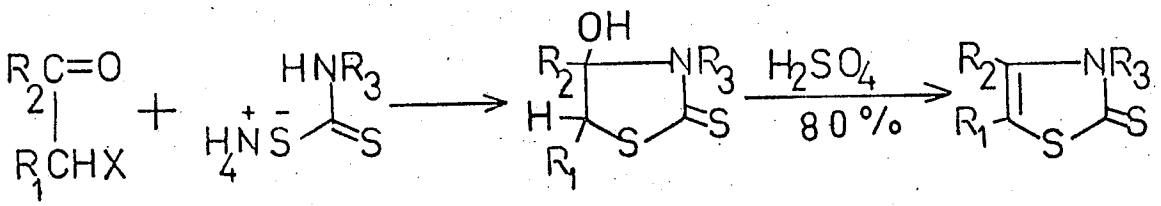


While the starting thiazoline thiones could be prepared through several routes, the following two approaches were found to be more convenient and give better yields.

In one method the alkylthiothiazolium salt 92 , was prepared in one step by the condensation of ∝-bromoketone with methyl N-methyldithiocarbamate. The salt 92 was then treated with pyridine to give the thione 93 .



A more direct approach was available through a general method reported[109] for the preparation of N-alkylthiones. This method was used with certain modifications and was extended to the preparation of N-arylthiones as well. Therefore N-phenyl or N-methylammonium dithiocarbamate was condensed with ∝-haloketones to afford the hydroxythiazolidine-thiones. These were dehydrated by 80% sulphuric acid solution to afford the thiazoline-2-thiones 93 .



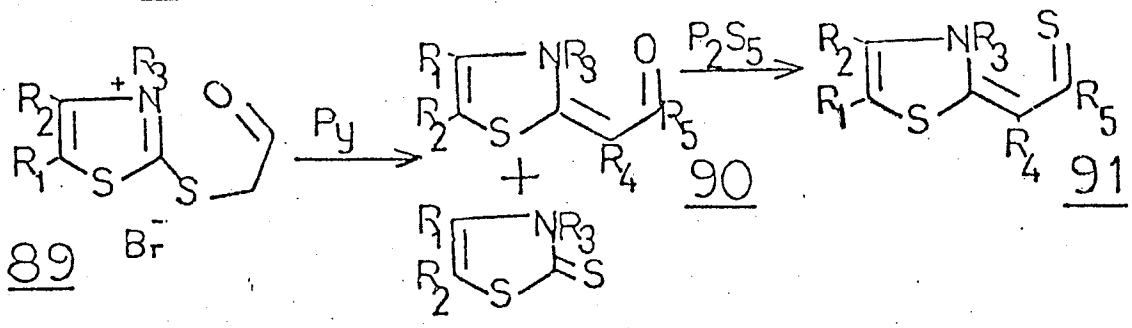
93

	R_1	R_2	R_3
a	H	Ph	Ph
b	Ph	Ph	Me
c	H	p.Tol	Me
d	H	Ph	Me
e	Ph	H	Me
f	— benzo —		Me

Of the thiones, the first three, 93a , 93b , and 93c were new. The benzocompound 93f was not prepared by this method but was obtained commercially.

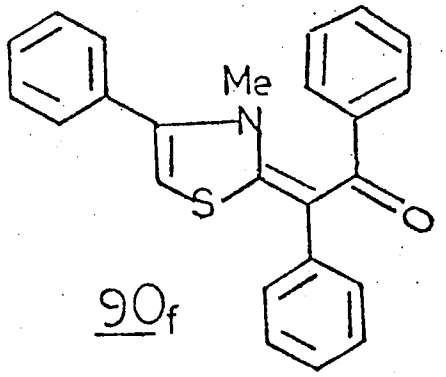
These thiones were further treated with phenacyl bromide, p.methylphenacyl bromide, or desyl chloride according to the procedure described by Knott[108]. It was observed, however, that when the salts obtained from the above reaction were treated with pyridine, they gave, besides the expected ketone 90 , a variable amount of the starting

thione 93 (30-35% yield) through a dealkylation process.



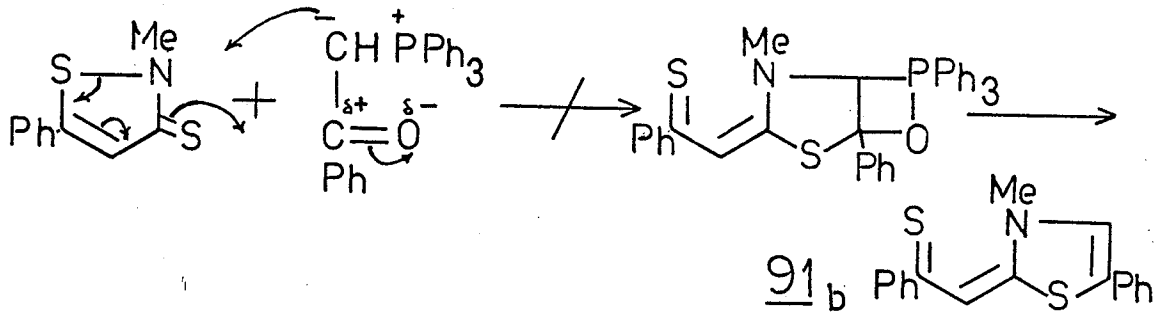
	R_1	R_2	R_3	R_4	R_5
a	H	Ph	Me	H	Ph
b	Ph	H	Me	H	Ph
c	H	p.Tol	Me	H	p.Tol
d	Ph	Ph	Me	H	Ph
e	H	Ph	Ph	H	Ph
f	H	Ph	Me	Ph	Ph
g	— benzo —		Me	H	Ph

The ketones 90 were smoothly thionated by phosphorus pentasulfide. The ketone 90f did not undergo thionation on treatment with phosphorus pentasulfide for a prolonged time. This was most probably due to the steric hindrance of the two phenyl groups on the side chain.



90f

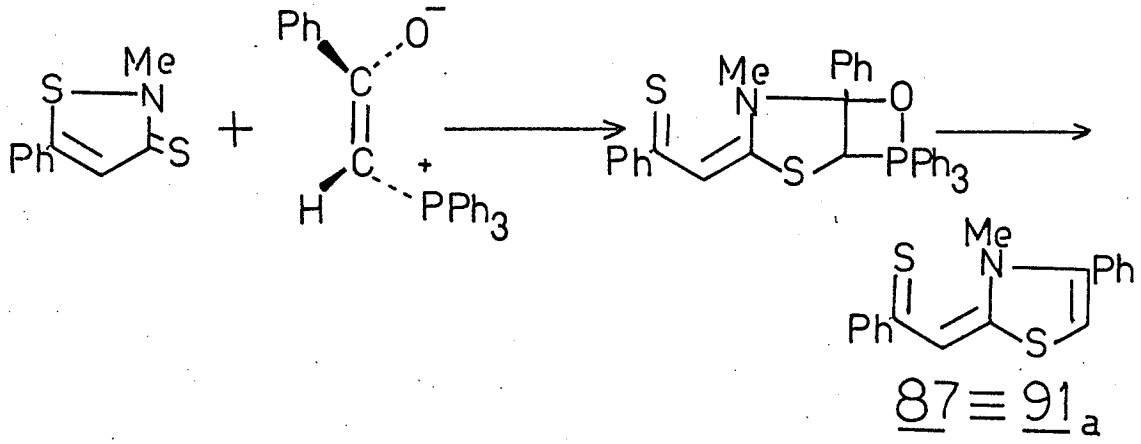
The exact structure of compound 87a was then settled by the comparison of its NMR spectrum, the melting point, and mixed melting point with the thiones 91a and 91b . Compound 87b was also compared to thione 91c obtained by this new approach. It was found that compounds 87a and 87b are in fact identical to compounds 91a and 91c in contradiction to earlier expectation based on electronic factors.



91 b

Zeliger et al.[110] has demonstrated by variable temperature NMR studies that the ∝-ketophosphorus ylids of the type used in this work exist exclusively in the cis-enolate configuration. Consequently the cycloaddition step is expected to proceed by a concerted mechanism, in the same way described by Huisgen[111] for 1,3-dipolar addition to alkenes and alkynes, where both direction of addition produces the same amount of σ bond energy, the interplay of electronic and steric effects is responsible for the orientation, with the last factor dominant.

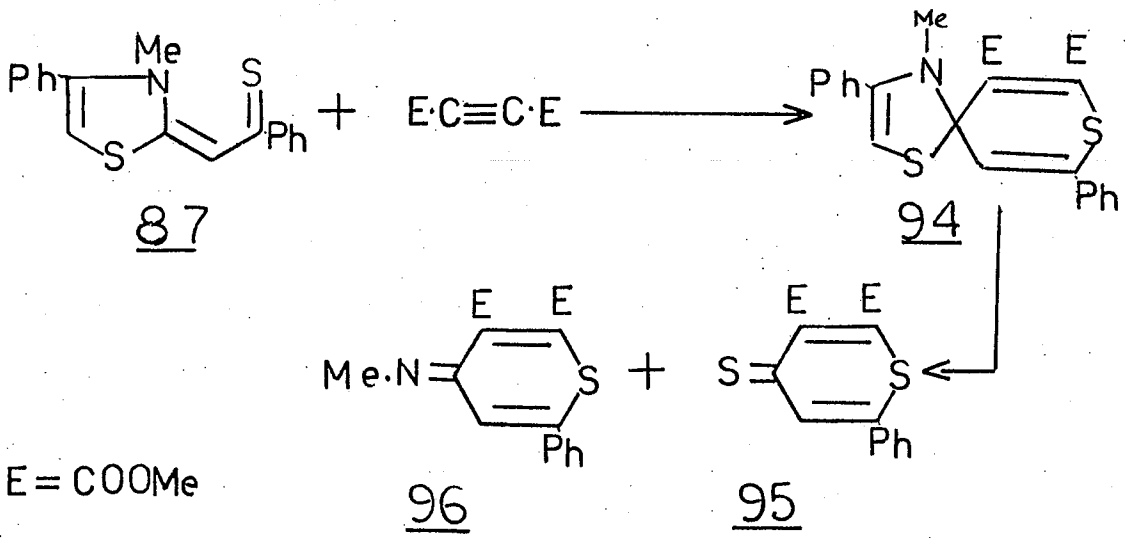
The fact that the steric factors are the predominant in this reaction is clearly demonstrated by the poor yield obtained from the reaction with the N-phenylisothiazolinethione, and the complete obstruction of the reaction by the extra phenyl in the 4,5-diphenylisothiazolinethione. The phenyl group in the 4-position would certainly interfere with the triphenylphosphonio group in the orientation shown below, which seems to be the orientation followed in this reaction.

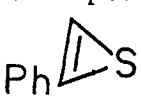


87 ≡ 91 a

The presence of phenyl substituent on the nitrogen would certainly interfere with the phenyl of the phenacyl group, however this effect is less drastic than that of the phenyl in the 4-position with the bulky triphenylphosphonio group and therefore, although it reduces the reaction yield sharply, it does not eliminate the reaction completely.

The thioacylmethylene structure of 87 was further proved by the fact that it was found to undergo further cycloaddition reaction with dimethyl acetylenedicarboxylate to form the adduct 94 ,similarly to the diadducts 79 and 80 mentioned above. But in this case the adduct appears to decompose into two compounds, separated by chromatography. Their NMR and mass spectra indicated that they have the structure 95 and 96.

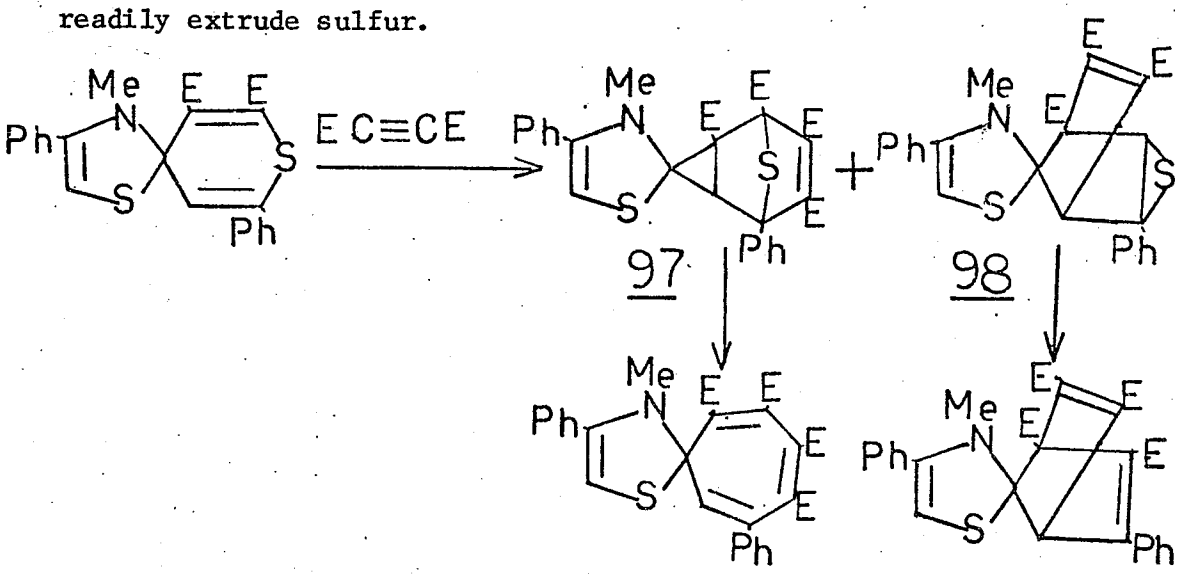


Compounds 95 and 96 seem to be formed from the adduct by loss of species corresponding to ph.C.CHNMe or CH.CphS, respectively. The exact fate of these species is not known. It is possible, however, that they have been extruded as phenylthiirene  , or phenyl-azirine, its nitrogen analogue  . These may decompose later

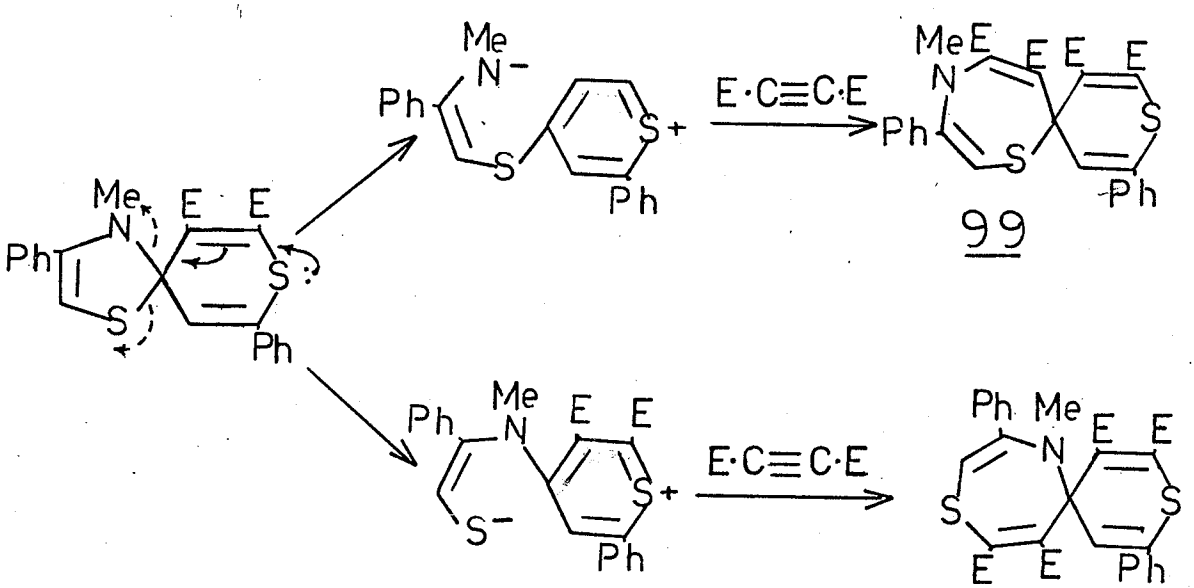
to phenylacetylene[112]. Both phenylthiirene and phenylazirine are anti-aromatic ring systems, like that of cyclobutadiene with only 4 π electrons. The thiirene molecule has been detected several times in the photorearrangement of isothiazoles[113] and dithioles[112]. The stability of these and other similar species were the subject of an interesting recent discussion[114].

The reaction of the thiazole derivative 87, with dimethyl acetylenedicarboxylate, gave besides compounds 95 and 96, a red crystalline material formed by combination of 87 with two molecules of the ester, as proved by NMR, mass spectra and elemental analysis. This adduct seems to exist in two isomeric forms separable by thin layer chromatography.

Several structures are possible for these diadducts. They could possibly be formed from the spiran adduct 94, by cycloaddition reaction (Diels-Alder type), to the diene system in the thiopyran ring. This would afford structures 97 and 98, (two diasteriomers). However structures 97 and 98 are not expected to be stable and should readily extrude sulfur.

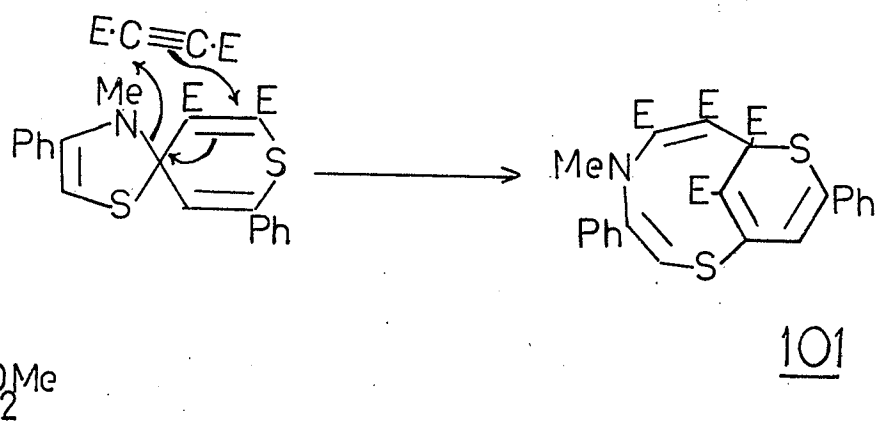


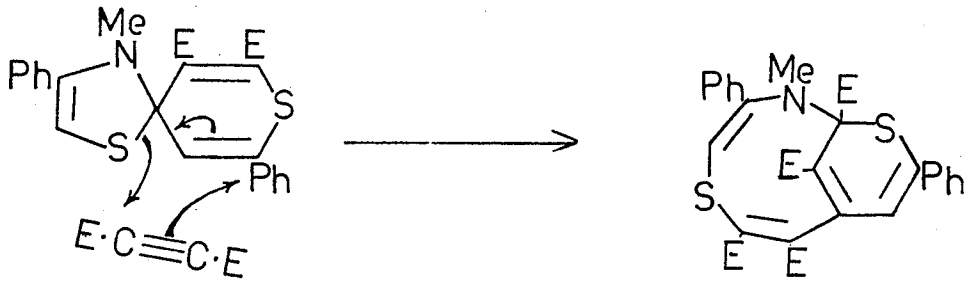
Another alternative structural possibility is initiated by electron shift from the thiopyran ring sulfur, leading to the opening of the thiazole ring of the spiro compound 94 , cycloaddition then leads to the new spirans 99 and 100 .



This possibility gains some support from the fact that the two other products of this reaction, namely compounds 95 and 96, are also formed through the opening of the thiazole ring.

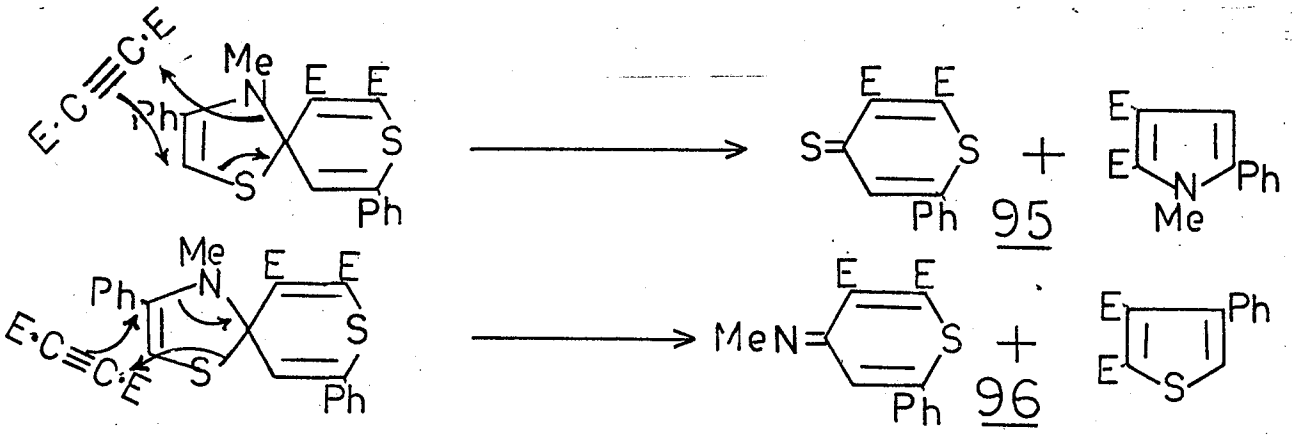
Finally, structures 101 and 102 could also be suggested. The mechanism of their formation is similar to a known reaction of pyrrole with dimethyl acetylenedicarboxylate[115].





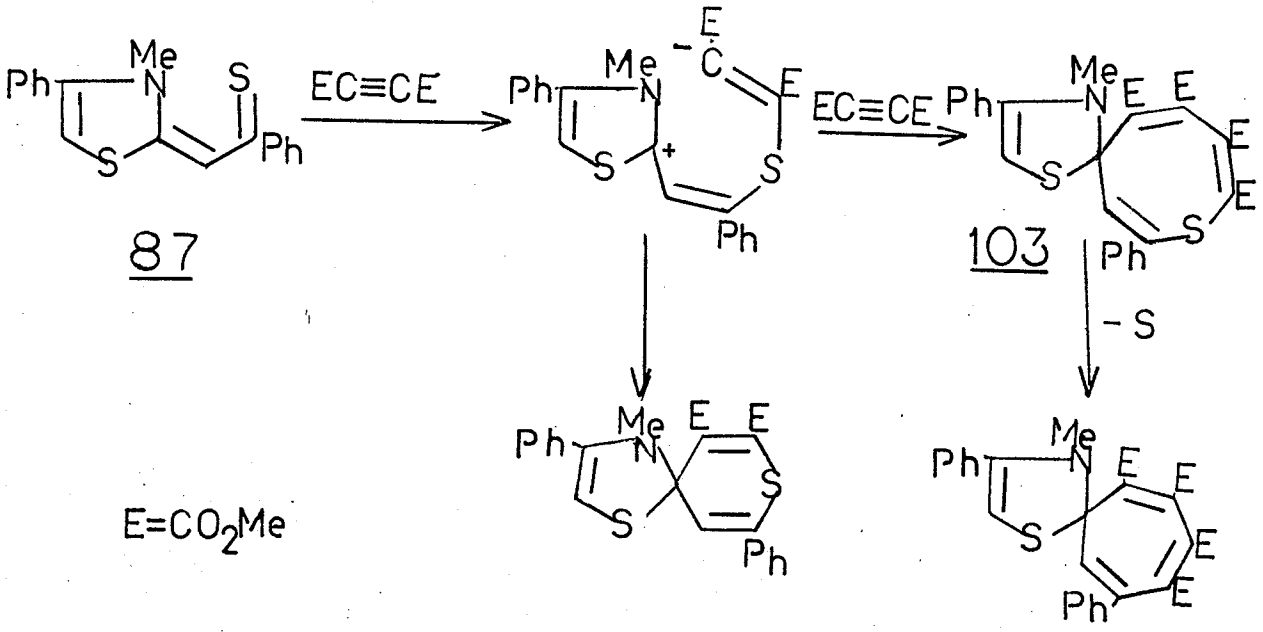
102

Formation of compounds 95 and 96 could also be explained through a similar mechanism.



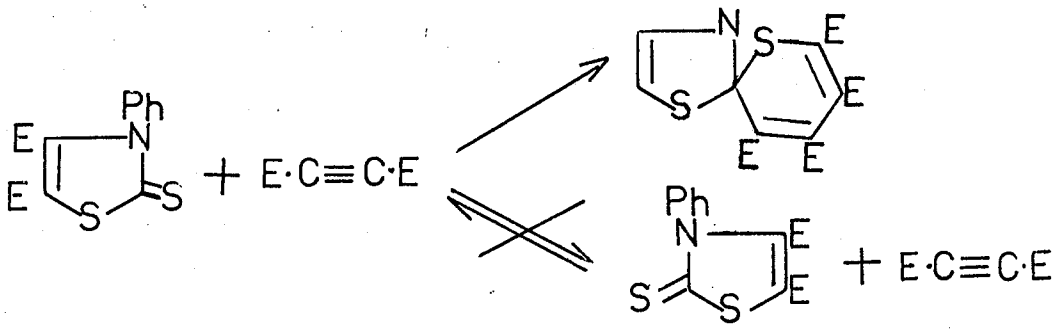
However the fact that neither the pyrrole nor the thiophene side-products has been detected from this reaction, might help to exclude such a mechanism.

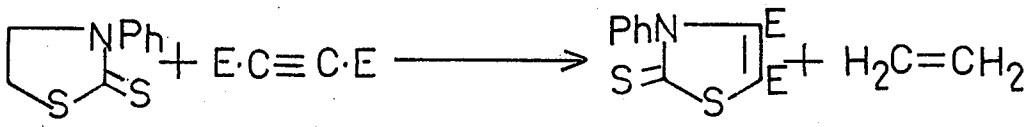
On the other hand, the diadduct could have been formed by the direct reaction of the thiazole derivative 87 , with two molecules of the ester without the intermediary of the spirocompound. This could take place in one of two ways; the first is by the cycloaddition of two molecules of the ester to the thiophenacyldiene side chain, to form the spiro-structure 103 . This reaction, if it does take place, has to be a two-step reaction and not concerted. Since it involves 4 pairs of electrons, it would be thermally disallowed[116].

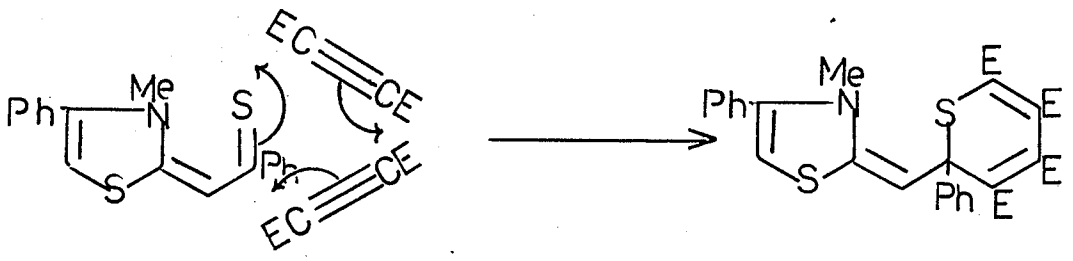


Compound 103 , again is expected to easily undergo sulfur extrusion, and moreover, it can only exist in one isomeric form while the obtained diadduct exists in two isomeric forms.

The other possibility is that the two ester molecules undergo cycloaddition to the thione group to form the six membered thiopyrane ring structure 104. This is similar to the addition of two molecules of dimethyl acetylenedicarboxylate to the thione group of thiazoline -2-thiones[117].

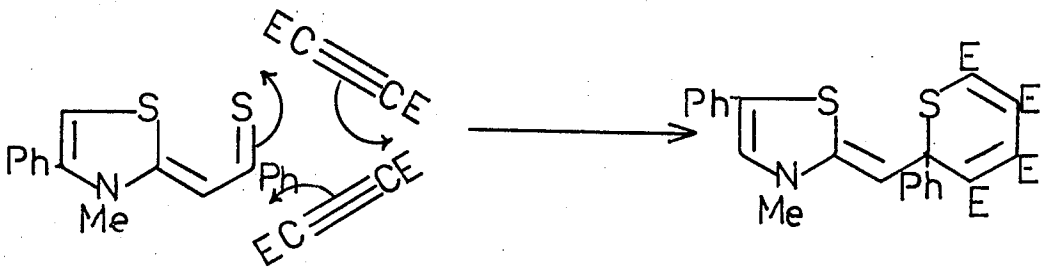






87 104

Depending on the original thiazole derivative 87, the adduct 104 , could also exist in the isomeric form 105 .



87 105

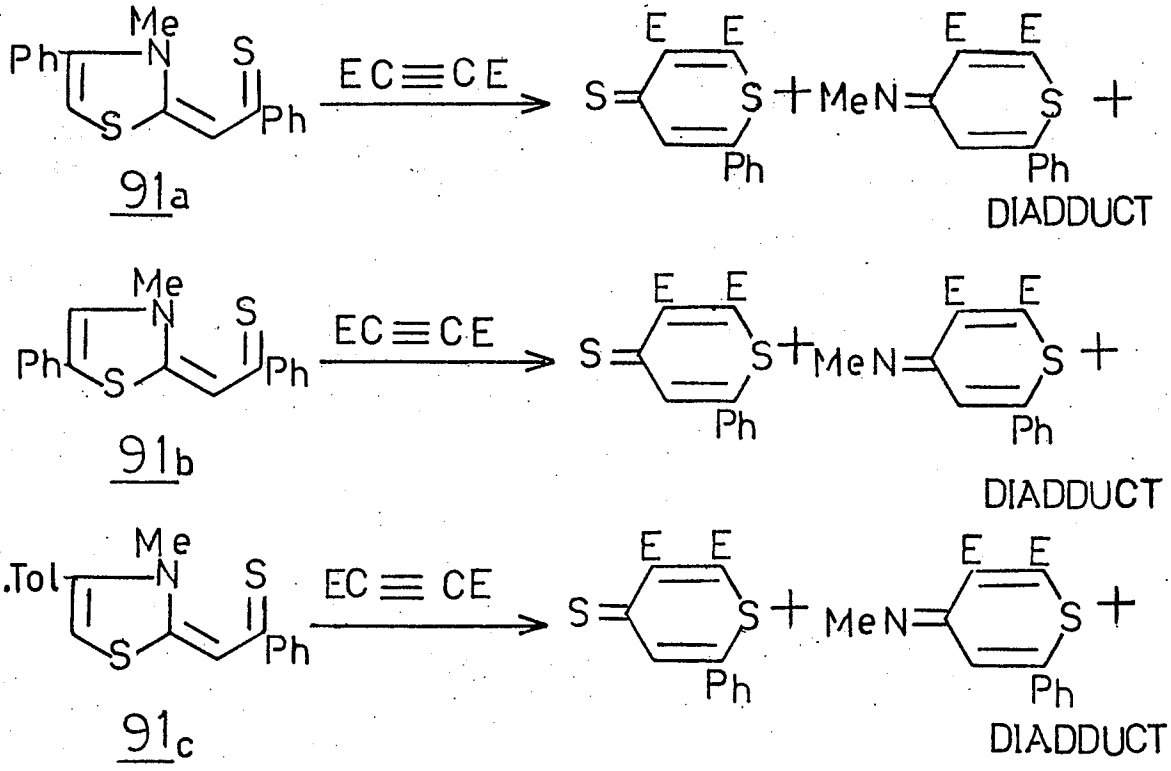
In order to try to distinguish between these various possibilities, a series of differently substituted structures of the thiazole derivative 87 was prepared, and their reaction with dimethyl acetylenedicarboxylate was studied to give information about the structure of the diadduct and the factors leading to the formation of the spiran monoadduct 94 and/or the diadduct.

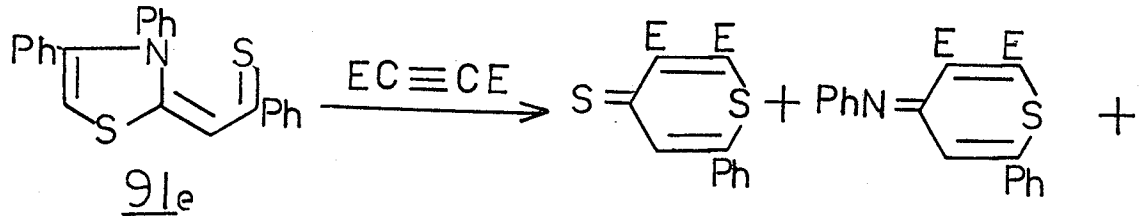
Treatment of the series of thiones 91 , prepared earlier, with equivalent amounts of dimethyl acetylenedicarboxylate afforded in most cases studied (91a , 91b , 91c , and 91f) the diadduct as well as the products 95 , and 96 obtained from the decomposition of the monoadduct. The N-phenyl equivalent of 96 was obtained instead in the case

of N-phenyl compound 91e .

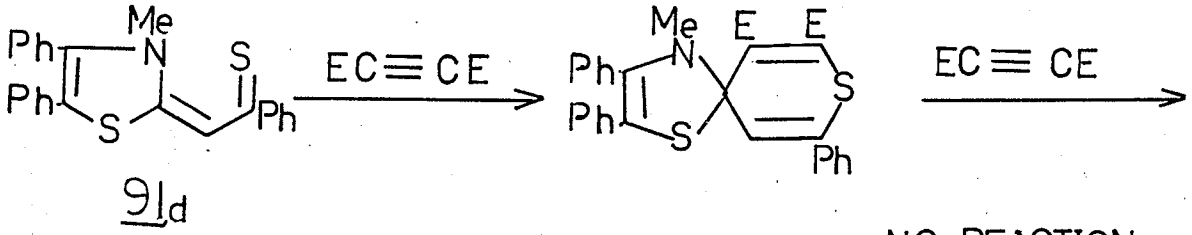
However in two cases, namely the benzo- and the 4,5-diphenyl compounds 91d , and 91g , only the monoadduct was obtained. No diadduct was found. The monoadduct was quite stable in both cases. This may be due to stabilization effect exerted by the benzo- or the extra phenyl group. Further treatment of the monoadduct with excess dimethyl acetylenedicarboxylate for prolonged times did not lead to the formation of diadduct, and the monadduct was recovered unchanged.

On the other hand, treatment of the starting thiones 91d or 91g , with four equivalent dimethyl acetylenedicarboxylate gave a mixture of both monoadduct and diadduct. The same results were also obtained by carrying out the reaction in a polar solvent as dioxane with an equivalent amount of dimethyl acetylenedicarboxylate.

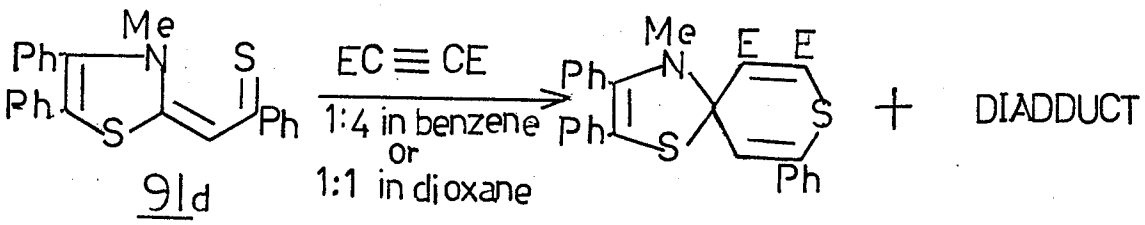




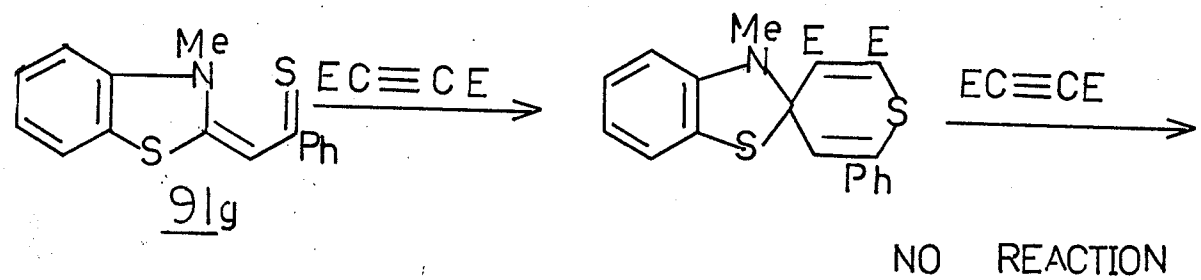
91e



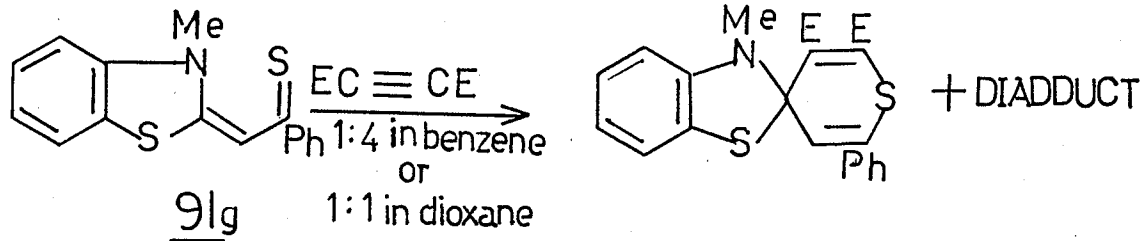
91d



91d



91g

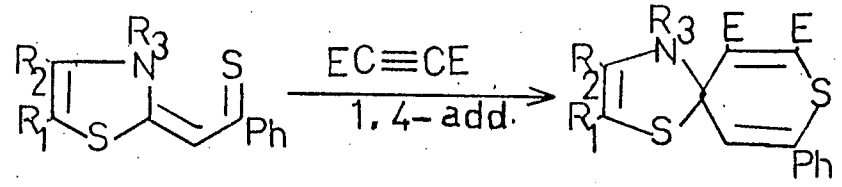


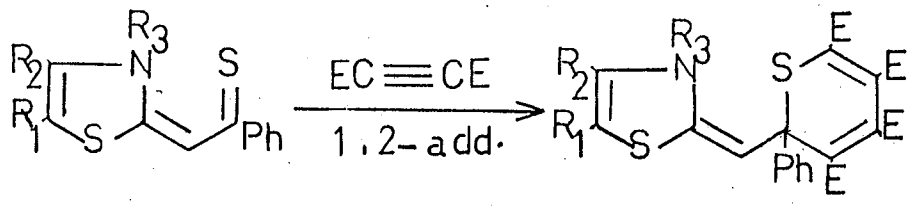
91g

This result suggests that the monoadduct is not a precursor for the diadduct and thus eliminates all the structures based on that assumption 97 - 102 .

It also suggests that formation of the monoadduct and/or the diadduct is actually a result of the two competitive diene reactions, the 1,4 - versus the 1,2-reaction mechanisms. The 1,4-mechanism is more favourable in all cases and gives the higher yield product (the monoadduct). Under certain conditions, the 1,2-mechanism will also take place. This condition was found to be in this case, the increased polarity of the solvent, or the excess dimethyl acetylene-dicarboxylate, which might just increase the polarity of the solvent. The interesting observation here is that the formation of the diadduct should be a nonconcerted reaction, otherwise increasing of the solution polarity would have no effect on its formation.

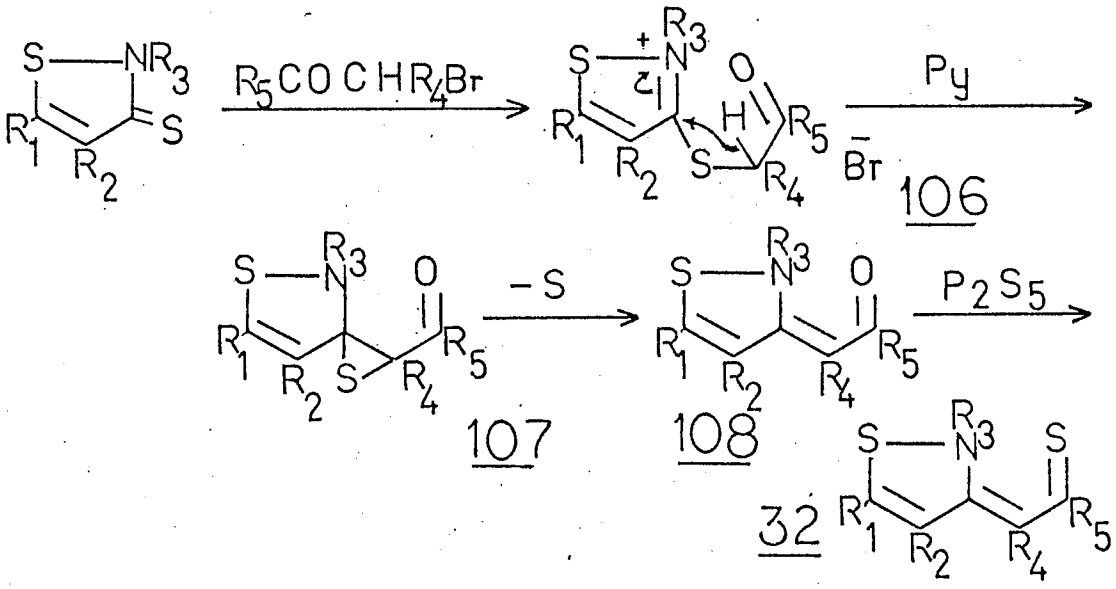
The two isomers of the diadduct were therefore, tentatively formulated as having structures 104 and 105 mentioned above. Further proof of the structure would require chemical degradation such as desulfurization. This however, seems to be extremely difficult in view of the low yield of the compounds.





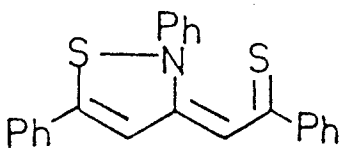
PREPARATION OF 3-THIOACYLMETHYLENEISOTHIAZOLES

Similarly to the scheme applied to the preparation 2-thioacylmethylene-1,3-thiazoles 91 , one would expect the following scheme to be also useful in the preparation of the elusive 3-thioacylmethyleneisothiazole system 32 .



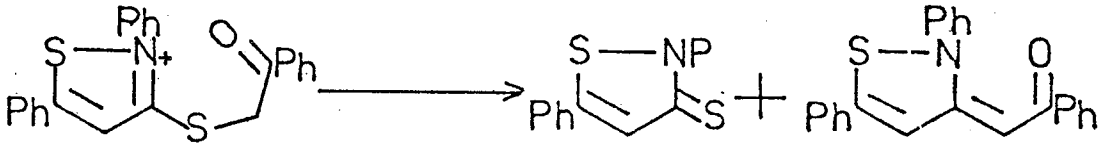
It was expected that steric factors in 106 would force the intramolecular nucleophilic attack of the activated methylene group to take place at carbon atom 3 rather than at the ring sulfur, and therefore afford the intermediate 107 which would extrude sulfur to give the keto-precursor of 32 compound 108 .

As a first trial in this direction, the preparation of 2,5-diphenyl-3-thiophenacylisothiazole 32a was attempted. It was supposed that this compound, being heavily substituted with phenyl groups, would be more stable than other analogues.



32a

Therefore treatment of 2,5-diphenylisothiazoline-3-thione with phenacyl bromide in boiling benzene afforded the bromide salt 106 . This, on treatment with pyridine, underwent two competing reactions, proton elimination to afford the intermediate 107, which extruded sulfur to give the ketone 108 (28% yield) or, alternatively, the salt underwent a dealkylation reaction to give back the starting thione (40% yield).

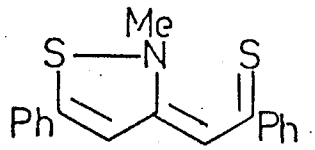


106 $\bar{Br}$ 108

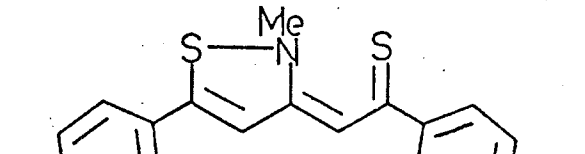
Thionation of 108 , with phosphorus pentasulfide in boiling benzene afforded the thione 32a , as deep pink crystals. The thione was stable at room temperature and at least at elevated temperatures over its melting point (128°C). The thione also gave satisfactory mass spectrum and elemental analysis. Although it gave a satisfactory NMR spectrum, it was of no value for intended variable temperature NMR studies, since it only showed a large complicated peak in the aromatic region. However the fact that this compound was obtained and was stable, proved that this system could exist and that a more useful analogue could probably be obtained. This was of certain value in regard

to the previous unsuccessful attempts to prepare such system.

The second compound in this series was the 2-methyl-5-phenyl -3-thiophenacylisothiazole 32b , obtained from 2-methyl-5-phenyl-isothiazolinethione, following the same reaction scheme described before for the preparation of 32a . The NMR of this compound which showed an N-methyl peak besides the phenyl protons was again of no great value for the NMR studies due to the indistinguishability of the two phenyl groups in the NMR spectrum.



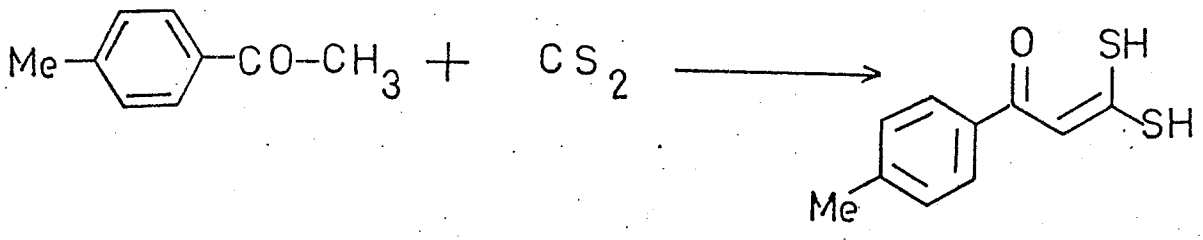
32b



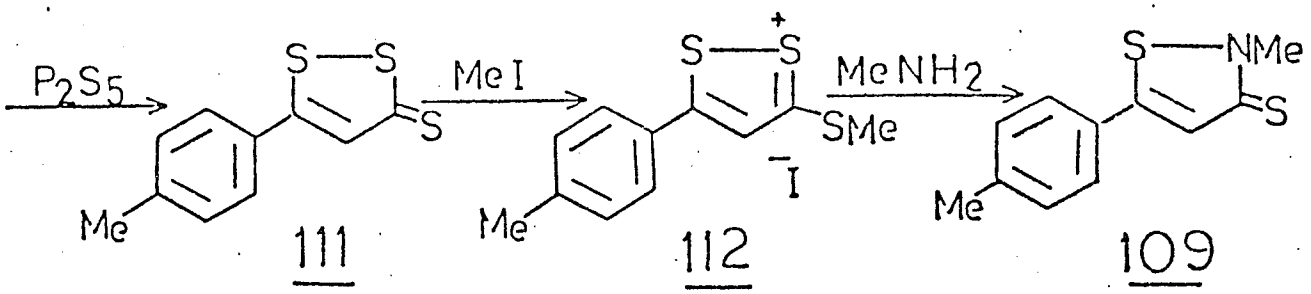
32c

The compound 2-methyl-5-p.tolyl-3-p.methylthiophenacylidene-isothiazole 32c , is expected to give more valuable NMR spectra for the intended variable temperature studies.

This compound was prepared from 2-methyl-5-p-tolylisothiazoline-3-thione 109 . This thione, which was new, was prepared according to the following scheme.



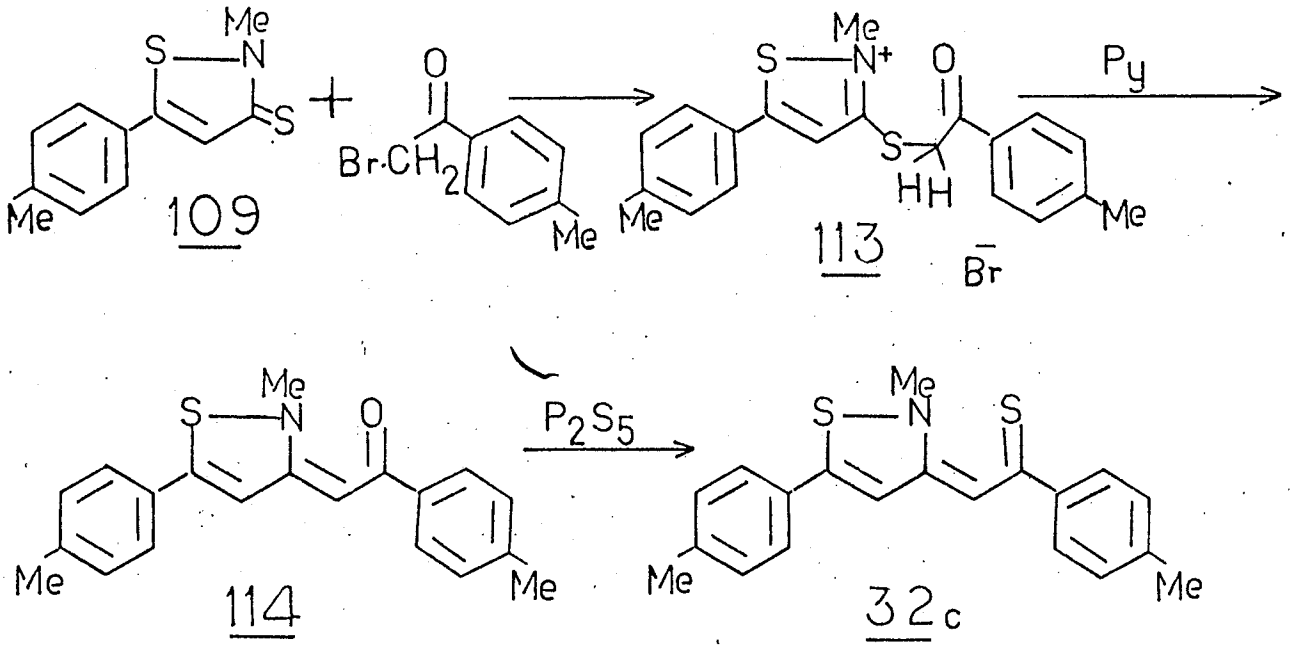
110



The dithiolethione 111 , was prepared by an approach similar to one described by Thuilier and Vialle[118] , with certain modifications. 1-p-Tolyl-3,3-dimercaptoprop-2-enone 110, was obtained from the condensation of p-methylacetophenone with carbon disulfide in a solution of sodium tertiary butoxide in 80% yield. The procedure described for thionation of 110 in xylene and toluene proved to be time and material consuming while that in benzene gave lower yield. It was more convenient, however, to carry out the thionation by dissolving the dimercaptan 110 in excess benzene, and refluxing for four hours with excess (two equivalent) phosphorus pentasulfide. The work-up in this approach was less laborious and the yield was higher (70% versus 62% reported for the reaction in xylene).

The thione obtained from the above was then alkylated with methyl iodide to afford the dithiolium iodide 112. This, on treatment with methylamine in ethanol according to the method of Le Coustumer and Mollier[44] , gave the desired isothiazoline thione 109 .

The thione 109 was then treated with p-methylphenacyl bromide affording the salt 113 , which on treatment with pyridine gave 114 the ketone precursor of 32c (in 25% yield). This was thionated with phosphorus pentasulfide in benzene to give the thione 32c (in 60% yield).



Compound 32c was then subjected to nuclear magnetic resonance examination to test the validity of the three hypotheses which have been put forward to explain the symmetry of trithiapentalenes (see Introduction). Because the central atom of 32c is incapable of valency shell expansion, any symmetry features exhibited by 32c would have to be due to single bond - no bond resonance or rapid tautomerism; and if these processes are important, the NMR spectra should indicate the equivalence of the two p.methyl groups.

When the ^{1}H NMR spectroscopy of 32c was performed in deuterochloroform solution over a temperature range between -40 and $0^{o}C$, the two para-methyl groups were nonequivalent. The protons of the two phenyl groups were also distinguishable while those belonging to the phenacylidene sidechain phenyl appeared as four 1H singlets, the protons of the phenyl group at the 5-position of the isothiazole ring appeared as one 4H singlet.

The spectra run in perdeuterotoluene, because of its aromatic

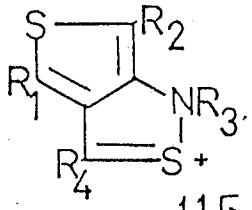
solvent effects[119-121] gave a better separation of the two methyl groups. A similar effect was also observed in the spectra run in tetrachlorobenzene.

No coalescence was observed in the spectra run in perdeuterotoluene or in tetrachlorobenzene, neither at room temperature nor at higher temperatures up to 190°C (the higher safety range for the NMR machine), indicating that there is rather a high energy barrier to interconversion of the two identical valency tautomers.

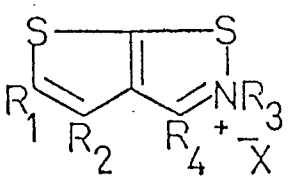
The failure of compound 32c to demonstrate suitable symmetry suggests that neither valency tautomerism nor single bond - no bond hypotheses are adequate in explaining the special properties of symmetry exhibited by the trithiapentalenes. The above results seem to support the hypotheses involving sulfur d-orbitals as to provide the most satisfactory explanation of the special properties of the trithiapentalenes.

PREPARATION OF THIENOISOTHIAZOLIUM SALTS

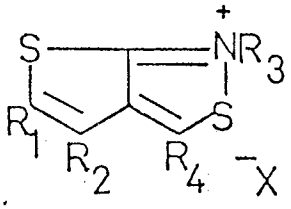
Of the six possible isomers of thienoisothiazolium salts 115 - 120 , none is as yet known.



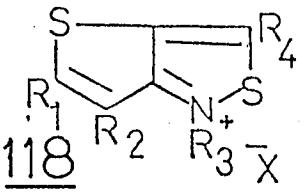
115



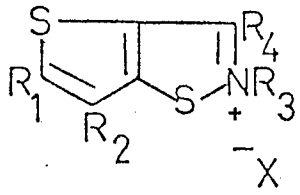
116



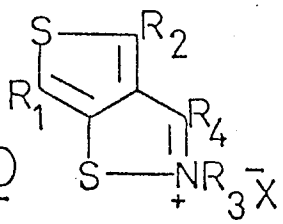
117



118

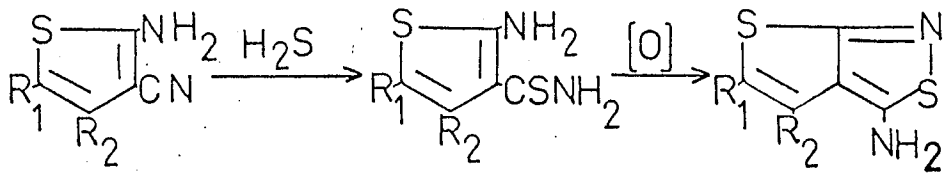


119



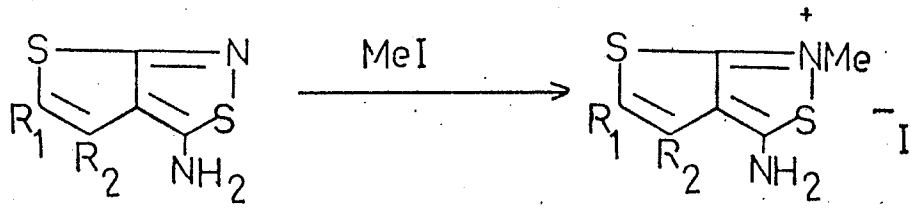
120

Of the thienoisothiazole system itself, only 3-aminothieno [2,3-c]isothiazole 121 has been prepared[122] from 2-amino-3-cyanothiophene by treatment with hydrogen sulfide followed by oxidative ring closure of the resulting 2-amino-3-thieophenethiocarboxamide.



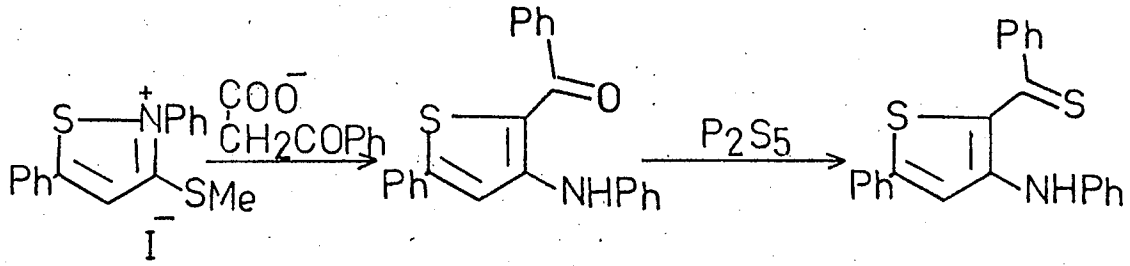
121

It would be expected that compound 121 would undergo simple alkylation, using methyl iodide or dimethyl sulfate, to afford the salt 117 . However this approach is restricted to the preparation of the 3-amino substituted derivatives of thienoisothiazolium salt 117 .

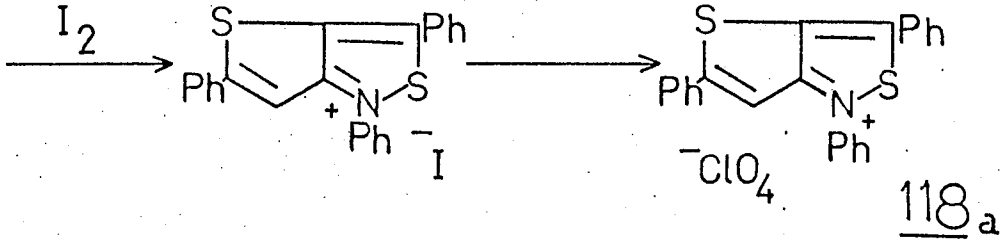


121 117

Another approach has been developed to prepare thieno[3,2-c] isothiazolium salt 118 and its derivatives. It was noticed during the study of nucleophilic attack on isothiazolium salts, that the reaction of sodium benzoylacetate with 3-methylthioisothiazolium salts afforded 2-benzoyl-3-aminothiophenes 44 . Treatment of these compounds with phosphorus pentasulfide in benzene would afford the thione 122 , and this thione is expected to undergo oxidation by iodine in ethanol to afford the thienoisothiazolium salts 118 , a process similar to the oxidative preparation of isothiazolium salts developed by McKinnon and Robak[24]. Following this approach, the 1,3,5-triphenyl thieno[3,2-c] isothiazolium cation was obtained as its iodide. Treatment with perchloric acid in acetic acid afforded the perchlorate 118a .



4f 44 122

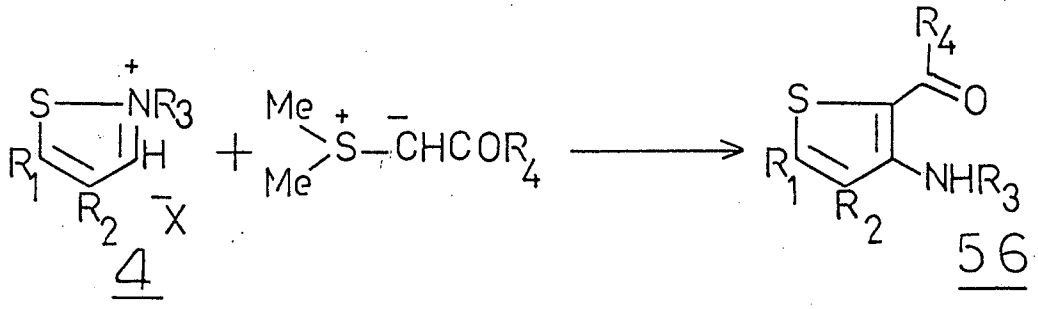


118a

It was advisable to isolate the cations as the perchlorate rather than the iodide, since the latter tends to exist as a mixture of monoiodide and triiodide, which give very poor elemental analysis.

The method described above, successfully afforded the expected 3-phenyl substituted thieno[3,2-c]isothiazolium salt 118a , and probably could be extended to the preparation of the 3-alkyl substituted derivatives (118 , R_4 = alkyl). However the main limitation of the procedure is due to the fact that the starting 3-methylthioisothiazolium salts are available through one source, that is the alkylation of the isothiazoline-3-thiones, which could only be obtained in low yield by the method of Le Coustumer and Mollier[44].

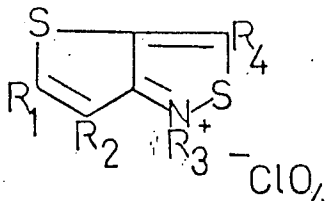
A more general approach was then needed for the preparation of thieno[3,2-c]isothiazolium salts, and this was found in the nucleophilic attack of sulfonium ylids on isothiazolium salts. As mentioned earlier ∝-keto substituted sulfonium ylids reacted with isothiazolium salts, lacking 3-substituents, to afford the 2-ketosubstituted-3-aminothiophenes 56 .



4 56

Compound 56 could undergo thionation and subsequent oxidation to afford thieno[3,2-c]isothiazolium salts. Since the starting isothiazolium salt 4 are available in good yield with a variety of substituents, and the sulfonium ylid is also available with both alkyl or aryl substituent (R_4 = alkyl or aryl), this method appears to afford a wide and

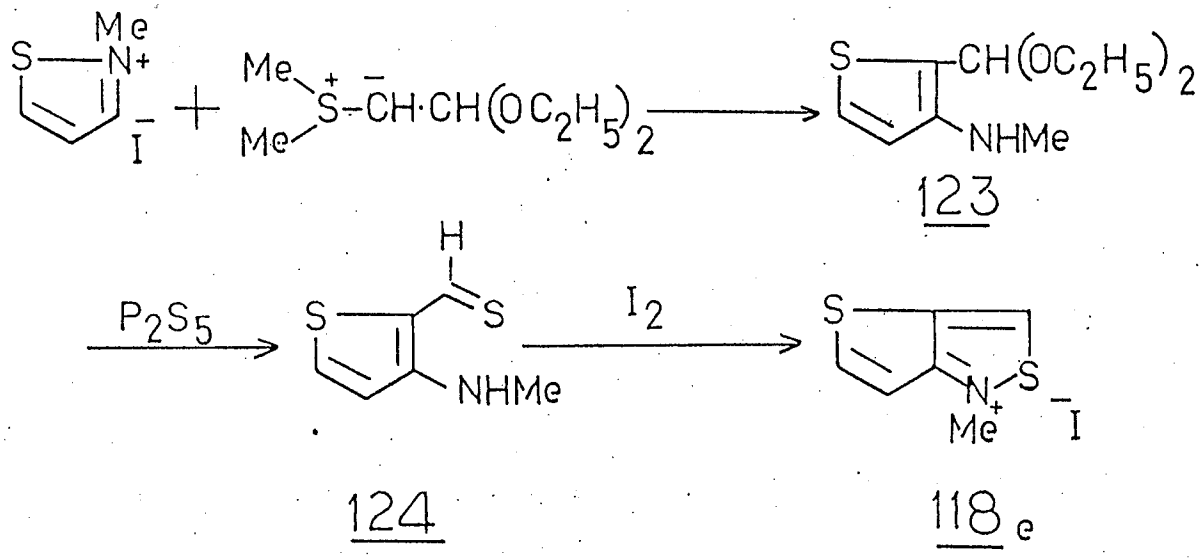
general method for the preparation of thieno[3,2-c]isothiazolium salts 118.



118

	R_1	R_2	R_3	R_4
a-	Ph	H	Ph	ph
b-	H	H	Me	ph
c-	Ph	H	Ph	Me
d-	H	Ph	Ph	ph
e-	H	H	H	Me

The thienoisothiazolium salt 118$_b$ with no substituents on the thiophene ring was obtained from the reaction of 2-methylisothiazolium perchlorate with phenacylidenedimethylsulfurane, following the above pathway. In order to prepare the salt 118e with no substituents on both rings except the nitrogen substituent, 2-methylisothiazolium salt was treated with diethoxyethylidenedimethylsulfurane. This was prepared from the reaction of dimethyl sulfide with bromoacetaldehyde diethylacetal, then treatment with sodium ethoxide.



123

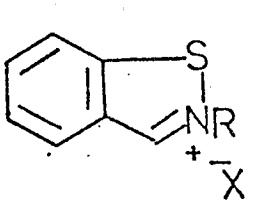
124

118 e

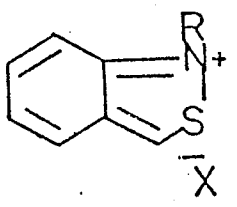
Thionation of the diacetal derivative 123 , followed by subsequent oxidation afforded only a minute amount of the salt 118e . This poor yield seems to be a result of the instability of the thioaldehyde compound 124 , obtained from the thionation of 123 . Thioaldehydes are known for their instability[57].

2,3-PYRIDINO-4,5-BENZOISOTHIAZOLIUM SALTS

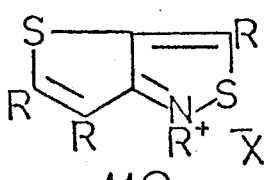
Isothiazolium salts condensed to a benzene ring are known to exist in two series, 1,2- and 2,1-benzoisothiazolium salts, 125 and 126 respectively. Isothiazolium salts condensed to heterocyclic ring are rarely known. In the last few pages, the preparation of one such system, the thienoisothiazolium salts 118 , has been discussed. The preparation of another such system, isothiazolopyridinium salts 127 , has been reported recently by Leaver et al.[35].



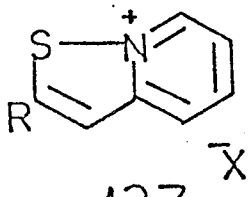
125



126



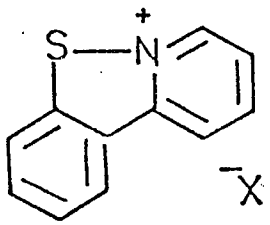
118



127

It is of interest to prepare the 2,3-pyridino-4,5-benzoisothiazolium salt 128 , in which the isothiazole system is condensed both to a benzene ring and to a heterocyclic ring.

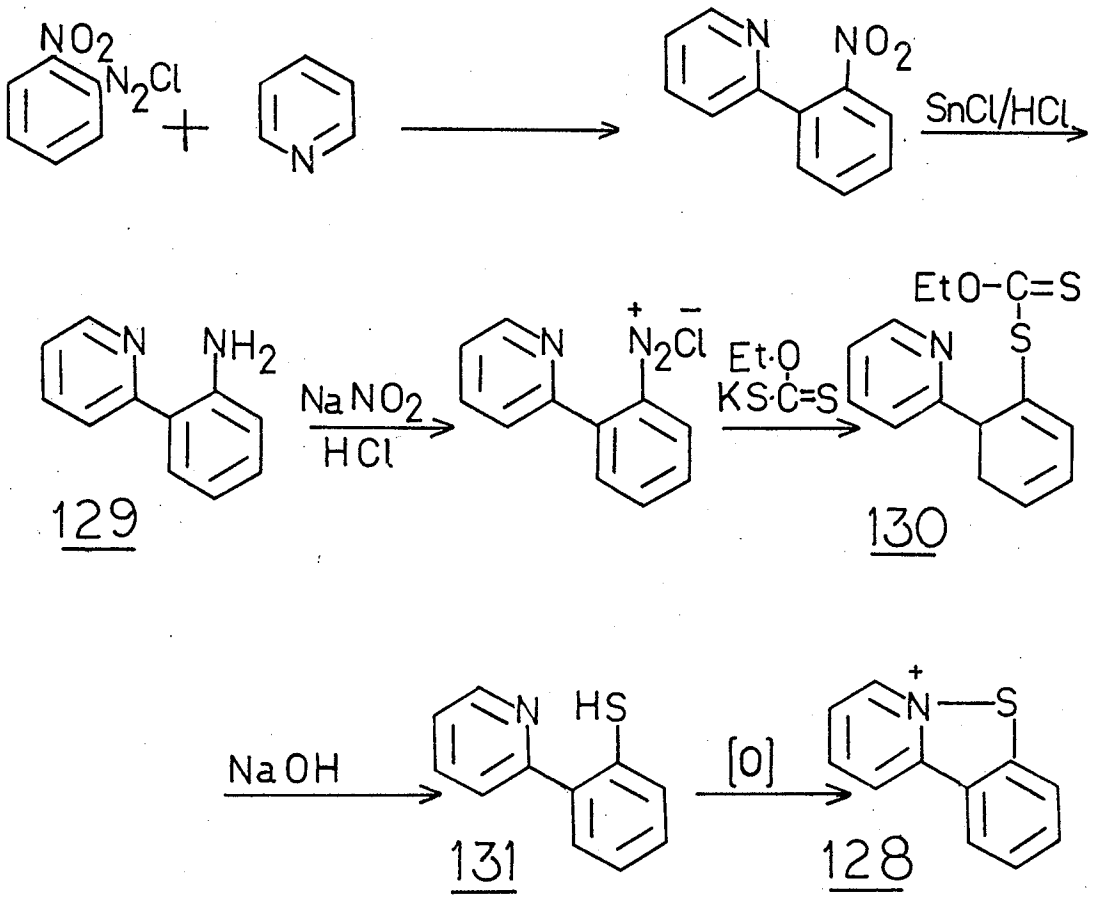
Attempt at preparation of such a compound was carried out according to the following scheme. 2,3, and 4-*o*-Nitrophenylpyridines were prepared from *o*-nitroaniline by the method of Butterworth and coworkers[123]. The 2,3, and 4 components of the product mixture were preferably separated by chromatography rather than fractional crystalization. The 2-component was then subjected to reduction by stannous



128

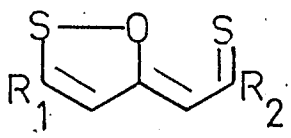
chloride in hydrochloric acid to afford the 2-(0.aminophenylpyridine) 129 .

Diazotization of 129 followed by Coupling with potassium ethyl xanthate, afforded the xanthate derivative 130 . This, on hydrolysis, gave the mercaptan 131. The mercaptan obtained was expected to undergo oxidation by either hydrogen peroxide in acetic acid or iodine in ethanol to afford the dibenzoisothiazolium salt 128 . While the first oxidation method did not appear to work, the second method afforded a very minute amount of salt-like material which was, however, too little to characterize.

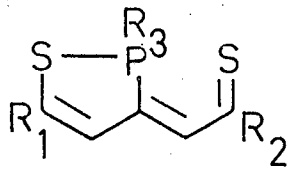


SUGGESTIONS FOR FUTURE RESEARCH

1. Evidence from the present work and from the last published literature appears to favour the hypothesis that invokes the use of sulfur d-orbitals to explain the symmetry of trithiapentalenes in solution. Further proof could be gained from the preparation and study of the two model compounds, 132 and 133 .



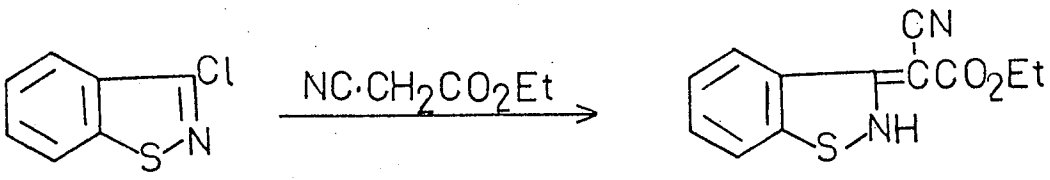
132

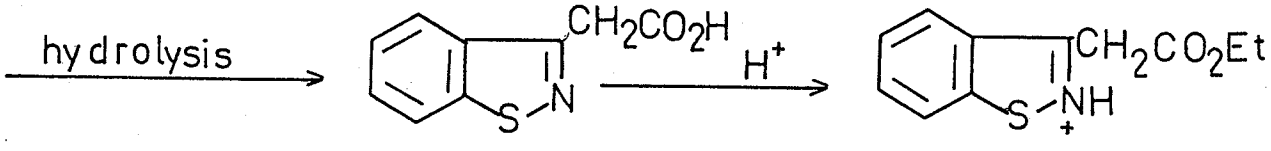


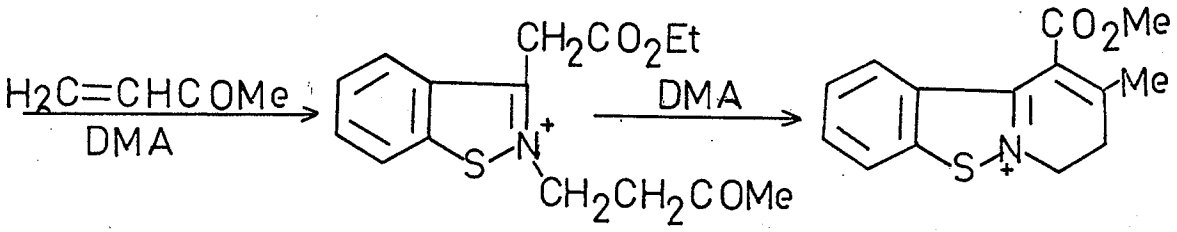
133

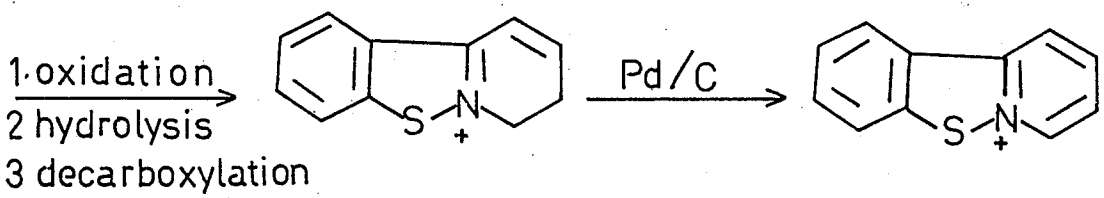
The first is incapable on valency shell expansion and therefore is expected to show properties similar to those of compound 32. On the other hand, compound 133 is expected to show properties similar to those of trithiapentalenes.

2. While the attempted synthesis of dibenzoisothiazolium salts 128 was not very successful, a recent publication by Chapman[130] reported the preparation of the isomeric thiazole isomer. Following the same approach, a possible route to 128 may be outlined in the scheme below.





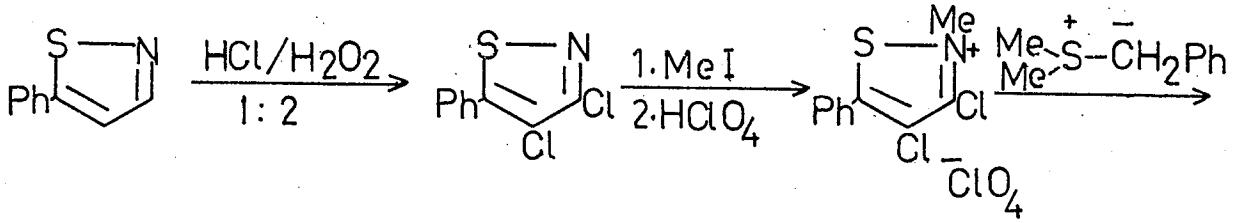


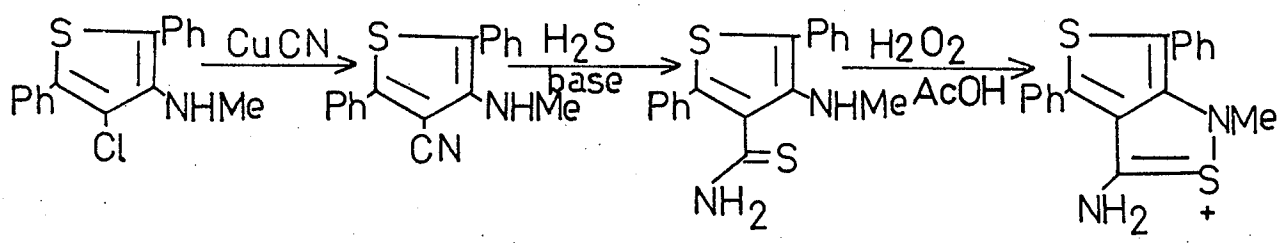


128

DMA = dimethylacetamide

3. Finally, an interesting possibility for future research involves the synthesis of a third isomeric system in the thieno isothiazole series. A possible route to the preparation of thieno [2,4-C] isothiazole is outlined in the following scheme.





EXPERIMENTAL

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded on a Varian A-56/60A spectrometer using $CDCl_3$ as solvent. Mass spectra were recorded on a Finnigan 1015 mass spectrometer. Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were performed by Alfred Bernhardt Laboratorium, 5251 Elbach über Engelskirchen, Fritz-Pregl-Strasse 14-16, West Germany.

The alumina for column chromatography was Camag band 507C supplied by Mondray Ltd. The silica gel for column chromatography was supplied by Davison Chemical with a mesh of 60-200, Grade H. The silica gel for thick or thin layer chromatography was Camag DSF-5 supplied by Mondray Ltd. Thick layer chromatographic plates were 1 mm. thick and prepared from a water base.

PREPARATION OF ISOTHIAZOLIUM SALTS

2-METHYLISOTHIAZOLIUM PERCHLORATE

Isothiazole (.85g , 0.01 mol) and dimethyl sulfate (1ml) were heated at 100°C for one hour. The mixture was treated with ether and the precipitated oil dissolved in acetic acid, and treated with 70% perchloric acid (0.5 ml). Colourless needles m.p. 145°C were obtained in 61% yield.

A sample of the perchlorate treated with aqueous sodium iodide gave the iodide identical (mixed m.p. and IR) with an authentic sample[16].

2-METHYL-4-PHENYLISOTHIAZOLIUM PERCHLORATE

The method of Bachers, McKinnon, and Buchshriber[29], was used to obtain the salt as off-white needles, m.p. 102°C, yield 85%.

2-METHYL-5-PENYLISOTHIAZOLIUM PERCHLORATE

(A) From 2-methyl-5-phenylisothiazoline-3-thione:

The thione was prepared from the reaction of 3-methylthio-5-phenyl -1,2-dithiolium iodide with methylamine, as described[44] except that the equivalent quantity of 40% ethanolic methylamine solution was used. Work up gave 5-phenyl-1,2-dithiole-3-thione, methyl-3- methylamino-dithiocinnamate, and 2-methyl-5-phenylisothiazoline-3-thione as described. When the reaction was performed with a fourfold excess of the amine solution and the mixture worked up as above, chromatography on 5% deactivated alumina gave initially 5-phenyl-1,2-dithiole-3-thione and methyl-3-methylaminodithiocinnamate. Extraction of a broad, strongly

adsorbed band with acetone gave a yellow oil which crystallized on scratching. Recrystallization from ethanol gave pale-yellow prisms, m.p. 96 - 98°C in 35% yield of N-methyl-3-methylaminothiocinnamide.

Analysis for $C_{11}H_{14}N_2S$,

Calculated: C, 64.21 ; H, 6.83 ; N, 13.59 ; S, 15.55

Found: C, 63.92 ; H, 6.89 ; N, 13.52 ; S, 15.64

NMR spectrum: τ 7.28 (3H doublet, J = 3.2 Hz, the amidic methyl), 7.00 (3H doublet, J = 3.2 Hz, the amine methyl), 5.02 (1H singlet, vinylic proton), 3.40 (1H band, the amidic NH), 2.68 (5H multiplet, the aromatic protons), - 1.20 (1H band, the amine NH, hydrogen bonded to C = S).

The mass spectrum: M^+ 206, calculated 206, 173 (M-SH).

The 2-methyl-5-phenylisothiazoline-3-thione, obtained above, (103.5 mg, 0.5 m mol) in acetic acid (4 ml) was treated with 30% aqueous hydrogen peroxide (0.15 ml). The solid dissolved almost immediately and the solution became dark-yellow. After one hour, the solution was treated with ether, and the precipitated oil treated with 70% perchloric acid (0.1 ml). The oil solidified and was recrystallized from acetic acid as pale-yellow plates identical (m.p. and I.R.) with an authentic specimen[29], yield 80%.

(B) From 3-phenyl-1,2-dithiolium perchlorate:

The perchlorate (1.035 g, 5 m mol) in ethanol (10 ml) was treated with 40% ethanolic methylamine solution (2 ml) and warmed gently with stirring until homogeneous. The red solution was treated with saturated

ethanolic iodine solution (2 ml), and 70% perchloric acid (1 ml) added. Dilution with ether and scratching gave a brown precipitate which was recrystallized from acetic acid containing perchloric acid, as yellow plates m.p. 144 - 145°C, identical (mixed m.p. and IR) with the above, yield 20%.

2-METHYL-4,5-DIPHENYLISOTHIAZOLIUM PERCHLORATE

(A) From 2-methyl-4,5-diphenylisothiazoline-3-thione: The thione was prepared from the reaction of 3-methylthio-4,5-diphenyl -1,2-dithiolium iodide (4.28 g, 0.01 mol) in tetrahydrofuran (70 ml), with 40% methylamine solution in ethanol (6 ml) at room temperature and stirred until homogeneous. The solution was evaporated and the residue chromatographed in benzene on 5% deactivated alumina. Two bands were obtained, a red band which gave 4,5-diphenyl-1,2-dithiole -3-thione (31%) on elution, and a strongly adsorbed yellow band, which was extracted with acetone. Evaporation of the solution gave a yellow solid which was recrystallized from ethanol as pale-yellow needles, m.p. 133° , 28% yield. Analysis for $C_{16}H_{13}NS_2$:

Calculated: C, 67.85 ; H, 4.59 ; N, 4.94 ; S, 22.62

Found: C, 67.82 ; H, 4.45 ; N, 5.01 ; S, 22.81 .

NMR spectrum: τ 6.21 (3H singlet, the methyl protons), 2.53 - 2.87 (10 H bands, the aromatic protons).

The mass spectrum: M^+ 283, calculated 283.

The thione was treated with hydrogen peroxide as for the previous compound. Pale-yellow needles, m.p. 99° , were obtained in

75% yield, which were identical (mixed m.p. and I.R.) to an authentic specimen.[29]

(B) From 3,4-Diphenyl-1,2-dithiolium Perchlorate:

This reaction was carried out as described for the previous synthesis, except that recrystallization was effected from acetone containing perchloric acid. Pale-yellow needles of the salt were obtained (25%), identical (mixed m.p. and I.R.) to an authentic specimen.

2-METHYL-5-METHYLTHIO-3-PHENYLISOTHIAZOLIUM PERCHLORATE

Methyl-3-methylaminodithiocinnamate (446 mg, 2 m mol) in ethanol (5 ml) was treated with saturated iodine solution until there was a slight permanent cloudiness. 70% perchloric acid (1 ml) was added, and dilution with ether produced yellow crystals. The product was recrystallized from acetic acid containing perchloric acid, as yellow needles m.p. 184 - 186°, 83% yield.

Analysis for C_{11} H_{12} N S_2 Cl O_4

Calculated: C, 41.05 ; H, 3.73 ; N, 4.35 ; S, 20.55 ; Cl, 11.05

Found: C, 41.07 ; H, 3.86 ; N, 4.23 ; S, 20.08 ; Cl, 10.92 .

NMR spectrum: in dimethylsulfoxide - d_6 , τ7.21 (3H singlet, the S - CH_3 group), 5.99 (3H singlet, the N - CH_3 group), 2.51 - 2.15 (5H bands, the aromatic protons).

2-METHYL-3-METHYLTHIO-5-PHENYLISOTHIAZOLIUM IODIDE

The method of Le Coustumer and Mollier[44] was used to obtain the salt as yellow needles of m.p. 165°C in yield 78%.

5-METHYLTHIO-2,4-DIPHENYLISOTHIAZOLIUM PERCHLORATE

2,4-Diphenylisothiazoline-5-thione[29] (0.566 g, 2 m mol) in n-butylacetate (10 ml) was treated with methyl iodide (2 ml) and allowed to stand. An oily precipitate which was deposited initially, crystallized on further standing. The mixture was diluted with ether, filtered, and the salt converted to the perchlorate in acetic acid containing perchloric acid. Recrystallization from acetic acid gave pale-yellow prisms, m.p. 158°C, identical (mixed m.p. and I.R.) with an authentic specimen[29].

2,4-DIPHENYLISOTHIAZOLIUM PERCHLORATE

The method of Bachers, McKinnon, and Buchshriber[29] was used to obtain the salt as yellow needles m.p. 158°C, in 34% yield.

2,5-DIPHENYLISOTHIAZOLIUM PERCHLORATE

The method of McKinnon and Robak[24] was used to obtain the salt as yellow needles, m.p., 199°C, in 52% yield.

2,4,5-TRIPHENYLISOTHIAZOLIUM PERCHLORATE

The method of McKinnon and Robak[24] was used to obtain the salt as yellow needles, m.p. 213°C, in 45% yield.

2,3,5-TRIPHENYLISOTHIAZOLIUM PERCHLORATE

The method of McKinnon and Robak[24] was used to obtain the salt as yellow needles, m.p. 256°C, in 48% yield.

2-METHYL-3-CHLORO-5-PHENYLISOTHIAZOLIUM PERCHLORATE

2-Methyl-5-phenylisothiazoline-3-thione[43] (0.207 g, 1 m mol) in benzene (5 ml) and thionyl chloride (1 ml) refluxed for one hour, the clear yellowish solution was evaporated off to give a dark-yellow oil which crystallized on cooling. Recrystallization from petroleum ether gave yellowish-pale needles m.p. 35°C[124]. The 3-chloro -5-phenylisothiazole obtained above was treated with dimethyl sulfate (1 ml) and heated at 100°C for one hour. The mixture was treated with ether and the precipitated oil dissolved in acetic acid and treated with 70% perchloric acid (0.5 ml), the salt was obtained as pale-yellow needles m.p. 97°C , yield 30%.

REACTIONS OF ISOTHIAZOLIUM SALTS

REACTION WITH SODIUM BENZOYLACETATE

General Method

The isothiazolium salts (~ 1 m mol) were added to a suspension in ethanol of sodium benzoylacetate (~ 1.5 m mol), prepared by addition of benzoylacetic acid[125] to a molar solution of sodium ethoxide in ethanol. The mixture was stirred and gently warmed until homogeneous. The mixture was then diluted with water, and the ether extract dried. Evaporation gave either crystalline material directly or oils which were purified by thin layer chromatography prior to crystallization. Products were recrystallized from ethanol or ethanol benzene, 1:1 mixture. Reactions and products are summarized in Table 1.

Treatment of 2-methyl-3-methylthio-4-phenylisothiazolium perchlorate with sodium benzoylacetate gave an oily product which, on examination by thin layer chromatography, gave the corresponding thiophene. However the first band on elution gave 30 mg of an orange oil, whose NMR had a broad band at -4.5τ , typical of β-amino-enethiones[128]. This was not analyzed, but an iodine oxidation in the presence of perchloric acid gave back the salt, confirming its structure as 3-phenyl-1-methylthio-1-methylaminoprop-1-ene-3-thione.

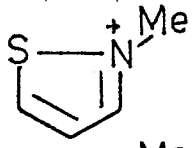
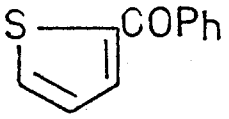
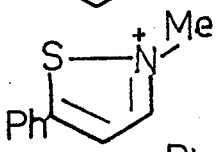
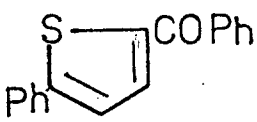
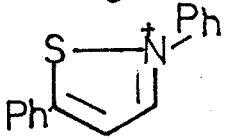
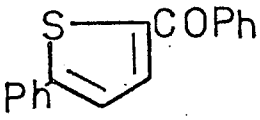
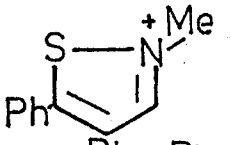
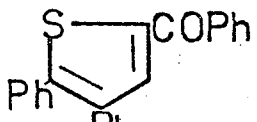
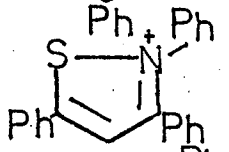
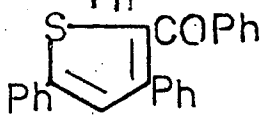
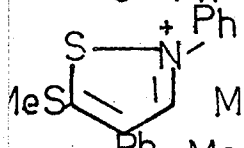
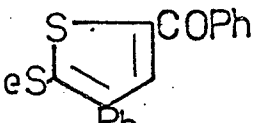
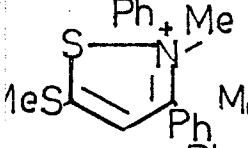
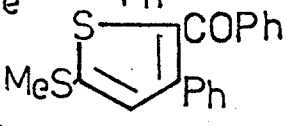
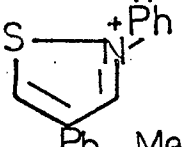
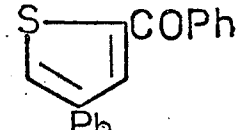
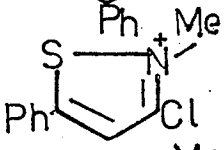
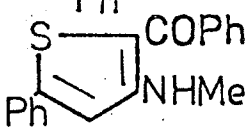
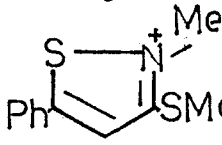
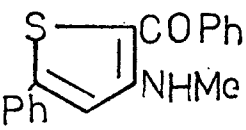
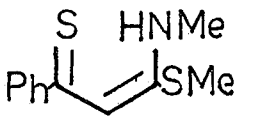
REACTIONS WITH HYDROGEN SULFIDE OR SODIUM HYDROGEN SULFIDE

General Methods

(a) The isothiazolium salts (~ 1 m mol) in ethanol (10 ml) were treated with equivalent quantities of ethanolic molar sodium hydrosulfide solution, and stirred until homogenous. The solutions were

Table 1

REACTIONS OF ISOTHIAZOLIUM SALTS WITH SODIUM BENZOYLACETATE

compound	product	yield	m.p.°C	analysis calcd, found	C	H	S	N
		71%	57[126]					
		63%	132[127]					
		63%	132					
		68%	150–152	C 81.13 F 81.17		4.71 4.84	9.41 9.51	
		42%	101[128]					
		77%	89–91	C 69.75 F 70.07		4.52 4.62	20.65 20.88	
		74%	32–33	C 69.75 F 70.04		4.52 4.69	20.65 20.85	
		40%	96	C 77.35 F 77.07		4.54 4.69	12.12 12.24	
		50%	103–109	C 73.51 F 73.45		5.12 5.25	10.95 10.91	4.76 4.67
	 + 	33% 15%						

diluted with water and ether-extracted.

(b) The salts (~1 m mol) in water suspension were treated with hydrogen sulfide and boiled 10 minutes. The mixtures were cooled and ether-extracted.

The ether extracts from (a) or (b) were dried, evaporated, and examined by thin layer chromatography. The results are summarized in Table 2. There was little to choose between the two methods, and yields and products by each were comparable when performed on identical compounds.

The sulfide obtained from the reaction of 2-methyl-4,5-diphenylisothiazolium perchlorate with hydrogen sulfide, could not be isolated sufficiently pure for analysis and was converted by treatment with perchloric acid into 3,4-diphenyl-1,2-dithiolium perchlorate[24], similarly to known methods[11].

REACTION OF 2,3,5-TRIPHENYLISOTHIAZOLIUM PERCHLORATE WITH SODIUM BENZENETHIOLATE

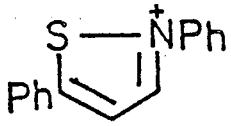
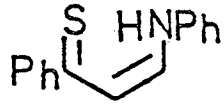
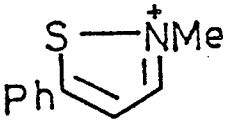
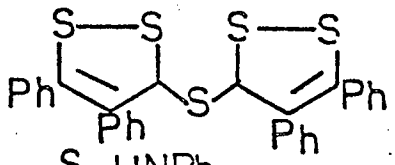
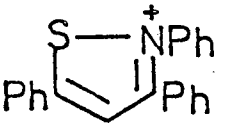
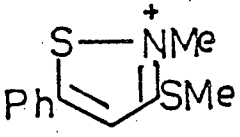
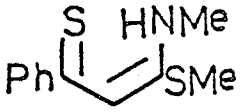
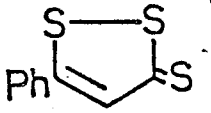
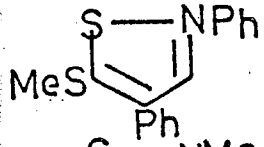
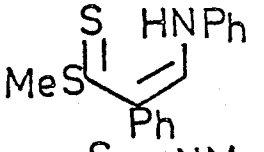
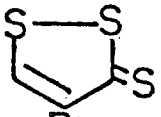
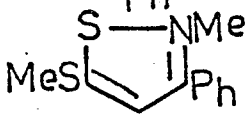
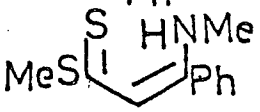
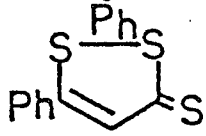
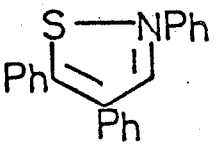
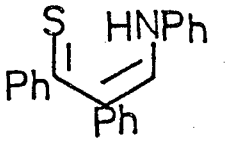
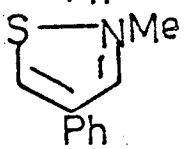
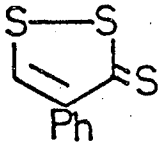
The isothiazolium salt (613.5 mg, 1 m mol) in ethanol (20 ml) was treated with the equivalent quantity of sodium benzenethiolate in ethanol (1 ml), and stirred until homogeneous. The dark-red solution was diluted with water and extracted with ether. Chromatography afforded 1-anilino-1,3-diphenylprop-1-ene-3-thione (81% yield), identical (mixed m.p. and I.R.) to an authentic sample[11]. Diphenyl disulfide (89 mg) was also isolated from the reaction mixture.

REACTION OF 2- METHYL-5-METHYLTHIO-3-PHENYLISOTHIAZOLIUM PERCHLORATE WITH SODIUM BENZENETHIOLATE

The reaction, performed as above, gave methyl β-methyl-

Table 2

REACTIONS OF ISOTHIAZOLIUM SALTS WITH HYDROGEN SULFIDE Method (a) OR SODIUM HYDROGEN SULFIDE Method (b)

Isothiazolium salt	Method	Products in order of elution	% yield
	(a)		52
	(a)		56
	(b)		40
	(b)		45
	(a)		32 ,  28
	(b)		45 ,  49
	(b)		43 ,  45
	(b)		20
	(b)		21

aminodithiocinnamate (in 59% yield), identical to an authentic specimen[44].

REACTION OF BIS-4-PHENYL-1,2-DITHIOL-3-YL SULFIDE WITH HYDROGEN SULFIDE

The sulfide [94] (0.2g) in water (10 ml) was boiled and a stream of hydrogen sulfide passed through. After 10 minutes the mixture was cooled and ether-extracted. The extract, on examination by thin layer chromatography, gave unreacted material, and 4-phenyl-1,2-dithiole-3-thione (30% yield). Boiling of the sulfide with sodium hydrogen sulfide gave similar results.

REACTION OF 2,5-DIPHENYLISOTHIAZOLIUM PERCHLORATE WITH SODIUM CYANIDE

The salt (0.238 g, 1 m mol) in ethanol (5 ml) was treated with sodium cyanide (0.05 g, 1 m mol). The mixture was warmed 5-10 minutes in a water-bath until homogenous, then diluted with water, and extracted with ether. The ether extract dried and evaporated to give dark oil, which on chromatography gave several bands of unidentified decomposition products.

THE REACTION OF 4,5-DIPHENYL-2-METHYL-3-METHYLTHIOISOTHIAZOLIUM IODIDE WITH SODIODIETHYL MALONATE

A solution of sodium ethoxide was prepared by adding (0.02 g, 1 m mol) of sodium to (5 ml) of super dry ethanol[131]. To this solution, 0.19g (1.2 ml) of diethyl malonate was added with stirring then (0.55 g , 1.2 m mol) of the salt was added. The stirring was continued for 10 minutes. The solution which became red on adding the salt, gradually became yellow and methyl mercaptan was evolved. Water was then added and the organic layer extracted by benzene. The benzene

solution was dried and evaporated to afford diethyl 4,5-diphenyl -3-methylimino-2,3-dihydrothiophene-2,2-dicarboxylate. Recrystallization from toluene by dissolving in the minimum quantity then leaving at 0°C for three days, gave yellow prisms of the 3-iminothiophene 50, m.p. 97°C.

Analysis for C_{23} H_{23} N S O_4 :

Calculated: C, 67.48 ; H, 5.62 ; N, 3.42 ; S, 7.82

Found: C, 67.47 ; H, 5.44 ; N, 3.15 ; S, 7.84

Mass spectrum: M^+ 409, calculated 409. NMR spectrum: showed that the compound exists in two isomers. τ8.8 - 9.1 (two superimposed methyl 6H triplets), 6.2 - 6.4 (two methylene 4H quartets and two N-methyl 3H singlets, 2.6 - 2.9 (the aromatic protons).

REACTION OF DIMETHYLMETHYLENESULFURANE WITH 2,4-DIPHENYLISOTHIAZOLIUM PERCHLORATE

A solution of (1 m mol) methyl lithium in anhydrous ether was added dropwise over several minutes to a stirred suspension of (1.2 m mol) trimethylsulfonium iodide, in (3 ml) tetrahydrofuran under nitrogen at 0°C. After stirring for 5 minutes, the isothiazolium salt (0.4 g, 1.2 m mol) was added, stirring was continued for 30 minutes at 0°C, and then for 1 hour at 25°C. Water was then added, the organic layer then extracted in benzene. The benzene solution was dried, evaporated, and the oil obtained was then chromatographed. The fastest eluting orange band afforded on evaporation orange oil which crystallized on trituration with methanol (30% yield), m.p. 204°C.

Mass spectrum M^+ 297, calculated 297. NMR spectrum: τ7.2 (3H singlet, the S-Me group), 2.7 - 3.1 (11H bands, the aromatic protons), 1.8 (the amino proton). The compound, however, seems to be unstable and attempt at purification for analysis was unsuccessful.

REACTION OF DIMETHYLMETHYLENESULFURANE WITH 2,4-DIPHENYL-5-METHYLTHIO-ISOTHIAZOLIUM PERCHLORATE

The reaction performed as above afforded orange prisms of 2,5-dimethylthio-3-anilinothiophene, m.p. 198°C in 28% yield.

Mass spectrum: M^+ 243 Calculated 243.

REACTION OF p. NITROBENZYLIDENESULFURANE WITH 2,4-DIPHENYLISOTHIA-ZOLIUM PERCHLORATE

The ylid (1 m mol) was prepared from the corresponding sulfonium salt by its treatment with molar quantity of sodium ethoxide in dry ethanol. A slight excess of the isothiazolium salt (~1.2 m mol) was then added. After stirring for 15 minutes, the mixture was diluted with water and the ether extract dried. Evaporation gave an oil which on chromatography afforded a main orange band which, on extraction and recrystallization from ethanol, afforded 2-p.nitrophenyl-3-anilino-4-phenylthiophene, as yellow-orange prisms of m.p. 158.

Analysis for C_{22} H_{16} N_2 S O_2 :

Calculated: C, 70.96 ; H, 4.3 ; N, 7.52 ; S, 8.6

Found: C, 70.71 ; H, 4.7 ; N, 7.52 ; S, 9.10

REACTION OF 2,4-DIPHENYLISOTHIAZOLIUM PERCHLORATE WITH DIETHYLBENZYL PHOSPHONATE

The reaction was performed according to the procedure of Fieser[132], to afford 2,4-diphenylthiophene as white crystals m.p. 121°C [lit 121°C][134], in 18% yield.

REACTION OF 4,5-DIPHENYL-3-METHYLISOTHIAZOLIUM PERCHLORATE WITH ETHOXYCARBONYLMETHYLDIETHYL PHOSPHONATE

The reaction performed as above tentatively afforded 3-methylamino -4,5-diphenylthiophene-2-ethyl carboxylate. Mass spectrum: M^+ 337, Calculated for $C_{20}\ H_{19}\ S\ O_2$, 337. The yield, however, was too low to allow for further investigation of the structure of the product.

REACTION 2-METHYL-5-METHYLTHIO-4-PHENYLISOTHIAZOLIUM PERCHLORATE WITH METHYLLITHIUM AND DIMETHYL ACETYLENEDICARBOXYLATE

Methyllithium (1 m mol) in ether was added dropwise to a stirred suspension of the isothiazolium salt (1.2 m mol) in anhydrous ether, under nitrogen. The stirring continued for 15 minutes. Then (1 m mol) of dimethyl acetylenedicarboxylate was added followed by 20 ml of benzene; the reaction mixture was heated gently to evaporate the ether, then refluxed for 5 hours. On chromatography, many bands were obtained. However the yellow band at the bottom of the plate afforded the expected product 60, as indicated by its mass spectrum M^+ 317; calculated for $C_{14}\ H_{15}\ S\ N\ O_2$, 317. The low yield of the reaction did not allow for further proof of the structure.

REACTION OF THE CYCLOPENTADIENYL ANION WITH 2,4-DIPHENYL-5-METHYLTHIOISOTHIAZOLIUM PERCHLORATE

Cyclopentadiene was obtained from the dimer according to the method described in Organic Syntheses[133]. A solution of (1 m mol) methyllithium in anhydrous ether was added to a solution of (1.2 m mol) cyclopentadiene in anhydrous ether under nitrogen at the dry ice temperature. After stirring for 5 minutes, the salt (0.4 gm , 1.2 m mol) was added, and stirring continued for another 30 minutes at room temperature. The solution was then diluted with water and the ether layer separated and dried. Evaporation gave dark oil which was chromatographed. The top dark blue band was extracted in benzene, which, on evaporation, afforded the crystalline pseudoazulene 62b , m.p. 278°C in 60% yield. Mass spectrum: M^+ 256 , calculated 256. Analysis for $C_{15}H_{12}S_2$:

Calculated: C, 70.31 ; H, 4.68 ; S, 25.0

Found: C, 69.69 ; H, 4.8 ; S, 24.67 .

NMR spectrum: τ7.5 (3H singlet, the S-Me group), 2.4 - 2.9 (9 H bands, the aromatic protons).

REACTION OF CYCLOPENTADIENYL ANION WITH 2,4-DIPHENYLISOTHIAZOLIUM PERCHLORATE

The reaction performed as above to afford the pseudoazulene 62a , as a dark grey plates of m.p. 250°C , mass spectrum 210^+ , calculated 210. Analysis for $C_{14}H_{10}S$:

Calculated: C, 80.00 ; H, 4.76 ; S, 15.23

Found: C, 79.20 ; H, 4.97 ; S, 14.91

REACTION OF THE INDENYL ANION WITH 2,4-DIPHENYL-5-METHYLTHIOISOTHIAZOLIUM PERCHLORATE

Methyllithium (1 m mol), in ether was added to indene (1.2 mol) in anhydrous ether (10 ml) under nitrogen. The solution was stirred for 30 minutes, then isothiazolium salt (0.4 g ~ 1.2 m mol) was added. Stirring was continued for another 30 minutes, then the solution diluted with water. The ether layer separated, dried, evaporated, and chromatographed in benzene. The major pink band afforded a dark pink oil (20% yield) which could not be crystallized, and was not analyzed. However the mass spectrum was M^+ 399 , M(- S) , 367. calculated for C_{25} H_{21} N S_2 399 .

NMR spectrum: τ7.5 (3H singlet, the S-Me group) , 2.5 - 3.2 (16H bands, the aromatic protons, and the amino hydrogen). Although no specific band could be assigned for the amino proton in the NMR spectrum, the I.R. spectrum proved the presence of this group by its characteristic absorption at frequency 3500 $cm.^{-1}$

PREPARATION OF ISOTHIAZOLINETHIONES

PREPARATION OF 2-ALKYL-4-PHENYLISOTHIAZOLINE-5-THIONES

4-phenyl-1,2-dithiole-3-thione (2.1g, 0.01 mol)[135] dissolved in carbon tetrachloride (50 ml) was slowly treated with a solution of bromine (1.76g, 0.011 mol) in carbon tetrachloride (20 ml) with stirring. The yellow solid formed was collected, washed with carbon tetrachloride, and briefly dried to remove excess carbon tetrachloride. The solid was added portionwise to solutions of the desired amines (~0.05 mol) in ethanol (50 ml). A vigorous reaction ensued. After 5 minutes the mixture was diluted with water and the product stirred with 10% hydrochloric acid. The products crystallized immediately or on trituration with ethanol and were recrystallized from ethanol or benzene-petroleum ether 1:1 mixture. The results are summarized in Table 3.

PREPARATION OF 2,5-DIPHENYLISOTHIAZOLINE-3-THIONE

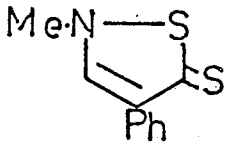
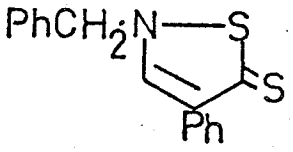
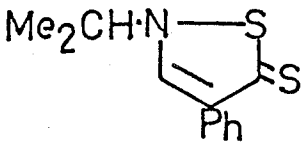
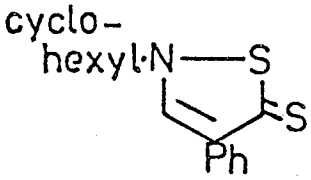
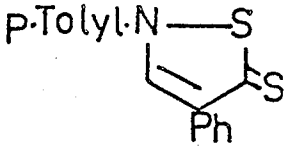
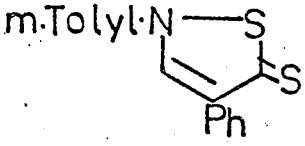
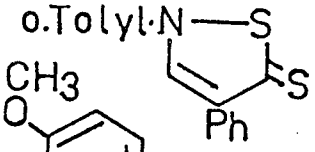
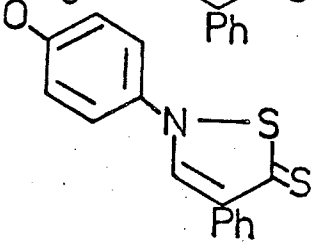
2,5 Diphenyl-3-methylthioisothiazolium perchlorate (383 mg, 1 m mol) in pyridine (10 ml) was refluxed for 5 minutes. The mixture was poured into water and ether extracted. The ether layer was washed with dilute hydrochloric acid, then with water, dried, evaporated to give yellow crystals. The product was recrystallized from acetic acid as yellow flakes, m.p. 160° (30% yield). Analysis for $C_{15}H_{11}NS_2$:

Calculated: C, 66.91 ; H, 4.09 ; N, 5.20 ; S, 23.79

Found: C, 66.74 ; H, 4.17 ; N, 5.29 ; S, 23.68

Table 3

PREPARATION OF 2-ALKYL-4-PHENYLISOTHIAZOLINE-5-THIONES

compound	m.p.°C	yield	analysis calcd, found	C	H	N	S
	150-152	73 %	C	57.97	4.35	6.76	30.91
			F	57.78	4.17	6.59	31.15
	120-122	61 %	C	67.84	4.59	4.59	22.64
			F	67.67	4.68	5.05	22.64
	120-121	55%	C	61.28	5.52	5.94	27.23
			F	61.09	5.44	5.76	27.21
	146-147	50%	C	65.31	6.18	5.09	23.25
			F	65.43	6.25	5.15	23.12
	178-179	52%	C	67.84	4.59	4.95	22.64
			F	67.71	4.76	4.79	22.54
	151-153	54 %	C	67.84	4.59	4.95	22.64
			F	67.71	4.68	4.94	22.69
	142-143	56 %	C	67.84	4.59	4.95	22.64
			F	67.68	4.48	4.98	22.40
	145-146	55%	C	64.21	4.34	4.68	21.40
			F	63.98	4.43	4.72	21.54

REACTION OF 2,4-DIPHENYLISOTHIAZOLINE-5-THIONE WITH DIBENZOYLACETYLENE

The thione (26.9 mg, 0.1 m mol) in benzene (2 ml) was added to a solution of dibenzoylacetylene (23.4 mg, 0.1 m mol) in hot benzene (2 ml). The solution turned red immediately. The solution was boiled briefly, then evaporated. A red oil was obtained which crystallized on standing. The product was recrystallized from toluene-ethanol, 1:1 mixture as red prisms, m.p. 162 - 163°C, yield 95%.

Analysis for C_{31} H_{21} O_2 S_2 N :

Calculated: C, 73.97 ; H, 4.16 ; S, 12.70 ; N, 2.77

Found: C, 73.85 ; H, 4.30 ; S, 12.63 ; N, 291

The mass spectrum: M^+ 503 , calculated 503.

REACTION OF 2,4-DIPHENYLISOTHIAZOLINE-5-THIONE WITH PHENYLACETYLENE

To the thione (269 mg, 1 m mol) in benzene (10 ml) was added phenylacetylene (102 mg, 1 m mol) and the mixture was refluxed 24 hours. Chromatography gave initially an orange band which was purified by rechromatography to give a red oil (20 mg). This could not be crystallized and appeared on chromatography to revert partially to starting material.

The mass spectrum: M^+ 371 , calculated 371 , the NMR spectrum: τ3.48 , 3.21 (1 H singlets, the vinyl protons), 2.95 - 2.45 (30 H bands, the aromatic protons), 1.95 (two superimposed 1 H singlets, the aldimine protons).

THE REACTION OF 2-METHYL-5-PHENYLISOTHIAZOLINE-3-THIONE WITH PHENYLACETYLENE

(A) To the thione(283 mg, 1 m mol) in benzene (10 ml) was added phenylacetylene (102 mg, 1 m mol) and the mixture was refluxed under nitrogen for 24 hours. Work up as above gave mainly starting material and a very poor yield of the expected 3-thioacylmethylene-1,2-isothiazole, mass spectrum: M^+ 309 , Calculated for C_{24} H_{19} N S, 309.

(B) The reaction carried out as above in xylene solution, but no significant improvement in the yield was obtained, although other bi-products were obtained.

REACTION OF 2,4-DIPHENYLISOTHIAZOLINE-5-THIONE WITH DIPHENYLACETYLENE

The thione (269 mg, 1 m mol) and the acetylene (178 mg, 1 m mol) in benzene were refluxed 26 hours. Chromatography indicated the formation of a red product but attempted isolation gave only starting materials.

REACTION OF 2,4-DIPHENYLISOTHIAZOLINE-5-THIONE WITH N-PHENYLMALEIMIDE

The thione (269 mg, 1 m mol) and N-phenylmaleimide (173 mg, 1 m mol) in benzene were refluxed 3 hours. Evaporation gave a yellow solid which was recrystallized from toluene as fine yellow crystals, m.p. 180 - 182°C (yield 76%). Analysis for C_{25} H_{18} O_2 N_2S_2 :

Calculated: C, 67.87 ; H, 4.07 ; N, 6.33 ; S, 14.49

Found: C, 67.69 ; H, 4.11 ; N, 6.45 ; S, 14.67

The NMR spectrum: τ 5.30 and 5.03 (2 H doublets, the dithiolane ring protons, J = 7.5 Hz), 2.82 - 2.40 (15 H bands, the

aromatic protons), 1.82 (1 H singlet, the aldimine proton), the I.R. spectrum: 1710 cm^{-1} (C=O str). The mass spectrum: m^+ 442 calculated 442.

REACTION OF 2,4-DIPHENYLISOTHIAZOLINE-5-THIONE WITH DIETHYL AZODICARBOXYLATE

The thione (269 mg, 1 m mol) and the ester (174 mg, 1 m mol) in benzene (10 ml) were refluxed together 10 hours. Chromatography gave only starting material and dark decomposition products.

REACTION OF 2-METHYL-4-PHENYLISOTHIAZOLINE-5-THIONE WITH DIMETHYL ACETYLENEDICARBOXYLATE

The thione (207 mg, 1 m mol) in benzene (10 ml) was mixed with a solution of the ester (142 mg, 1 m mol) in benzene (10 ml) and warmed briefly. The red solution was evaporated to yield an orange oil which crystallized on trituration under ethanol. The product was crystallized from ethanol as red needles, m.p. 111°C in 82% yield.

Analysis for $C_{16}H_{15}O_4NS_2$:

Calculated: C, 54.95 ; H, 4.29 ; N, 4.02 ; S, 18.05

Found: C, 55.05 ; H, 4.30 ; N, 3.90 ; S, 18.21 .

The NMR spectrum: τ 6.46 (3 H doublet, the nitrogen methyl, J = 2.0 Hz), 6.25 and 6.16 (two 3 H singlets, the ester methyls), 2.68 (5 H singlet, the aromatic protons), 2.07 (1 H doublet, the aldimine proton, J - 2.0 Hz); the IR spectrum: 1705 cm^{-1} (C=O); the mass spectrum M^+ 349, calculated 349.

REACTION OF DIMETHYL-2-(1-PHENYL-2-METHYLIMINOETHYLIDENE)-1,3-DITHIOLE -4,5-DICARBOXYLATE WITH DIMETHYL ACETYLENEDICARBOXYLATE

The dithiole (359 mg, 1 m mol) and the ester (142 mg, 1 m mol) in benzene (20 ml) were refluxed 48 hours. Examination by t.l.c. indicated that some decomposition had occurred but the product was mainly the aldehyde 77 (56% yield).

REACTION OF DIMETHYL 2-(1-PHENYL-2-PHENYLIMINOETHYLIDENE)-1,3-DITHIOLE -4,5-DICARBOXYLATE WITH DIMETHYL ACETYLENEDICARBOXYLATE

Treatment of equimolar quantities in boiling benzene for 48 hours gave only starting material.

REACTION OF 2-BENZYL-4-PHENYLISOTHIAZOLINE-5-THIONE WITH DIMETHYL ACETYLENEDICARBOXYLATE TO FORM DIMETHYL α-PHENYLFORMYLMETHYLENE -4,5-DICARBOXYLATE 77

The thione (283 mg, 1 m mol) in benzene (10 ml) was treated with dimethyl acetylenedicarboxylate (142 mg, 1 m mol). The solution turned red immediately and was evaporated to give a red oil. This could not be crystallized, even after t.l.c., but trituration under ethanol gave the aldehyde 77 as orange prisms m.p. 127-129°, from benzene (61%). The product was identical (mixed m.p., I.R. NMR) to an authentic sample[104].

REACTION OF 2-METHYL-5-PHENYLISOTHIAZOLINE-3-THIONE WITH DIMETHYL ACETYLENEDICARBOXYLATE

The thione (207 mg, 1 m mol) and the ester (142 mg, 1 m mol) in benzene (10 ml) were refluxed 24 hours. The mixture gradually turned dark. Chromatography using chloroform as an eluent yielded three main fractions. The first eluted gave starting material (30%)

and a second orange band which was purified by further chromatography. Evaporation yielded 79 as an orange oil which could not be crystallized (37%).

The NMR spectrum: τ 7.16 (3 H singlet, the N-methyl), 6.32-6.08 (four 3 H singlets, the ester protons, not properly resolved), 3.56 (1 H singlet, the methine proton), 2.60-2.51 (5 H bands, the aromatic protons); the mass spectrum M^+ 491, calculated 491.

A third dark fraction appears to consist of polymeric material and was not further investigated.

REACTION OF 2-METHYL-4,5-DIPHENYLISOTHIAZOLINE-3-THIONE WITH DIMETHYL ACETYLENEDICARBOXYLATE

The thione (283 mg, 1 m mol) was treated with the ester (142 mg, 1 m mol) as above. Chromatography using chloroform as an eluent gave a number of bands. The first eluted was starting thione (50%). An orange band next eluted gave on evaporation a red oil, which crystallized from methanol as red prisms, m.p. 159-160°C (21%). Use of a twofold excess of ester increased the yield to 68%.

Analysis for $C_{28}H_{25}NO_8S_2$:

Calculated: C, 59.26 ; H, 4.40 ; N, 2.46 ; S, 11.28

Found: C, 59.36 ; H, 4.28 ; N, 2.51 ; S, 11.18 .

The NMR spectrum: τ 7.26 (3 H singlet, the N-methyl), 6.30 and 6.24 (two 6 H singlets, the ester methyls, not properly resolved), 2.70 (10 H singlet, the aromatic protons). The mass spectrum M^+ 567, calculated 567.

Examination of another more strongly adsorbed band gave a

dark red solid which crystallized as dark red needles, m.p. 255°C, from methanol (7 mg). The mass spectrum M^+ 535, calculated for $C_{28}H_{25}NO_8S$ 535.

REACTION OF 2,5-DIPHENYLISOTHIAZOLINE-3-THIONE WITH DIMETHYL ACETYLENE-DICARBOXYLATE

2,5-Diphenylisothiazoline-3-thione (26.9 mg, 0.1 m mol) and the ester (14.2 mg, 0.1 m mol) in benzene (15 ml) were refluxed 24 hours. The solvent on evaporation gave a yellow oil, which on chromatography yielded the spiran diadduct (51%), identical (mixture m.p. and mass spectrum) to an authentic specimen[89].

REACTION OF 2-METHYL-5-PHENYLISOTHIAZOLINE-3-THIONE WITH PHENACYLIDENE-TRIPHENYLPHOSPHORANE

The thione (207 mg, 1 m mol) and the phosphorane (380 mg, 1 m mol) were melted together and heated under nitrogen for one hour at 180°C. The red mixture was dissolved in benzene and chromatographed. A number of bands were obtained but the first red band eluted gave a red oil which crystallized on standing and was recrystallized from benzene as orange prisms m.p. 144-145°C yield 36%.

Analysis for $C_{18}H_{15}NS_2$:

Calculated: C, 69.85 ; H, 4.85 ; N, 4.53 ; S, 20.62

Found: C, 70.04 ; H, 4.71 ; N, 4.54 ; S, 20.84 .

The NMR spectrum: τ 6.44 (3 H singlet, the methyl protons), 3.57 (1 H doublet, the thiazoline proton, split by the exocyclic methine proton, J = 1 Hz), 2.90-2.06 (11 H bands, the aromatic protons and the exocyclic methine proton); the mass spectrum M^+ 309,

calculated 309.

Other bands from the chromatogram gave starting thione and triphenylphosphine oxide.

REACTION OF 2-METHYL-5-PHENYLISOTHIAZOLINE-3-THIONE WITH p.METHYL-PHENACYLIDENETRIPHENYLPHOSPHORANE

The reaction carried out as above gave the thioacylidene-thiazole as red prisms, m.p. 185, from toluene (41%).

Analysis for $C_{19}H_{17}NS_2$:

Calculated: C, 70.59 ; H, 5.26 ; N, 4.33 ; S, 19.81

Found: C, 70.41 ; H, 5.28 ; N, 4.36 ; S, 19.66 .

The NMR spectrum: τ 7.55 (3 H singlet, the aromatic methyl), 6.39 (3 H singlet, the N-methyl), 3.50 (1 H doublet, J = 1.0 Hz the thiazoline proton), 2.79-2.05 (10 H bands, the aromatic and the exo-cyclic methine protons); the mass spectrum M^+ 323, calculated 323.

REACTION OF 4,5-DIPHENYLISOTHIAZOLINE-3-THIONE WITH PHENACYLIDENE-TRIPHENYLPHOSPHORANE

The reaction carried out as above gave a poor yield (>10%) of the thiophenacylidenethiazole, identical (mixed m.p. and NMR) with an authentic sample prepared by another route (see below).

REACTION OF 2-METHYL-4,5-PHENYLISOTHIAZOLINE-3-THIONE WITH PHENACYL-IDENETRIPHENYLPHOSPHORANE

The reaction carried out as above gave mainly starting thione and triphenylphosphine oxide plus other products but no thiophenacyl-idenethiazole.

PREPARATION OF 2-METHYLTHIO-3-METHYL-4-PHENYLTHIAZOLIUM PERCHLORATE

Methyl-N-methyldithiocarbamate (1.21g, 10 m mol) and phenacyl bromide (1.99g, 10 m mol) , in ethanol (10 ml) were refluxed for 24 hours. The mixture was cooled and perchloric acid (0.5 ml) was added, then dilution with ether afforded pale yellow precipitate. The precipitate was then recrystallized from acetic acid as colorless flakes, m.p. 132°C in 80% yield. Analysis for $C_{11}H_{12}NS_2ClO_4$:

Calculated: C, 41.05 ; H, 3.73 ; N, 4.35 ; S, 19.95 ; Cl, 11.04

Found: C, 40.59 ; H, 3.69 ; N, 4.28 ; S, 19.42 ; Cl, 10.89

NMR spectrum: τ 6.9 (3 H singlet, the S-Me group), 6.2 (3 H singlet, the N-Me group), 2.0-2.3 (6 H band, the aromatic protons, the phenyl and thiazole protons). Refluxing the salt (320 mg, 1 m mol) in pyridine (10 ml) for 5 min., dilution with water and extraction in ether afforded the 3-methyl-4-phenylthiazolinethione identical to a sample prepared by another method (see below).

PREPARATION OF 2-METHYLTHIO-3-METHYL-5-PHENYLTHIAZOLIUM PERCHLORATE

α-Bromo,α-phenylacetaldehyde (1.99 g, 10 m mol) and methyl N-methyldithiocarbamate (1.21 g, 10 m mol), were treated as above to afford colorless flakes m.p. 127°C in 72% yield. Treatment with saturated aqueous potassium iodide solution afforded the iodide identical to an authentic sample[136].

PREPARATION OF 3,4-DIPHENYL-4-THIAZOLINE-2-THIONE

The general method for preparing N-alkyl-4-thiazoline-2-thiones, described by Humphlett and Lamon[109] was used with certain

modifications.

Thus to a solution of potassium acetate (9.8 g, 0.1 mol) in methanol(50 ml), aniline (9.3 g, 0.1 mol) was added on stirring. The temperature was kept below 10°C in ice-brine bath. Carbon disulfide (6.2 ml, 0.1 mol) was added dropwise. The solution was let stand for 2 hours, then phenacyl bromide (9.89 g, 0.05 mol) was added portionwise to the stirred solution. After 3 hours the solution was diluted with water (~50 ml), evaporation of the methanol and cooling, afforded a crude white precipiate. The precipitate was filtered off, dried and dissolved in 80% sulfuric acid solution (~30 ml). After one-half hour, water was added and the thione precipitated as crude pale yellow crystals, which was then recrystallized from benzene or ethanol as white needles, m.p. 159°C, in 72% yield.

Analysis for $C_{15}H_{11}S_2N$:

Calculated: C, 66.90 ; H, 4.00 ; N, 5.00 ; S, 23.79

Found: C, 66.77 ; H, 4.00 ; N, 4.86 ; S, 23.51 .

PREPARATION OF 3-METHYL-4-p.TOLYL-4-THIAZOLINE-2-THIONE

This was prepared according to the method above using p.methylphenacyl bromide. The thione was obtained as pale yellow crystals m.p. 110 in 60% yield. Mass spectrum M^+ 221, calculated 221.

Analysis for $C_{11}H_{11}S_2N$,

Calculated: C, 69.84 ; H, 5.82 ; N, 7.40 ; S, 16.93

Found: C, 69.54 ; H, 5.51 ; N, 6.94 ; S, 16.90 .

PREPARATION OF 4,5-DIPHENYL-3-METHYLTHIAZOLINE-2-THIONE

The above method was followed using desyl chloride. The thione was obtained as white crystals, m.p. 178, in 65% yield. Mass spectrum M^+ 283, calculated 283. Analysis for $C_{16}H_{13}S_2N$:

Calculated: C, 67.8 ; H, 4.5 ; N, 5.02 ; S, 22.61

Found: C, 67.58 ; H, 4.89 ; N, 4.53 ; S, 22.48

PREPARATION OF 2-THIOPHENACYLIDENEBENZOTHIAZOLE

Benzothiazoline-2-thione (2.81 g, 10 m mol) and phenacyl bromide (1.99 g, 10 m mol) were condensed according to the method described by Knott[108]. The salt obtained was washed with ether, and treated with pyridine (10 ml), and refluxed till homogeneous. The mixture was then diluted with water and extracted in benzene. The benzene extration washed with dilute hydrochloric acid and then with water, dried and evaporated. The crystalline precipitate afforded two bands on chromatography, an upper one which corresponded to the starting thione, and a lower band which was extracted and recrystallized from benzene, m.p. 176°C [lit. 176°C], yield 30%.

Thionation was carried out by refluxing the ketone (0.5 g) with P_2S_5 (1.0 g) in benzene for four hours. The benzene solution was filtered and washed with sodium bicarbonate solution, dried and evaporated. The thione obtained was then purified by chromatography and recrystallized from benzene as orange crystals m.p. 148, in 60% yield. Mass spectrum: M^+ 283, calculated 283. Analysis for $C_{16}H_{13}NS_2$

Calculated: C, 67.8 ; H, 4.5 ; N, 4.9 ; S, 22.61

Found: C, 67.5 ; H, 4.8 ; N, 4.84 ; S, 22.74 .

NMR: τ 6.2 (3 H singlet, the N-methyl group), 8.2-8.9 (10 H bands, the aromatic protons and the methine proton).

PREPARATION OF 3-METHYL-4-p.TOLYL-2-THIOPHENACYLIDENETHIAZOLE

The method described above was used to obtain the ketone as pale yellow needles m.p. 164°, yield 28%. Analysis for $C_{19}H_{17}NS$:

Calculated: C, 74.26 ; H, 5.53 ; N, 4.56 ; S, 10.42

Found: C, 74.11 ; H, 5.59 ; N, 4.58 ; S, 10.44 .

Thionation afforded the thioacylidenethiazole as red prisms, m.p. 185°C, 65% yield, identical [mixed m.p. and NMR] with an authentic sample obtained from the reaction 2-methyl-5-phenylisothiazoline thione with p.methylphenacylidenetriphenylphosphorane.

PREPARATION 3-METHYL-4-PHENYL-2-THIOPHENACYLIDINETHIAZOLE

The reaction was carried as above to give the product as orange prisms, m.p. 144-145°C, identical [mixed m.p. and NMR] with an authentic sample obtained from the reaction of 2-methyl-5-phenyl-isothiazoline-3-thione with phenacylidenetriphenylphosphorane.

PREPARATION OF 3-METHYL-5-PHENYL-2-THIPHENACYLIDENETHIAZOLE

The same procedure as above was used to give the product as orange prisms m.p. 197. Mass spectrum: M^+ 309, calculated for $C_{18}H_{15}NS_2$ 309. NMR spectrum: τ 6.45 (3 H singlet, the N-methyl), 2.98 (1 H singlet the thiazoline proton), 1.9-2.8 (11 H bands, the aromatic and the methine exocyclic protons).

PREPARATION OF 3-METHYL-4,5-DIPHENYL-2-THIOPHENACYLIDENETHIAZOLE

By the synthesis above, the ketone m.p. 183°C was obtained as white needles recrystalized from benzene, in 35% yield.

Analysis for $C_{24}H_{19}NSO$:

Calculated: C, 78.04 ; H, 5.149 ; N, 3.79 ; S, 8.67

Found: C, 78.22 ; H, 5.06 ; N, 3.73 ; S, 8.97 .

Mass spectrum: M^+ 369 , calculated 369.

Thionation afforded the thione as red prisms, m.p. 167, mass spectrum M^+ 385, calculated 385. NMR spectrum: τ 6.5 (3 H singlet, the N-methyl protons) 2.4-2.9 (16 H bands, the aromatic and the exocyclic methine protons).

PREPARATION OF 3,4-DIPHENYL-2-THIOPHENACYLIDENETHIAZOLE

The ketone was obtained according to the above synthesis as white needles m.p. 160°C in 38% yield. Thionation gave the thione as red prisms m.p. 145°C, yield 54%. Mass spectrum: M^+ 371, calculated for $C_{23}H_{17}NS_2$, 371. NMR spectrum: τ 3.4 (1 H singlet, the thiazoline proton), 2.5-2.9 (16 H bands, the aromatic protons and the exocyclic methine hydrogen).

REACTION OF 3-METHYL-4-PHENYL-2-THIOPHENACYLIDENETHIAZOLE WITH DIMETHYL ACETYLENEDICARBOXYLATE

The thiazole (309 mg, 1 m mol) was refluxed under nitrogen with dimethyl acetylenedicarboxylate (142 mg, 1 m mol) for seven hours in dry benzene. The solvent was then evaporated and the residue chromatographed over silica gel in chloroform to give three bands. The upper most yellow band on evaporation gave a yellow oil, 95 (30% yield).

Mass spectrum: M^+ 320, calculated for $C_{15}H_{12}O_4S$, 320. NMR spectrum: τ 6.4 and 7.2 (two 3 H singlets, the ester methyl groups), 2.6 (1 H singlet, the ring hydrogen).

The second band gave a greenish yellow oil 96 (22% yield) mass spectrum M^+ 317, calculated for $C_{16}H_{15}NO_4S$, 317. NMR spectrum: τ 6.7 and 7.2 (two 3 H singlets, the ester methyl groups), 6.2 (3 H singlet, the N-methyl), 2.6 (1 H singlet, the ring hydrogen).

The third band afforded the diadduct as red crystals (18% yield). It was recrystallized from benzene pet.ether 1:1 solution. Analysis for $C_{30}H_{27}NS_2O_8$:

Calculated: C, 60.70 ; H, 4.55 ; N, 2.36 ; S, 10.79

Found: C, 60.54 ; H, 4.92 ; N, 2.25 ; S, 10.98 .

Mass spectrum: M^+ 593; calculated, 593; NMR spectrum, τ 7.4, 6.9, 6.4, and 6.1 (four 3 H singlets, the ester groups), 6.0 (3 H singlet, the N-methyl), 4.8 (1 H singlet, the vinyl hydrogen), 3.6 (1 H singlet, the thiazoline proton), 2.4-2.8 (10 H bands the aromatic protons).

REACTION OF 3-METHYL-5-PHENYL-2-THIOACYLMETHYLENETHIAZOLE WITH DIMETHYL ACETYLENEDICARBOXYLATE

The reaction carried out as above afforded three bands on chromatography, the upper two on extraction in benzene gave compounds 95 and 96 respectively. These were identical [mass spectrum and NMR] to the ones obtained in the previous reaction. The third band afforded the diadduct as orange oil mass spectrum: M^+ 593; calculated for $C_{30}H_{27}NS_2O_8$, 593 .

REACTION OF 3,4-DIPHENYL-2-THIOACYLMETHYLENETHIAZOLE WITH DIMETHYL ACETYLENEDICARBOXYLATE

The reaction was performed under the above conditions and on chromatography the uppermost band afforded compound 95 identical [mass spectrum and NMR] to the ones obtained above. The second band afforded compound 96e; mass spectrum, M^+389; calculated for $C_{21}H_{17}NO_4S$, 389. The third band afforded the diadduct as brown crystalline material which was recrystallized from benzene, mass spectrum, M^+655; calculated for $C_{35}H_{29}NS_2)_8$, 655. The low yield of the diadduct, however, did not allow for further analysis.

REACTION OF 3-METHYL-4-p.TOLYL-2-THIOPHENACYLIDENETHIAZOLE WITH DIMETHYL ACETYLENEDICARBOXYLATE

The reaction performed as above. The first two bands afforded the same products 95 and 96, obtained above, [mass spectrum, and NMR]. The third orange band also afforded the diadduct which, in this case gave the mass spectrum M^+607; calculated for $C_{31}H_{29}NS_2O_8$, 607.

REACTION OF 3-METHYL-2-THIOPHENACYLIDENEBENZOTHIAZOLE WITH DIMETHYL ACETYLENEDICARBOXYLATE

(1) The reaction performed as above to afford only the monoadduct as a yellowish oil, mass spectrum: M^+425; calculated for $C_{22}H_{19}SO_4$, 425. NMR spectrum: τ 7.2 and 6.45 (two, 3 H singlets, the ester methyls), 6.22 (3 H singlet, the N-methyl), 3.65 (1 H singlet), 2.4-3.3 (9 H bands, the aromatic protons).

(2) When the reaction was performed using excess dimethyl acetylenedicarboxylate (4:1), two bands were obtained, the upper yellow band corresponding to the monoadduct. The lower orange band afforded

the diadduct, mass spectrum: M^+567; calculated for $C_{28}H_{25}NS_2O_8$, 567. NMR spectrum: τ 7.8, 7.34, 6.65, 6.3 (four, 3 H singlets, the ester methyls), 6.15 (3 H singlet, the N-methyl), 2.25-3.1 (10 H bands the aromatic protons and the exocyclic methine proton).

(3) Carrying out the reaction (1:1 mixture) in dioxane afforded two bands as above, corresponding to the mono and diadduct respectively.

REACTION OF 4,5-DIPHENYL-3-METHYL-2-THIOPHENACYLIDENETHIAZOLE WITH DIMETHYL ACETYLENEDICARBOXYLATE

(1) Performing the reaction 1:1 mixture afforded only the monoadduct, mass spectrum: M^+527; calculated for $C_{30}H_{25}NSO_4$, 527.

(2) In the case of 1:4 reaction, a mixture of both the monoadduct and the diadduct were obtained, mass spectrum: M^+669; calculated for $C_{36}H_{31}NS_2O_8$, 669.

PREPARATION OF 2-METHYL-5-p.TOLYL-1,2-ISOTHIAZOLINE-3-THIONE

The method of Thuilier and Vialle[118] was used with some modifications to obtain the 1,2-dithiole-3-thione which was then alkylated and treated with methylamine to afford the thione according to the method of Mollier[44] described earlier.

Therefore, t-butylalcohol (37 g) in benzene (800 ml), and sodium wire (16 g), were refluxed 48 hours. The unreacted sodium was then removed, and p.methylacetophenone (33.5 g) was added followed by 19 g of carbon disulfide. Work-up as indicated afforded the 3,3-dimercapto-1-tolylprop-2-ene-1-one, as yellow crystals m.p. 84°C [Lit 84-85°C] in 80% yield.

Thionation was then carried out by refluxing the

dimercaptotolylpropenone (52.5 g, 1/4 mol) with phosphorus pentasulfide (150 g) in benzene for four hours. Filtration of the benzene solution, and evaporation afforded brown precipitate which was recrystallized from ethyl acetate as the dithiolthione m.p. 120°C [lit 120°C] in 70% yield.

Treatment of the dithiolethione (1 m mol) with methyl iodide (1 m mol) in ethyl acetate, reflux for four hours, filtration, afforded the 3-methylthio-5-tolyl-1,2-dithiolium iodide. This was treated with methylamine as described[44] to afford 2-methyl-4-p.tolylisothiazoline-3-thione, 25% yield, m.p. 129-130°C. Analysis for $C_{11}H_{11}NS_2$:

Calculated: C, 69.84 ; H, 5.82 ; N, 7.40 ; S, 16.93

Found: C, 69.20 ; H, 5.80 ; N, 7.14 ; S, 16.57 .

NMR spectrum: τ 7.65 (3 H singlet, the paramethyl group), 6.3 (3 H singlet, the N-methyl), 2.9 (1 H singlet, the isothiazole ring proton), 2.5-2.7 (4 H bands, the aromatic protons).

PREPARATION OF 3-(THIO p.METHYLPHENACYLMETHYLENE)-5-TOLYL-1,2-ISOTHIAZOLE

5-Tolyl-2-methylisothiazoline-3-thione was condensed with p.methylphenacyl bromide as described before for 4-thiazoline-2-thiones, to afford the salt as white crystals m.p. 175°C in 55% yield.

Analysis for $C_{20}H_{20}S_2NBr$:

Calculated: C, 55.30 ; H, 4.6 ; N, 3.22 ; S, 14.74 ; Br, 18.43

Found: C, 55.00 ; H, 4.81 ; N, 3.05 ; S, 14.45 ; Br, 18.14

Treatment with pyridine afforded the ketone as colorless needles m.p. 165°C, yield 25%. Thionation by reflux with phosphorus pentasulfide in benzene for four hours, filtration, drying, and evaporation

afforded a reddish oil which was purified by chromatography to give red prisms m.p. 161°C in 20% yield. Analysis for $C_{20}H_{19}S_2N$:

Calculated: C, 71.21 ; H, 5.63

Found: C, 71.03 ; H, 5.46

Mass spectrum: M^+ 337; calculated 337.

NMR spectrum: This was obtained on samples dissolved in perduterated chloroform, d-toluene, or trichlorobenzene, in degassed sealed tubes and over the temperature range -40° to +190°C.

The spectrum at -40° in d-chloroform showed the two para-methyl peaks as two 3 H singlets at τ 7.5, and 7.6, and the N-methyl at 6.32 as 3 H singlet, at 3.5 (1 H singlet, the isothiazoline hydrogen), at 2.1, 2.27, 2.79, and 2.95 (four 1 H singlets, the aromatic protons of the sidechain phenyl), at 2.6 (4 H singlet, the aromatic protons of the isothiazoline phenyl).

The two paramethyl peaks showed no coalescence over the temperature range experimented. The differentiation between the two phenyls was not clear in the case of d-toluene.

PREPARATION OF 3-THIOPHENACYLMETHYLENE-2,5-DIPHENYLISOTHIAZOLE

This was obtained by the above synthesis as violet needles m.p. 128°C, yield 30%. Mass spectrum: M^+ 371; calculated 371.
NMR spectrum: 2.2-2.9 (16 H bands, the aromatic protons and exocyclic methine hydrogen).

PREPARATION OF 3-THIOPHENACYLMETHYLENE-2-METHYL-5-PHENYLISOTHIAZOLE

Following the synthesis above the compound was obtained as yellow needles, m.p. 160°C, in 28% yield. Analysis for $C_{18}H_{15}NS_2$:

Calculated: C, 69.90 ; H, 4.85 ; N, 20.71 ; S, 4.53

Found: C, 70.25 ; H, 4.66 ; N, 20.93 ; S, 4.55 .

Mass spectrum: M^+ 309; calculated 309.

PREPARATION OF 1,3,5-TRIPHENYLTHIENO[3,2-C] ISOTHIAZOLIUM PERCHLORATE

Equimolecular quantities of phenacyl bromide and dimethyl sulfide were added together and left overnight. The precipitate that formed was filtered, washed with ether, and dried to afford dimethylphenacylsulfonium bromide as white crystals, m.p. 192, in yield over 95%.

The sulfonium salt (1 m mol) was added to the molar quantity of sodium ethoxide (1 m mol) in dry ethanol. After stirring for five minutes, a slight excess of 2,5-diphenylisothiazolium perchlorate (~1.2 m mol) was added. After stirring for 15 minutes, the mixture was diluted with water, and the ether extract dried and evaporated. Purification by chromatography afforded the 2-benzoylthiophene compound 44 which was identical with authentic sample obtained from the reaction of sodium benzoylacetate with 3-methylthio-2,5- isothiazolium perchlorate.

The 2-benzoylthiophene derivative (1 m mol) in benzene (10 ml) and (1.5 m mol) phosphorus pentasulfide were refluxed for four hours. The benzene solution was then filtered and washed with saturated sodium bicarbonate solution, dried and evaporated to afford the thiobenzoyl derivative 122, mass spectrum M^+ = 371; calculated for $C_{23}H_{17}NS_2$

371.

2-Thiobenzoyl-3-anilino-5-phenylthiophene (2 m mol) in ethanol (5 ml) was treated with saturated iodine solution, and diluted with ether. The precipitate was filtered off and treated with 70% solution of perchloric acid in acetic acid to produce yellow crystals. The product was then recrystallized from acetic acid containing perchloric acid as yellow needles m.p. 241°C, in 38% yield.

Analysis for $C_{23}H_{16}NS_2ClO_4$

Calculated: C, 58.78 ; H, 3.40 ; N, 2.98 ; S, 13.63 ; Cl, 7.56

Found: C, 58.85 ; H, 3.34 ; N, 2.52 ; S, 13.24 ; Cl, 7.7

PREPARATION OF 1-METHYL-3-PHENYLTHIENO[3,2-C]ISOTHIAZOLIUM PERCHLORATE

The reaction performed as above using 2-methylisothiazolium perchlorate and dimethylphenacylidenesulfonium ylid, gave off-white needles, m.p. 204°C, in 30% yield. Analysis for $C_{12}H_{10}NS_2ClO_4$:

Calculated: C, 43.43 ; H, 3.01 ; N, 4.22 ; S, 19.3 ; Cl, 10.7

Found: C, 43.35 ; H, 3.46 ; N, 3.88 ; S, 19.4 ; Cl, 10.04

PREPARATION OF 1,3,4-TRIPHENYLTHIENO[3,2-C]ISOTHIAZOLIUM PERCHLORATE

The reaction performed as above using dimethylphenacylidene-sulfonium ylid and 2,4-diphenylisothiazolium perchlorate gave yellow needles, m.p.222°C, yield 40%. Analysis for $C_{23}H_{16}NS_2ClO_4$:

Calculated: C, 58.78 ; H, 3.40 ; N, 2.98 ; S, 13.63 ; Cl, 7.56

Found: C, 58.67 ; H, 3.55 ; N, 2.58 ; S, 13.80 ; Cl, 6.80 .

PREPARATION OF 3-METHYL-1,5-DIPHENYLTHIENO[3,2-C]ISOTHIAZOLIUM PERCHLORATE

α-Bromoacetone was added to an equimolecular quantity of dimethyl sulfide and allowed to stand for 30 minutes,to afford the sulfonium salt as a very strong lachrymatory oil. The oil was washed with ether and used immediately since it seemed to polymerize in a matter of hours into a dark sticky resin.

The ylid obtained from the treatment of the salt with sodium ethoxide in ethanol was then allowed to react with 2,5-diphenyl-isothiazolium perchlorate as described above. The reaction afforded yellow crystals of m.p. 237 in 35% yield. Analysis for $C_{18}H_{14}NS_2ClO_4$:

Calculated: C, 53.0 ; H, 3.43 ; N, 3.43 ; S, 15.7 ; Cl, 8.71

Found: C, 52.79 ; H, 3.63 ; N, 3.21 ; S, 15.04 ; Cl, 8.74 .

ATTEMPTED PREPARATION OF 1-METHYLTHIENO[3,2-C]ISOTHIAZOLIUM PERCHLORATE

Equimolecular quantities of bromoacetaldehydediethylacetal and dimethyl sulfide were left overnight,the sulfonium salt formed as an oil. The oil washed several times with ether, treated with sodium ethoxide to form the ylid, and allowed to react with 2-methylisothiazolium perchlorate according to the procedure mentioned above. Thionation and iodine oxidation afforded very poor yield of the iodide salt. The extremely poor yield did not allow for further treatment with perchloric acid to obtain the perchlorate or carry on sufficient purification for analysis.

ATTEMPTED PREPARATION OF 2,3-PYRIDINO-4,5-BENZOISOTHIAZOLIUM SALTS

2,3, and 4-*o*-Nitrophenylpyridine were prepared by the method of Butterworth and Coworkers[123]. The 2,3, and 4-components of the product mixture were preferably separated by chromatography rather than fractional crystallization. The 2-component (1 g), in concentrated hydrochloric acid (2 ml) was added to a solution of stannous chloride (6 g) in concentrated hydrochloric acid (12 ml), and warmed on steam-bath for one hour. 2-*o*-Aminophenylpyridine, liberated by the addition of aqueous sodium hydroxide, was extracted with ether, recovered (0.6g), dissolved in a mixture of concentrated hydrochloric acid (4 ml) and water (6 ml) and diazotised at 5-10°C with sodium nitrite (0.3g) in water. Potassium ethyl xanthate (1g)dissolved in water was then added, and the mixture heated on steambath for ten minutes, then the product hydrolysed with sodium hydroxide. The mercaptan was then extracted in benzene and recovered as yellow crystals (10 mg).

When The mercaptan was dissolved in ethanol (2 ml) and treated with saturated iodine solution, a minute amount of salt-like material was obtained.

REFERENCES

REFERENCES

1. H. C. Longuet-Higgins, Trans,Farad.Soc. 45, 173, (1960).
2. A. Adams and R. Slack, Chem. and Ind., 1232, (1956).
3. K. R. H. Wooldridge, Advances in Heterocyclic Chemistry, 14, 2, (1972).
4. A. Adams and R. Slack, J. Chem. Soc., 3061, (1959).
5. a) J. Goerdeler and H. W. Pohland, Chem. Ber. 94, 2950, (1961).
   b) J. Goerdeler and H. W. Pohland, ibid. 96, 526, (1963).
   c) J. Goerdeler and H. W. Pohland, ibid. 98, 4040, (1965).
6. J. Goerdeler and U. Krone, ibid. 102, 2273, (1969).
7. J. Goerdeler, Angew Chem., Int. Ed. 2, 693, (1963).
8. A. Bruno, and G. Purrello, Gazz. Chem. Ital. 96, 1009, (1966).
9. D. N. McGregor, U. Corbin, J. E. Swigor, and L. C. Cheney, Tetrahedron 25, 389, (1969).
10. D. Leaver and W. A. H. Robertson, Proc. Chem. Soc. 252, (1960).
11. D. Leaver, D. McKinnon, and W. A. H. Robertson, J. Chem. Soc., 32, (1965).
12. R. A. Olofson, J. M. Landsberg, R.O. Berry, D. Leaver, W. A. H. Robertson, and D. M. McKinnon, Tetrahedron 22, 2119, (1966).
13. F. Hübenett, F. H. Flock, W. Hansel, H. Heinze, and H. Hoffmann, Angew Chem., Int. Ed. 2, 714, (1963).
14. W. R. Hatchard, J. Org. Chem., 29, 660, (1964).
15. a) W. D. Crow, and N. J. Leonard, J. Org. Chem. 30, 2660, (1965).
    b) W. D. Crow, and I. Gosney, Tetrahedron 26, 1463, (1970).
    c) W. D. Crow and I. Gosney, Aust. J. Chem. 19, 1693, (1966), ibid. 20, 2729, (1967), ibid. 22, 765, (1969).

16. P. Chaplen, R. Slack, and K. R. Woldridge, J. Chem. Soc., 4577, (1965).

17. J. A. White, and R. C. Anderson, J. Heterocyclic Chem. 6, 199, (1969).

18. H. A. Staab, and A. Mannchreck, Chem. Ber. 98, 1111, (1965).

19. R. A. Olofson, and J. M. Landesberg, J. Am. Chem. Soc. 88, 4263, (1966).

20. A. Hordvik, Quart, Rep. Sulphur Chem. 5, 21, (1970).

21. A. Hordvik, and K. Julshamn, Acta. Chem. Scand. 26, 343, (1972).

22. L. Pauling, The Nature of the Chemical Bond, 3rd Ed., Cornell University Press, Ithaca, (1960).

23. J. M. Landesberg, and R. A. Olofson, Tetrahedron 22, 2135 (1966).

24. D. M. McKinnon, and E. A. Roback, Can. J. Chem. 46, 1855, (1968).

25. H. P. Benschop, A. M. Van Oosten, D. Platenberg, and C. Van Hooidonk, J. Med.Chem. 13, 1208, (1970).

26. R. Mayer, H. J. Hartmann, and J. Jentzsch, J. Prakt, Chem. 312, 31, (1966).

27. G. LeCoustumer and Y. Mollier, C. R. Acad. Sci. Paris, Ser. C , 270, 433, (1970).

28. D. G. Jones, and G. Jones, J. Chem. Soc. C, 707, (1969).

29. G. E. Bachers, D. M. McKinnon, and J. M. Buchshriber, Can. J. Chem. 50, 2568, (1972).

30. S. M. Loosmore, Ph.D. thesis, Chem. Dept. U. of Manitoba, (1974).

31. J. Goerdeler and H. W. Pohland, Chem. Ber. 94, 2950, (1961).

32. J. Faust, Z. Chem. 7, 306, (1967).

33. G. E. Bachers, M. Sc. thesis, Chem. Dept., U. of Manitoba, (1971).

34. F. Boberg and W. Von Gentzkow, Ann., 256, (1973).

35. Graham G. Abott and Derek Leaver, Chem. Comm , 150, (1973).

36. E. Klingsberg, J. Org. Chem. 28, 529, (1963).

37. F. T. Lee and G. P. Volpp, J. Heterocycl. Chem. 7, 415, (1970).

38. P. Sykes, and H. Ullah, J. Chem. Soc. Perkin I, 2305, (1972).

39. P. Sykes, and H. Ullah, Chem. and Ind., 1162, (1973).

40. M. St. C. Flett, J. Chem. Soc., 347, (1953).

41. A. J. Beber, and R. A. Mathes, Ind. Eng. Chem. 41, 2637, (1949).

42. A. Lawson and H. V. Morley, J. Chem. Soc., 1103, (1956).

43. H. Behringer, J. Kilger, and R. Wiedenmann, Tet . Lett., 1185, (1968).

44. G. Le Coustumer and Y. Mollier, Bull. Soc. Chim. Fr., 3076, (1970).

45. Y. Mollier, and N. Lozac'h, Bull. Soc. Chim. Fr., 614, (1961).

46. G. Le Coustumer, and Y. Mollier, C. R. Acad. Sci. Paris, 1423, (1968).

47. J. Goerdeler and W. Mittler, Chem. Ber. 96, 944, (1963).

48. J. Faust, Z. Chem., 8, 170, (1968).

49. W. D. Crow, and N. J. Leonard, J. Org. Chem. 30, 2660, (1965).

50. W. D. Crow, and N. J. Leonard, Tet . Lett., 1477, (1964).

51. F. Wille, L. Capeller, and A. Steiner, Angew Chem. 74, 467, (1962).

52. N. J. Leonard and G. E. Wilson, Tet . Lett., 1471, (1964).

53. S. N. Lewis, G. A. Miller, M. Hausman, and E. C. Szamborski, J. Heterocyclic Chem. 8, 572, (1971).

54. J. L. Charlton, S. M. Loosmore, D. M. McKinnon, Can. J. Chem. 52, 3021, (1974).

55. a) R. Mayer and K. Gewald, Angew. Chem. Int. Ed. 6, 294, (1967).
b) R. Mayer, H. J. Hartmann, and J. Jentzsch, J. Prakt Chem. 31, 312, (1966).
c) C. R. Mayer, and J. Jentzsch, ibid. 23, 113, (1964).

56. J. L. Adelfang, J. Org. Chem. 31, 2388, (1966).

57. D. M. McKinnon, and J. Buchshriber, Can. J. Chem. 49, 3299, (1971).

58. F. Boberg and W. Von Gentzkow, J. Prakt. Chem., 964, (1973).

59. N. Lozac'h, Advances in Heterocyclic Chem. 13, 161, (1971).

60. R. A. W. Johnstone, and S. D. Ward, Theor. Chim. Acta, 14, 420, (1969).

61. R. J. Beer, Specialist Per. Reports of Chem. Soc., Org. S , Se, Te, 2, 497 (1973).

62. S. Bezzi, M. Mammi and C. Garbuglio, Nature 182, 247, (1958).

63. Q. Shen, and K. Hedberg, J.Am. Chem. Soc. 96, 289, (1974).

64. R. Gleiter, V. Hornung, B. Lindberg, S. Högberg, N. Lozac'h, Chem. Phys. Lett. 11, 401, (1971).

65. A. Hordvik, and K. Julshamn, Acta Chem. Scan. 23, 3611, (1969).

66. A. Hordvik, E. Sletten, and J. Sletten, Acta Chem. Scand. 20, 2001, (1966).

67. E. Kingsberg, Quart. Rev., 537, (1969).

68. D. T. Clark, and D. Kilcast, Tetrahedron 27, 4367, (1971).

69. D. Leaver, and D. M. McKinnon, Chem. and Ind., 461, (1964).

70. K. Maeda, Bull. Chem. Soc. Japan 33, 1466, (1960).

71. K. Maeda, ibid. 34, 785, (1961).

72. K. Maeda, ibid. 34, 1166, (1961).

73. R. Gleiter, and R. Hoffmann, Tetrahedron 24, 5899, (1968).

74. D. T. Clark, Int. J. of Sulfur Chem. C, 11, (1972).

75. E. Brown, D. Leaver, D. M. McKinnon, J. Chem. Soc., 642, (1968).

76. L. K. Hansen, A. Hordvik, and L. J. Saethre, Chem. Comm., 222, (1972).

77. E. A. Roback, M. Sc. thesis, Chem. Dept., U. of Manitoba, (1968).

78. D. M. McKinnon, and J. Y. Wong, Can. J. Chem. 49, 2018, (1971).

79. M. S. Chauhan, D. M. McKinnon, Can. J. Chem. 53, 1336, (1975).

80. E. Klingsberg, J. Org. Chem. 33, 2915, (1968).

81. H. Behringer, and J. Falkenberg, Chem. Ber. 102, 1585, (1969).

82. D. Reid, and J. D. Symon, Chem. Comm., 1314, (1969).

83. a) F. Leung, and S. C. Nyburg, Chem. Comm. 707, (1970).

b) F. Leung, and S. C. Nyburg, ibid. 137, (1969).

84. a) F. Leung, and S. C. Nyburg, Can. J. Chem. 49, 167, (1971).

b) F. Leung, and S.C. Nyburg, ibid. 50, 324, (1972).

85. J. Dingwall, A. Ingram, D. Reid, J. Symon, J. Chem. Soc., Perkin I, 2351, (1973).

86. K. R. H. Wooldridge, Advances in Heterocyclic Chem. 4, 107, (1965).

87. E. Klingsberg, Chemistry and Industry, 1568, (1960).

88. E. Klingsberg, J. Am. Chem. Soc. 83, 2934, (1961).

89. E. Klingsberg, and A. Schreiber, J. Am. Chem. Soc. 83, 2934, (1961).

90. D. Leaver, W.A.H. Robertson, and D.M. McKinnon, J. Chem. Soc., 5106, (1962).

91. E. Brown, D. Leaver, and D.M. McKinnon, J. Chem. Soc. C, 1202, (1970).

92. D. M. McKinnon, Ph.D. thesis, University of Edinburgh, (1963).

93. H. Boshagen, W. Geiger, and H. Medenwald, Chem. Ber. 103, 3166, (1970).

94. H. Newman, and R. B. Angier, Chem. Comm. 353, (1967).

95. M. Davis, Advances in Heterocyclic Chem. 14, 43, (1972).

96. O. Aki, Y. Nakagawa, and K. Sirakawa, Chem. Pharm. Bull. 20, 2372, (1972).

97. H. Boshagen, H. Feltkamp and W. Geiger, Chem. Ber. 100, 2435, (1967).

98. P. Rioult, and J. Vialle, Bull. Soc. Chim. Fr., 2883, (1967).

99. F. Boberg, and J. Knoop, Ann. 708, 148, (1967).

100. M. Maguet, Y. Poirier, and J. Teste, Bull. Soc. Chim. Fr. 1503, (1970).

101. U. Schmidt, A. Lüttringhaus, and F. Hübinger, Ann. 631, 138, (1960).

102. M. Ahmed, J. M. Buchshriber, and D. M. McKinnon, Can. J. Chem. 48, 1991, (1970).

103. J. M. Buchshriber, D. M. McKinnon, and M. Ahmed, Can. J. Chem. 47, 2039, (1969), and references therein.

104. H. Boshagen, H. Feltkamp, and W. Geiger, Ber. 100, 2435, (1967).

105. S. Davidson and D. Leaver, Chem. Comm., 540, (1972).

106. D. B. Denny, and S. T. Ross, J. Org. Chem. 27, 998, (1962).

107. P. Ykman, G. l'Abbe, and G. Smets, Tetrahedron 27, 5623, (1971).

108. E. B. Knott, J. Chem. Soc. 916, (1955).

109. W. J. Hamphlett, R. W. Lamon, J. Org. Chem. 29, 2146, (1964).

110. H. Zeliger, J. Snyder, and H. Bestmann, Tett. Lett., 3313, (1970).

111. R. Huisgen, Angew. Chem. Int. Ed. 2, 633, (1963).

112. H. Kato, M. Kawamura, and T. Shiba, Chem. Comm., 959, (1970).

113. G. Vernin, C. Riou, H.J.M. Dou, L. Bouscasse, Bull.Soc. Chim. Fr., 1743, (1973).

114. M. E. Volpin, Y.D. Koreshkov, V. G. Dulova, and D.N. Kursanov, Tetrahedron 18, 107, (1962).

115. a) R. M. Acheson, A. R. Hands, and J. M. Vernon, Proc. Chem. Soc., 164, (1961).

b) R. M. Acheson, and J. M. Vernon, J. Chem. Soc., 1148, (1962).

116. R. B. Woodward, and R. Hoffmann, Angew. Chem., Int. Ed. 8, 781, (1969).

117. G. Gueden, and J. Vialle, Bull. Soc. Chim. Fr., 270, (1973).

118. A. Thuillier, and J. Vialle, Bull. Soc. Chem. Fr., 1398, (1959).

119. R. Wasylishen, T. Schaefer, and R. Schwenk, Can. J. Chem. 48, 2885, (1970).

120. A. A. Bothner-By, and R. E. Glick, J. Chem. Phys., 26, 1651, (1957).

121. A. D. Buckingham, T. Schaefer, and W. G. Schneider, J. Chem. Phys. 32, 1227, (1960).

122. Von K. Gewald, M. Hentschel, and R. Heikel, J. Prakt. Chem. 315 539, (1973).

123. E. C. Butterworth, I.M. Heilbron, and D. H. Hey, J. Chem. Soc., 349, (1940).

124. J. Goerdeler, and M. Roegler, Ber. 103, 112, (1970).

125. R. Meyer, and K. Togel, Ann. 55, 347, (1906).

126. W. Minnis, Org. Synth. 12, 62, (1932).

127. G. Pfister-Guillouzo, and N. Lozac'h, Bull. Soc. Chim. Fr., 153, (1963).

128. D. Leaver, unpublished results.

129. C. Paulmier, Y. Mollier, and N. Lozac'h, Bull. Soc. Chim. Fr., 2462, (1965).

130. D. D. Chapman, J. K. Elwood, D. W. H. Heseltine, H. M. Hess, and D. W. Kurtz, Chem. Comm., 647, (1974).

131. A. I. Vogel, A Text Book of Practical Org. Chem. 3rd Ed., J. Wiley, N.Y. (1957).

132. L. F. Fieser, Experiments in Organic Chemistry. 2nd Ed. D. C. Heath and Co., Boston, N.Y. (1941).

133. R. B. Moffett, Org. Syntheses. Coll. Vol. IV, 238, (1963).

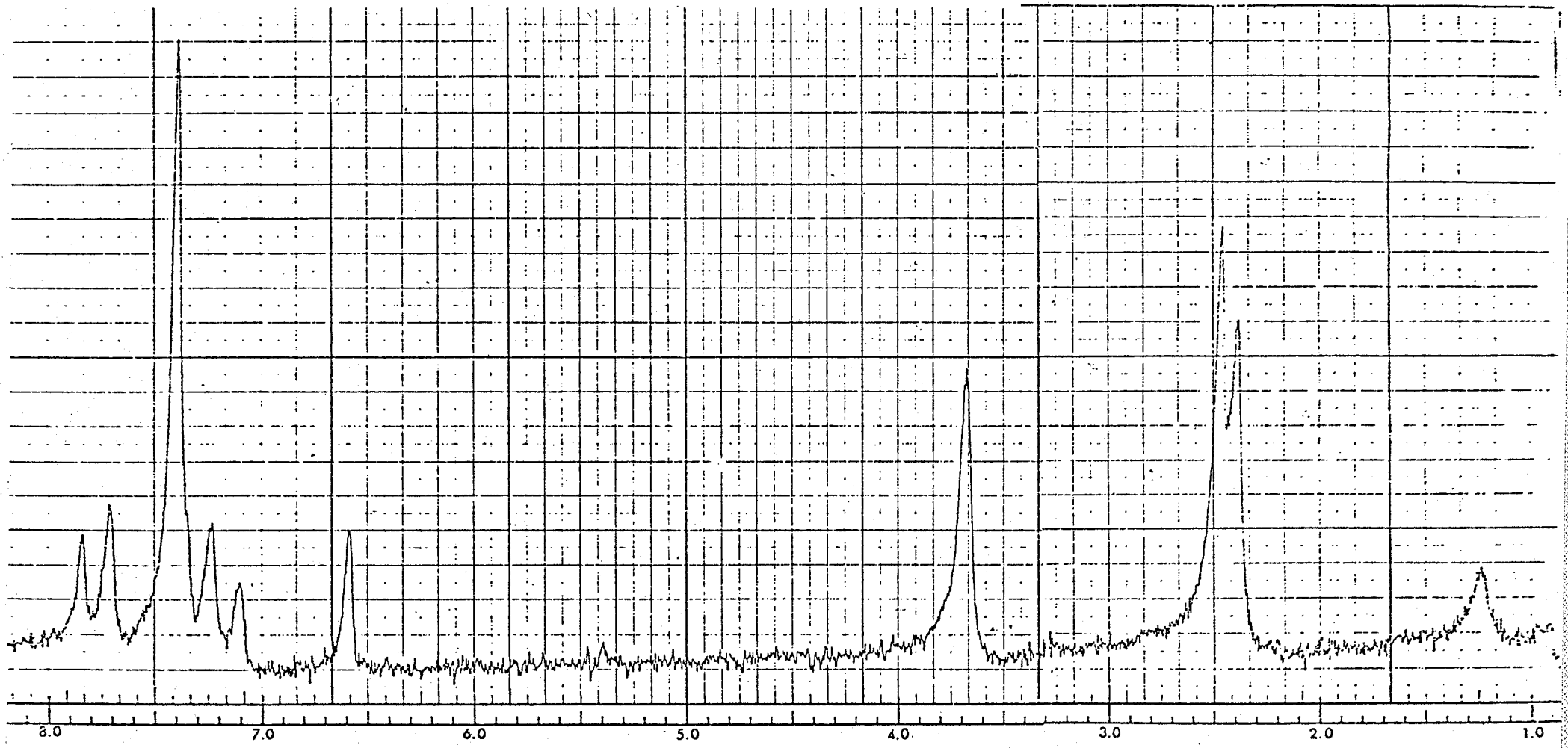
134. E. Campaigne, J. Am. Chem. Soc. 66, 684, (1944).

135. E. K. Fields, J. Am. Chem. Soc. 77, 4255, (1955).

136. G. Kjellin, and J. Sandström, Acta Chem. Scand. 23, 2879, (1969).

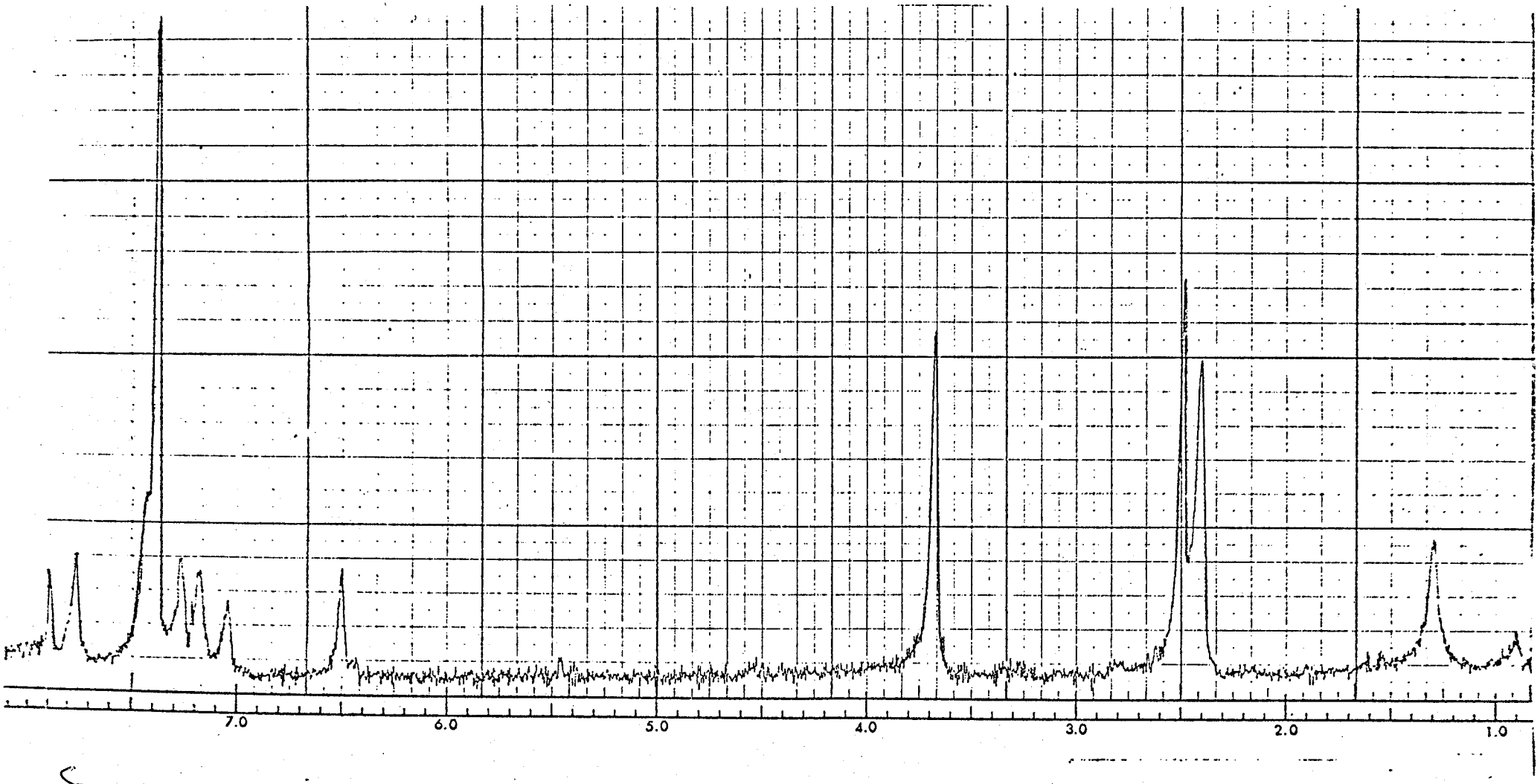
NMR SPECTRUM OF COMP. 32c

in $DCCl_3$ at $-40^{\circ}C$



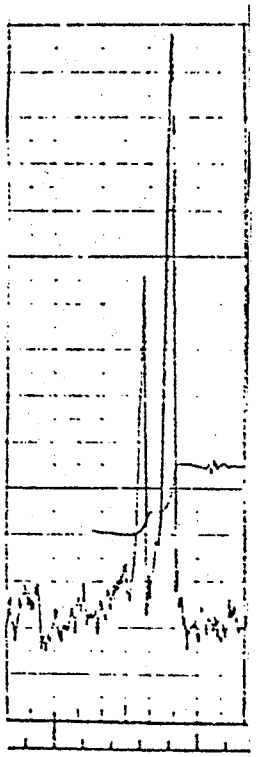
NMR SPECTRUM OF COMP. 32_c

in $DCCl_3$ at 0°C



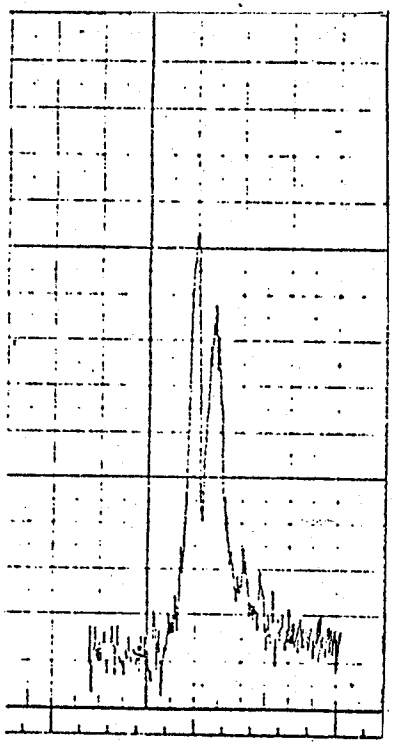
NMR SPECTRUM OF COMP. 32c

in d-Toluene at 25°C

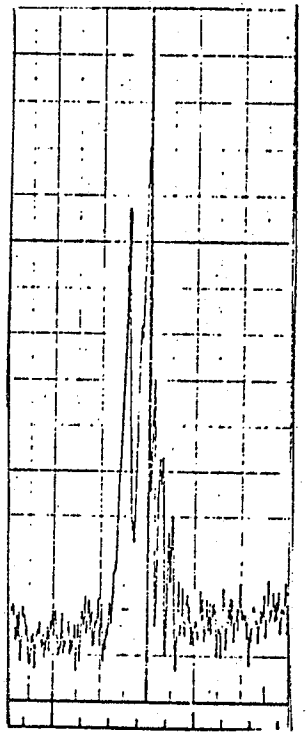


S

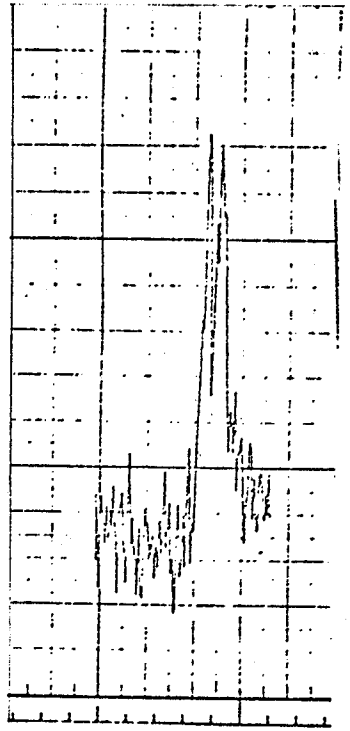
in Tetrachloro-benzene at 100°C



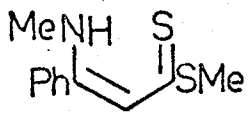
in d Toluene at 120°C

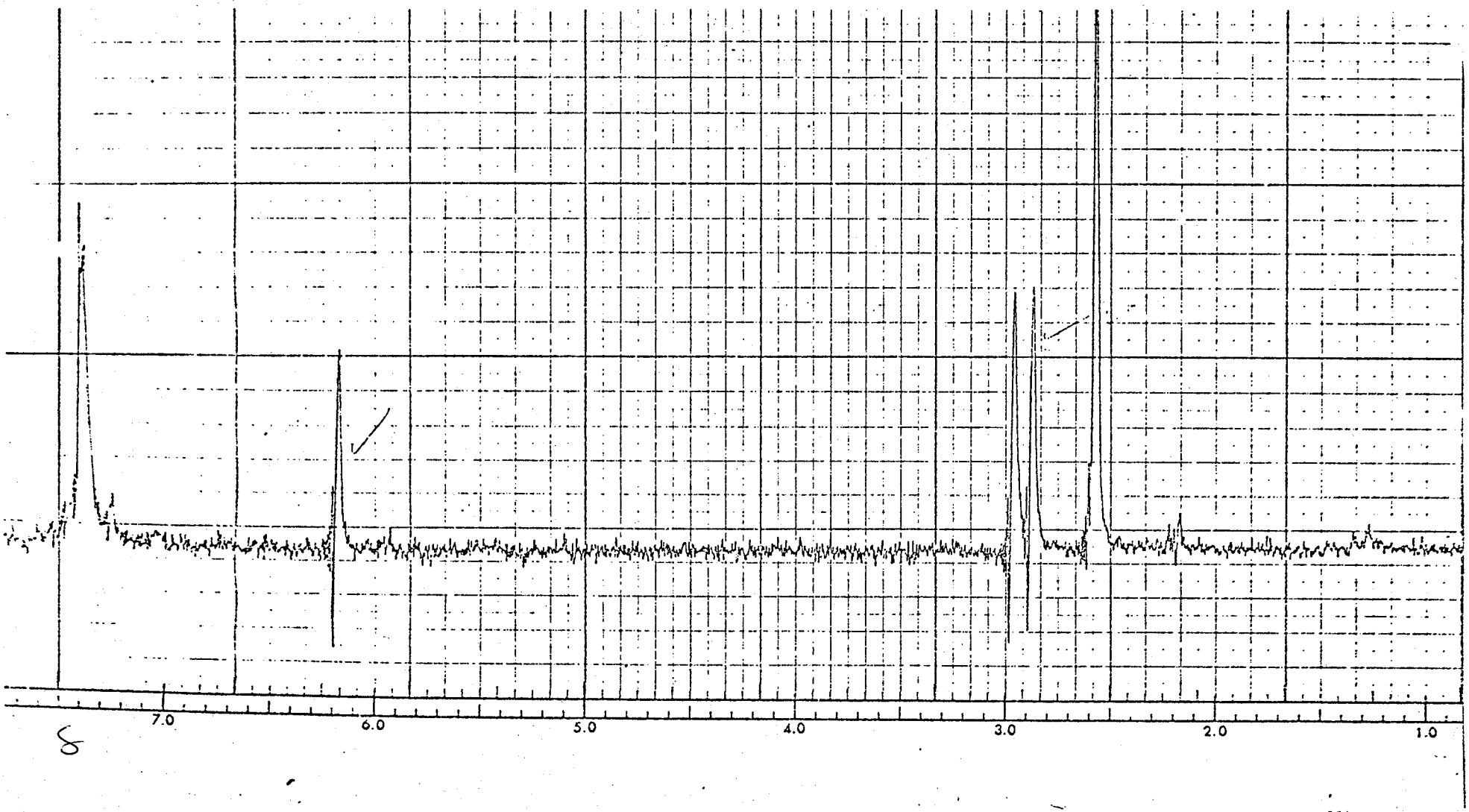


in Tetracloro-benzene at 190°C

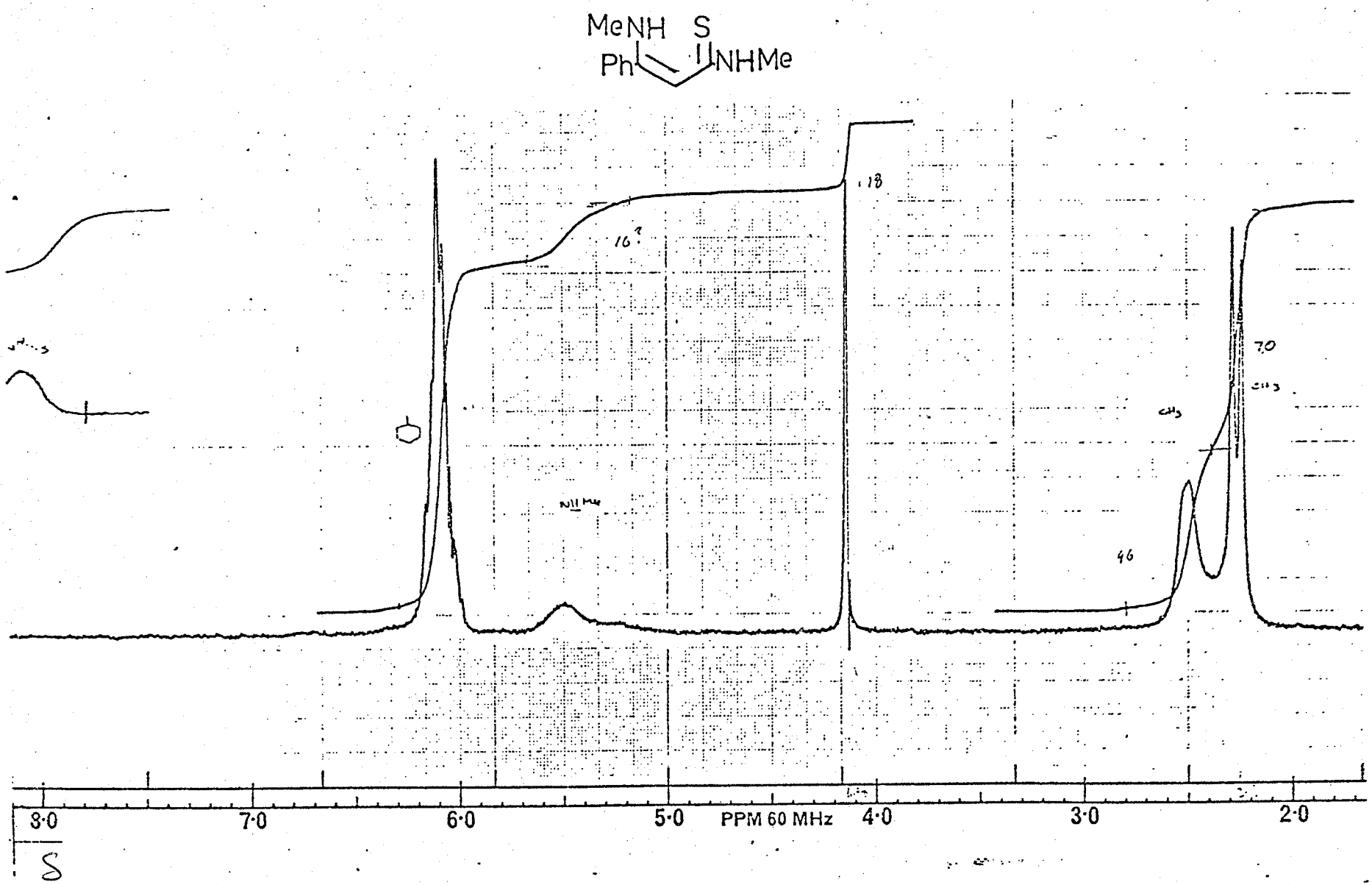


NMR SPECTRUM OF COMP. 4.2

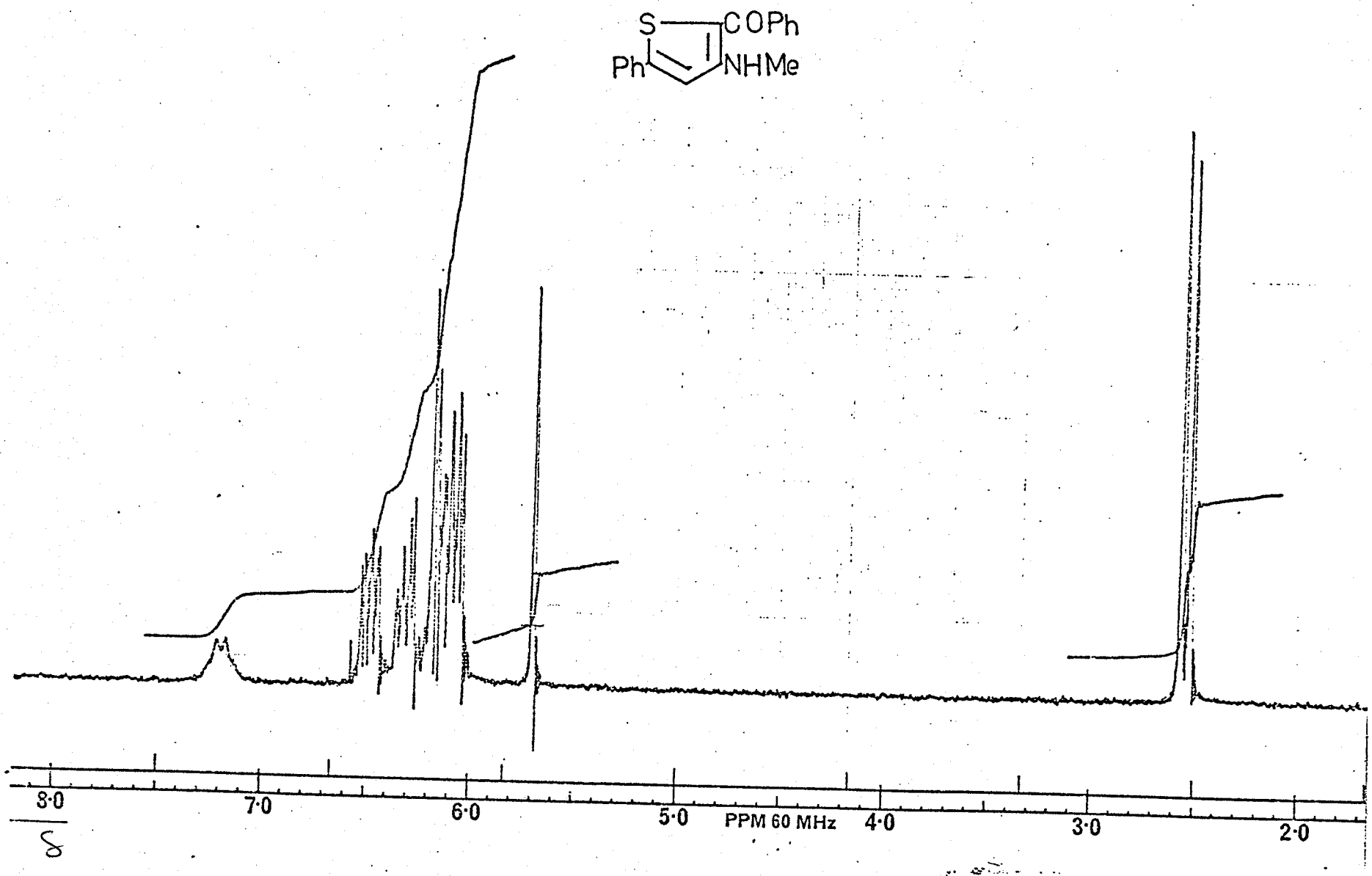




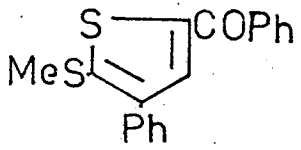
NMR SPECTRUM OF COMP. 4.3



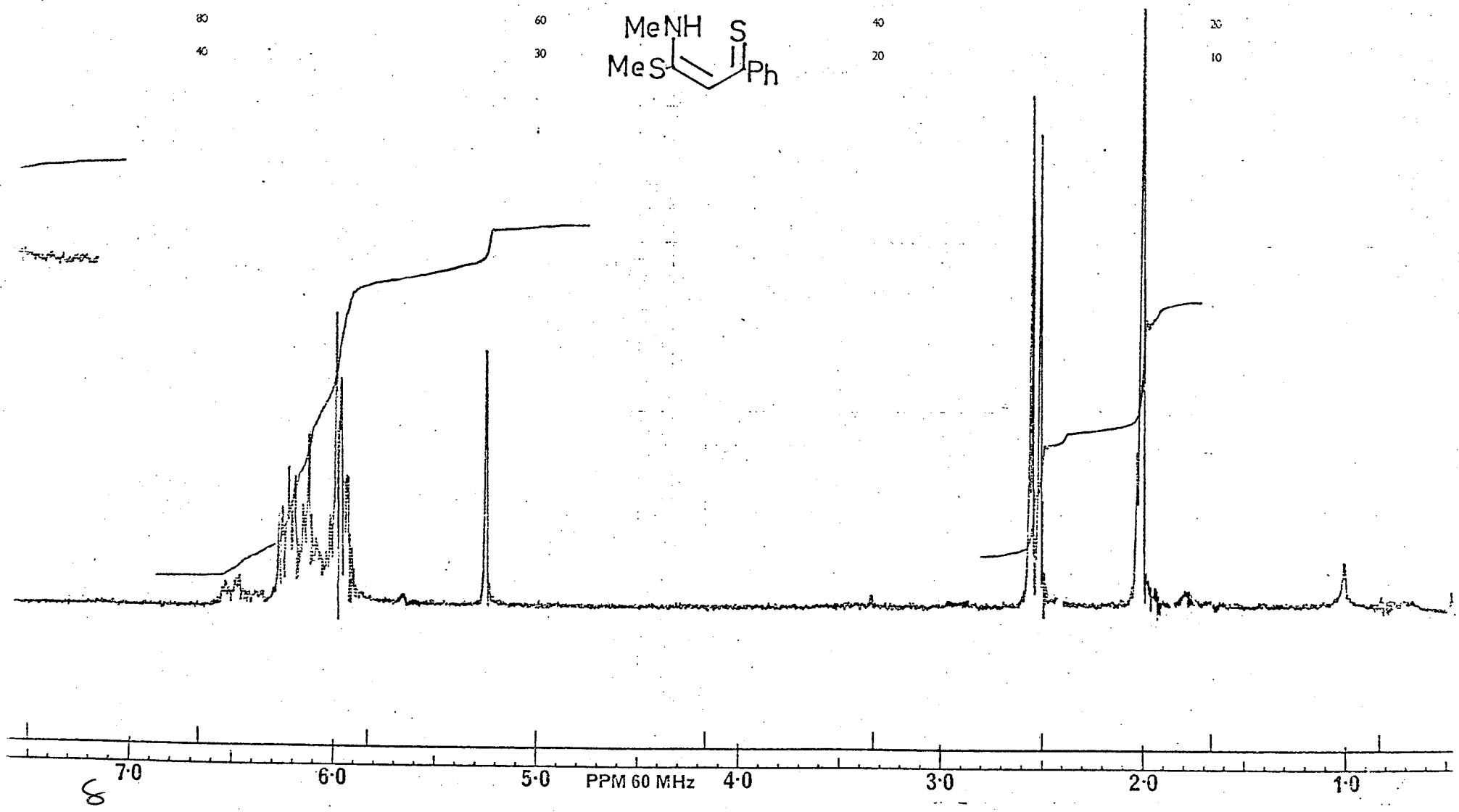
NMR SPECTRUM OF COMP. 4.4



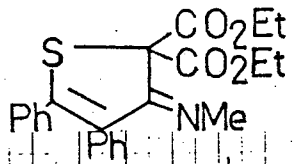
NMR SPECTRUM OF COMP. 45

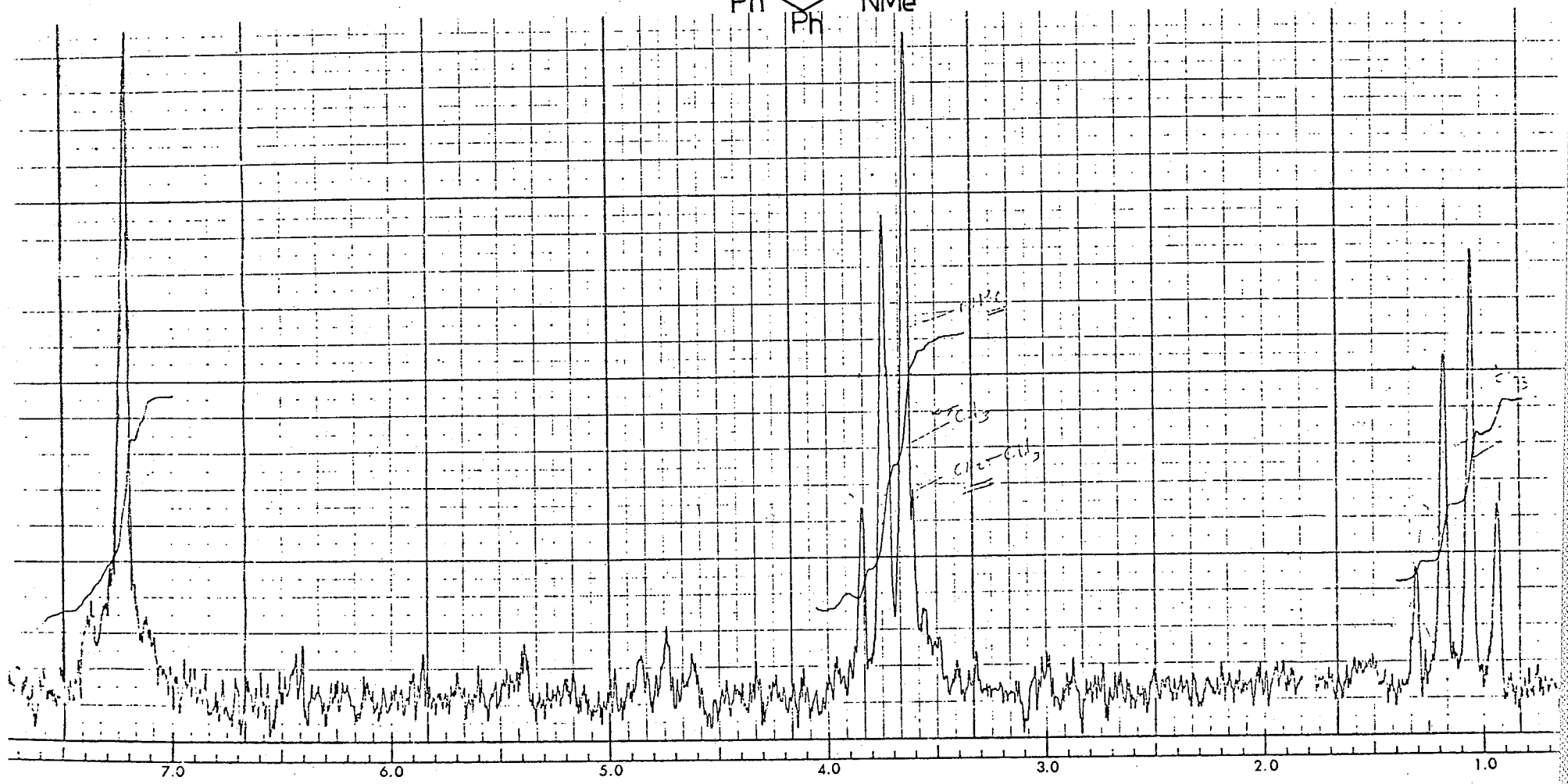


NMR SPECTRUM OF COMP. 46

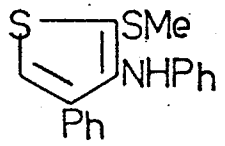


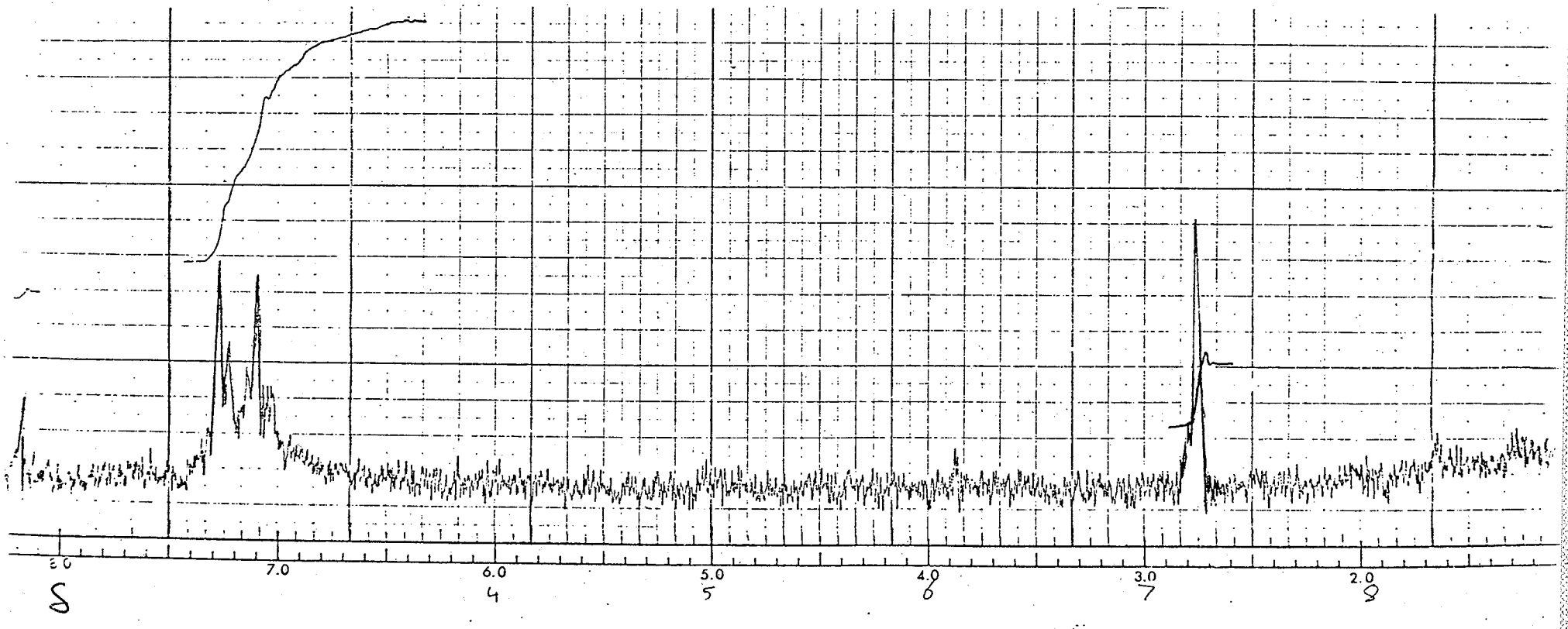
NMR SPECTRUM OF COMP. 50



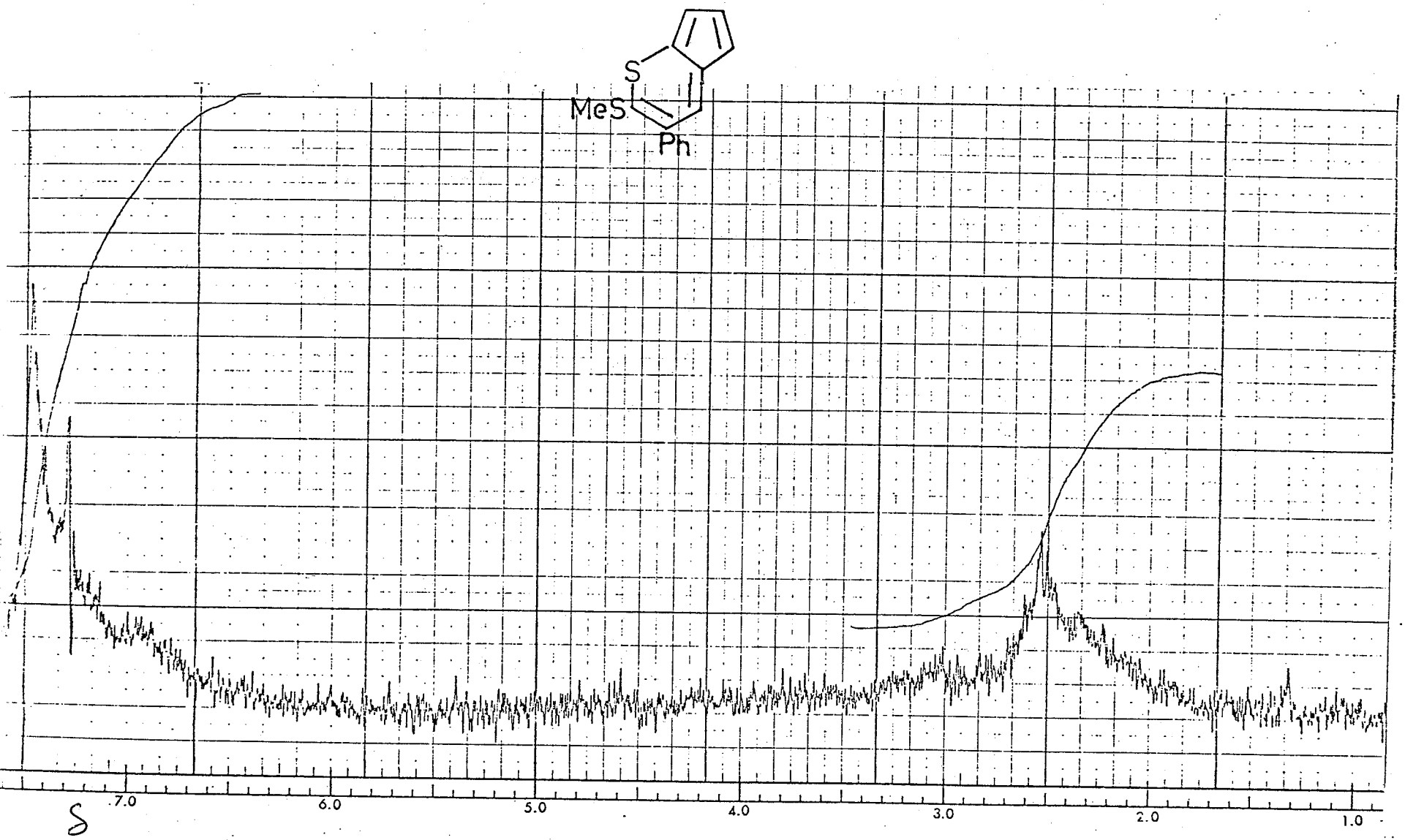


NMR SPECTRUM OF COMP. 52

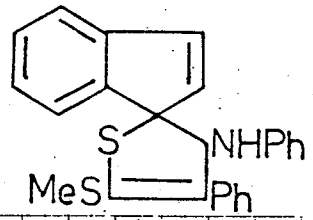


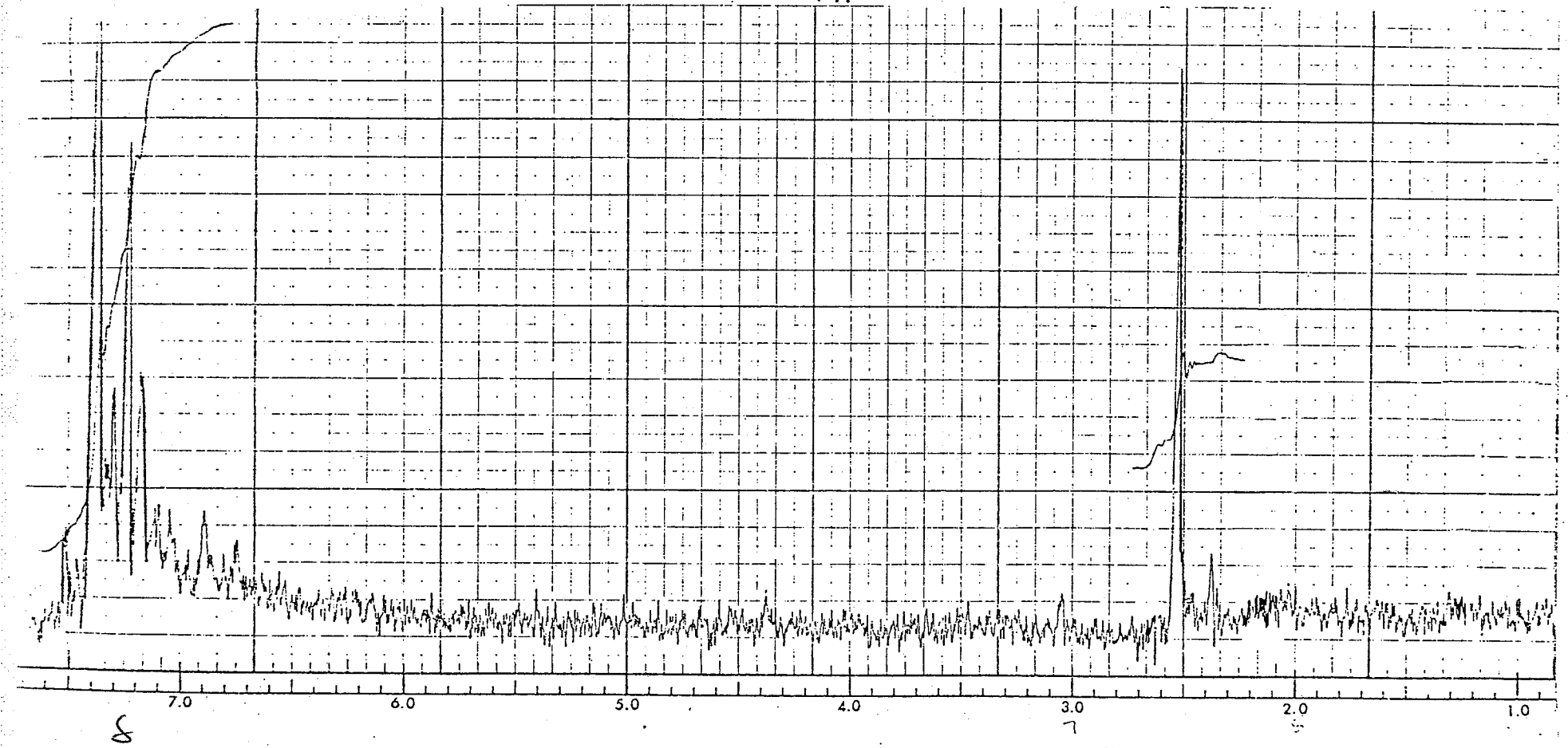


NMR SPECTRUM OF COMP. 62

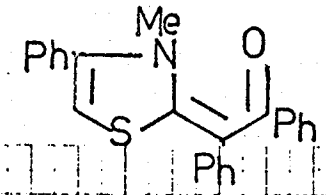


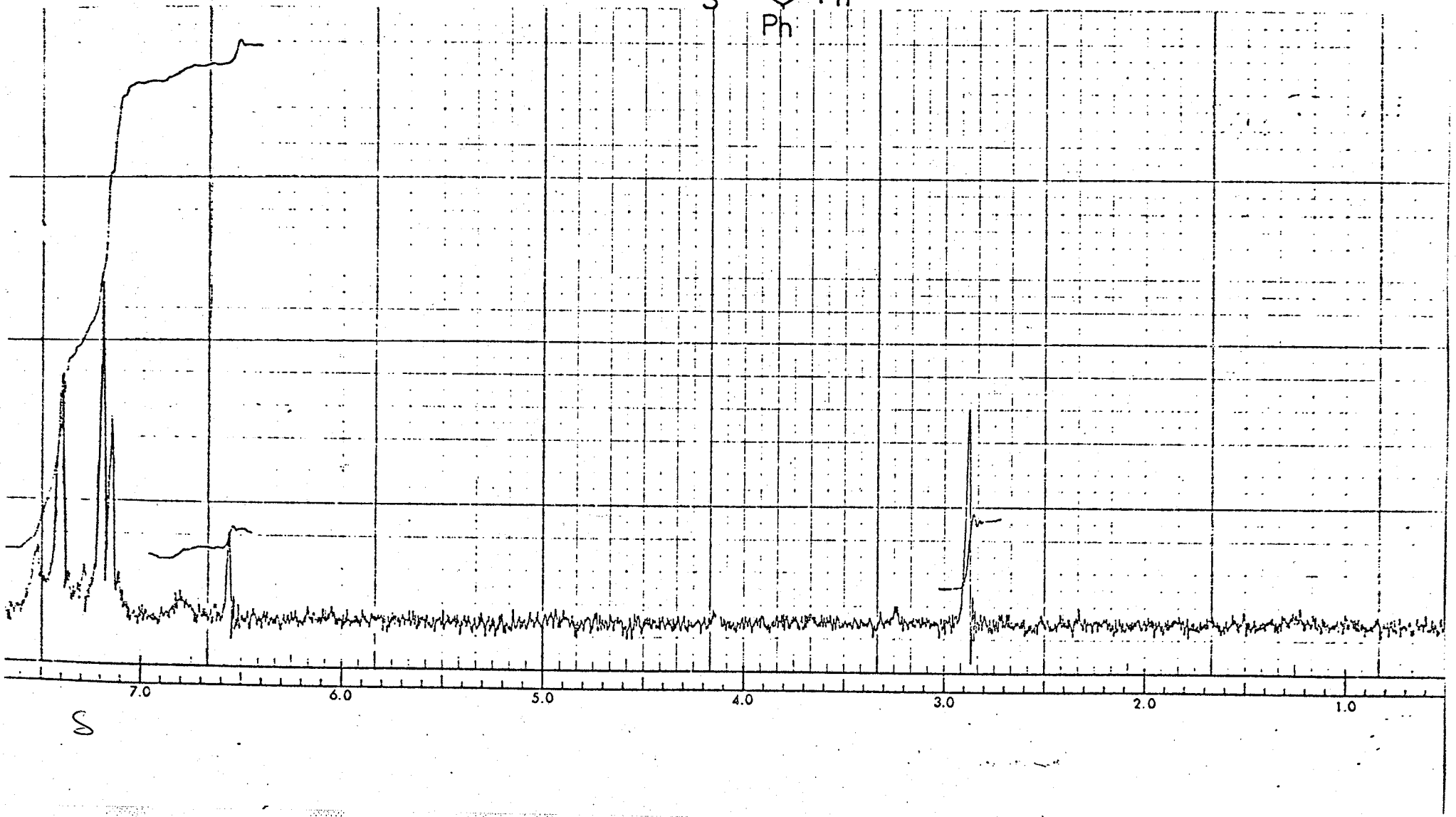
NMR SPECTRUM OF COMP. 64.



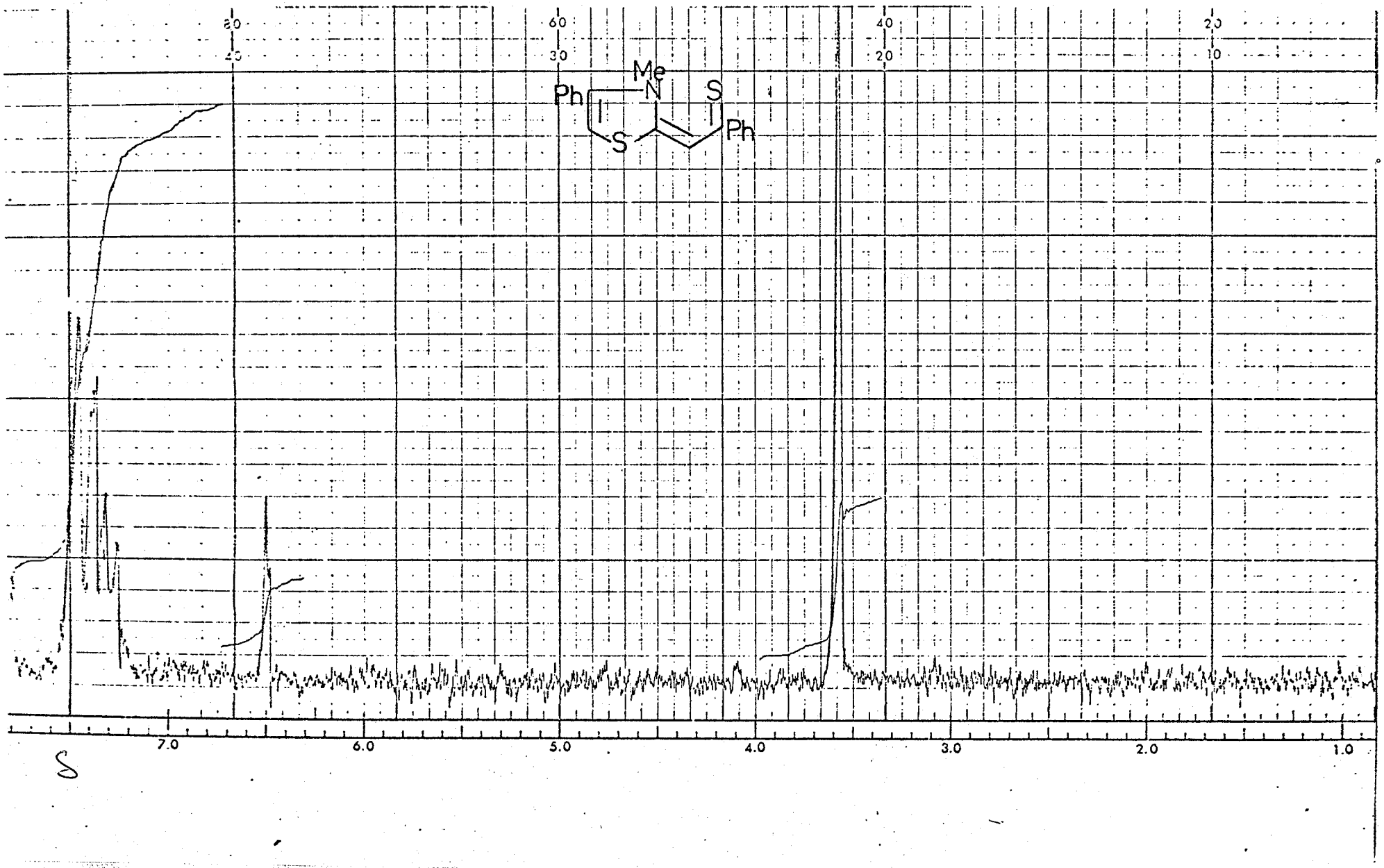


NMR SPECTRUM OF COMP. 90f

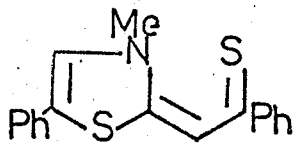


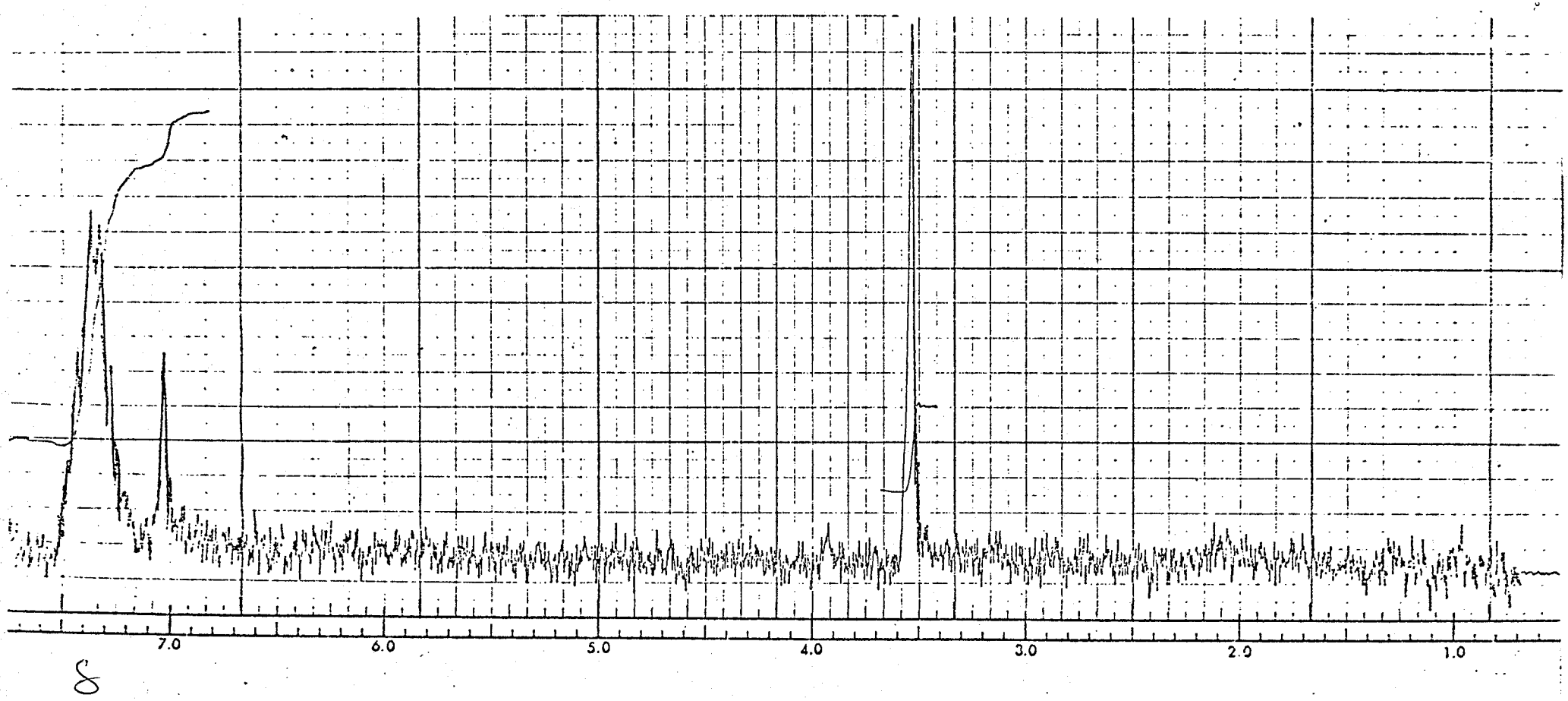


NMR SPECTRUM OF COMP. 91a

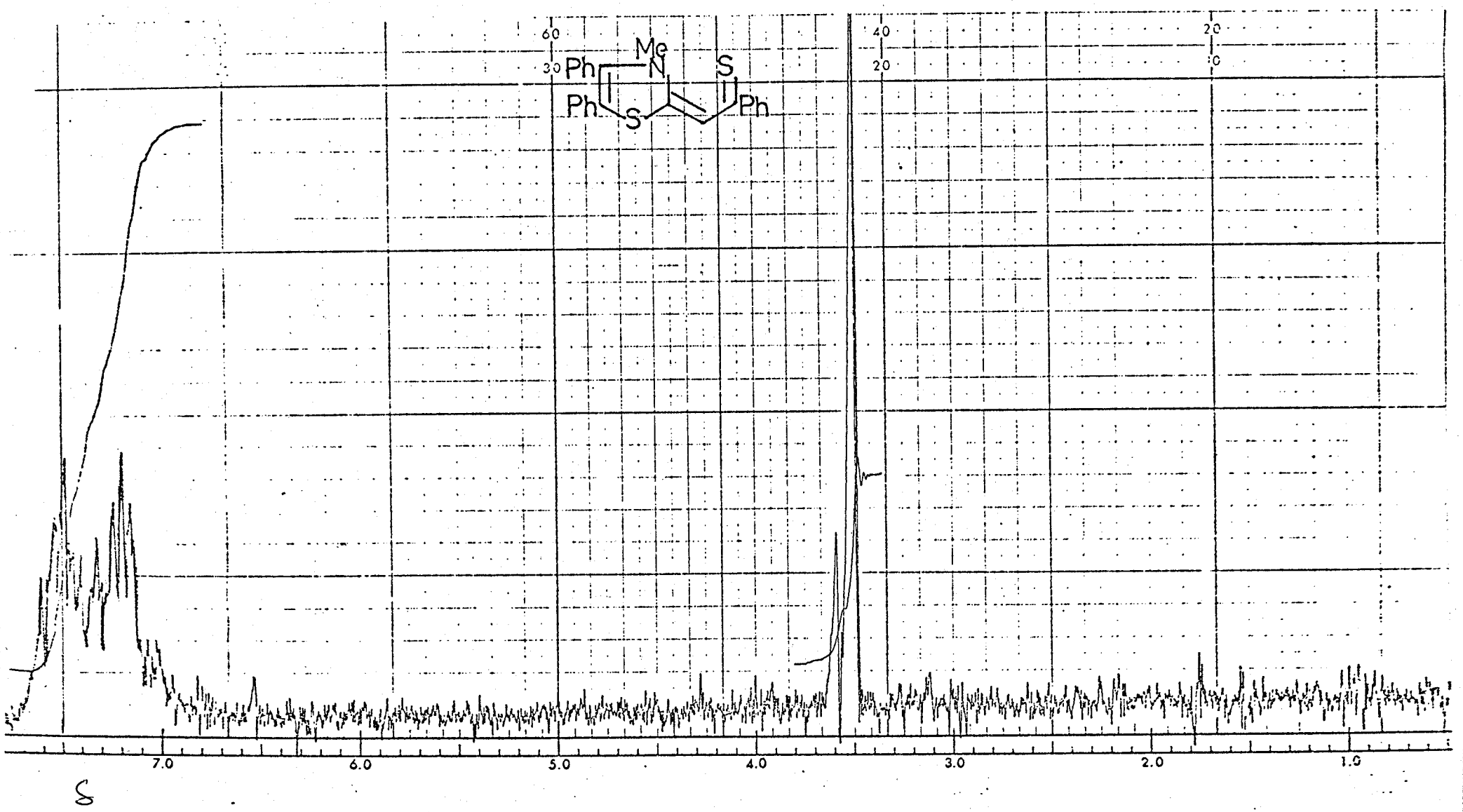


NMR SPECTRUM OF COMP. 91b

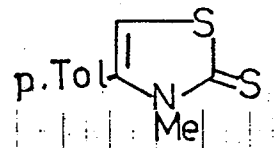


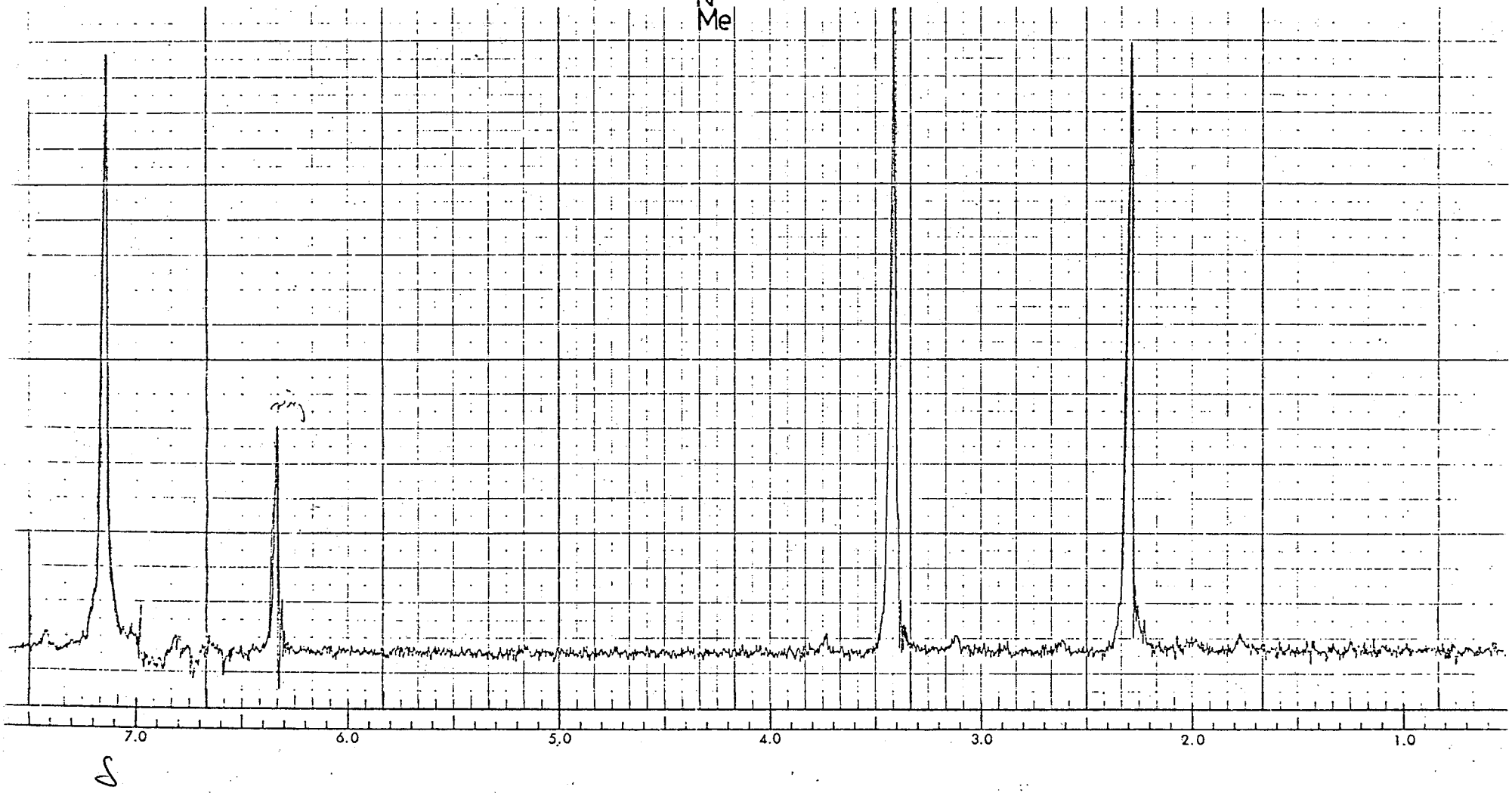


NMR SPECTRUM OF COMP. 91d

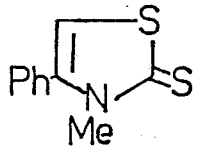


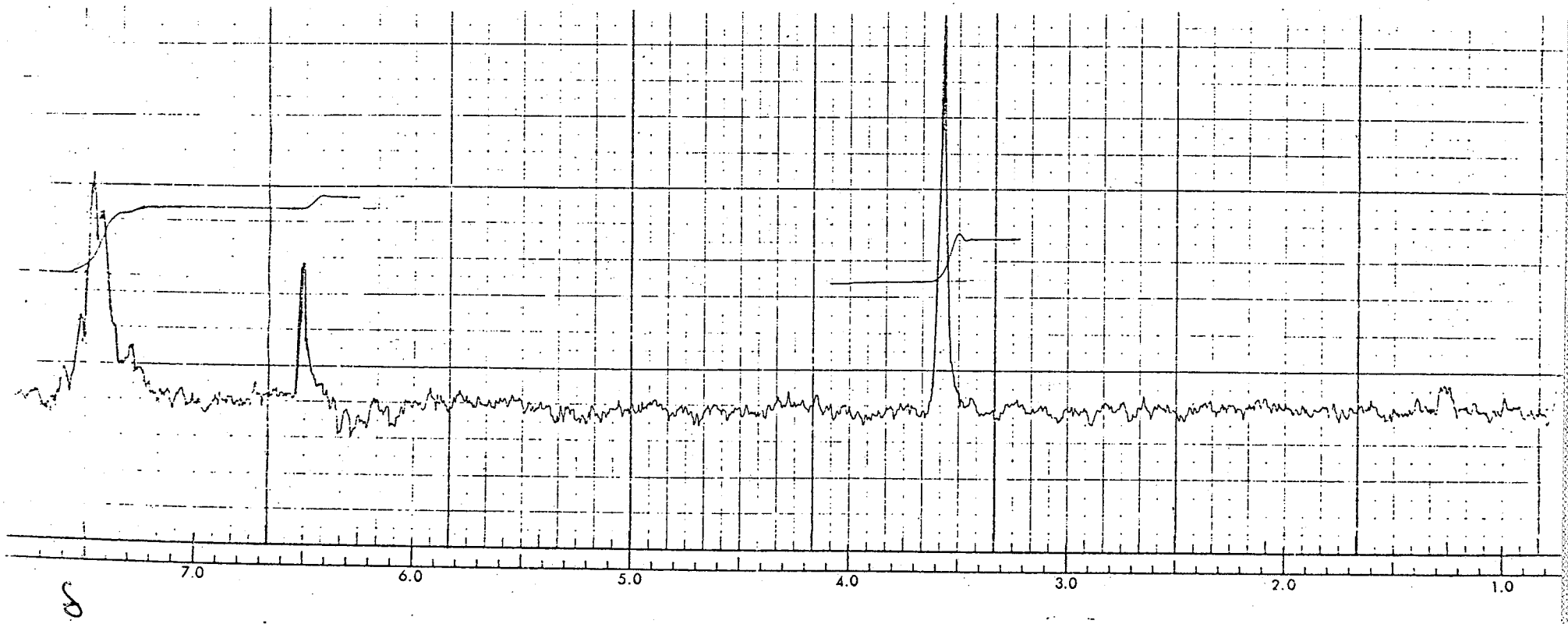
NMR SPECTRUM OF COMP. 93c



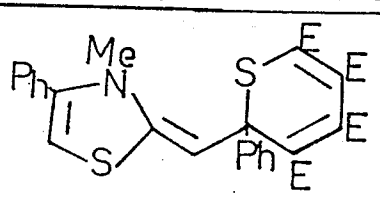


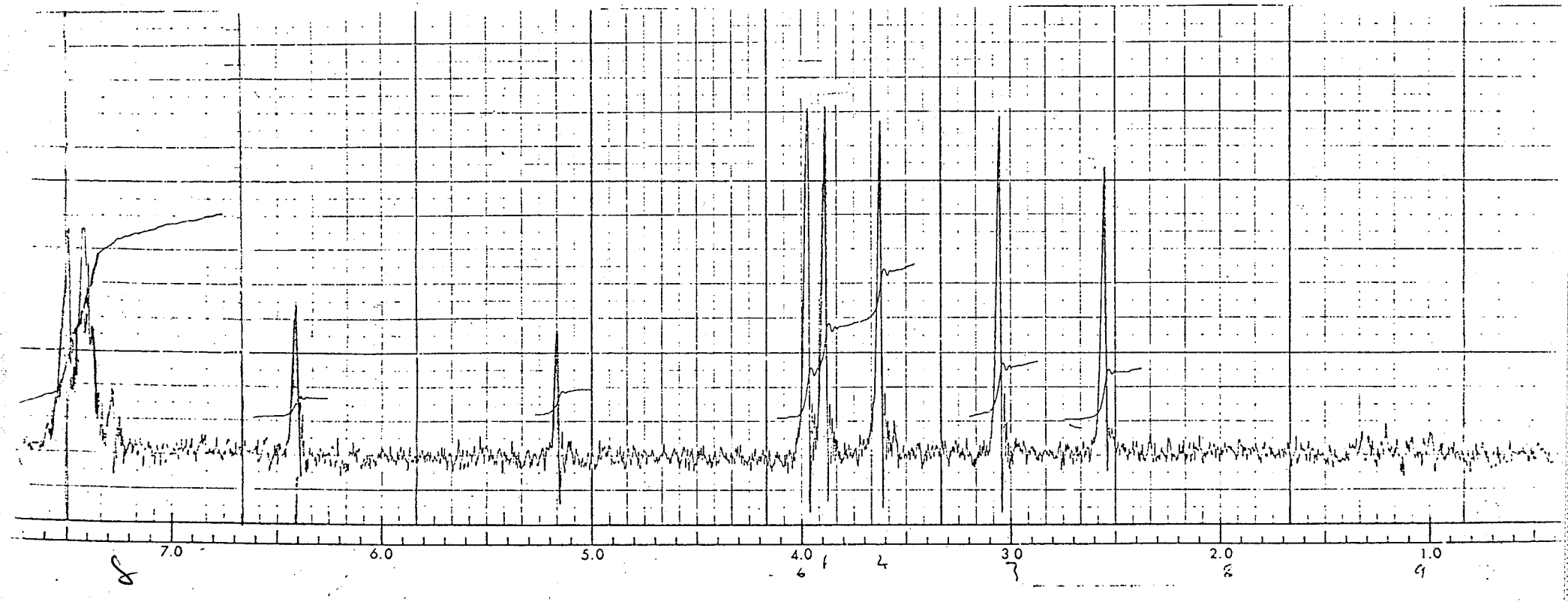
NMR SPECTRUM OF COMP. 93$_d$



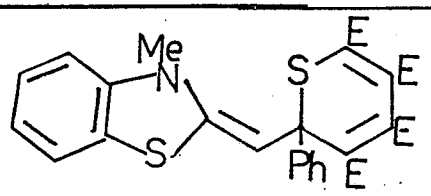


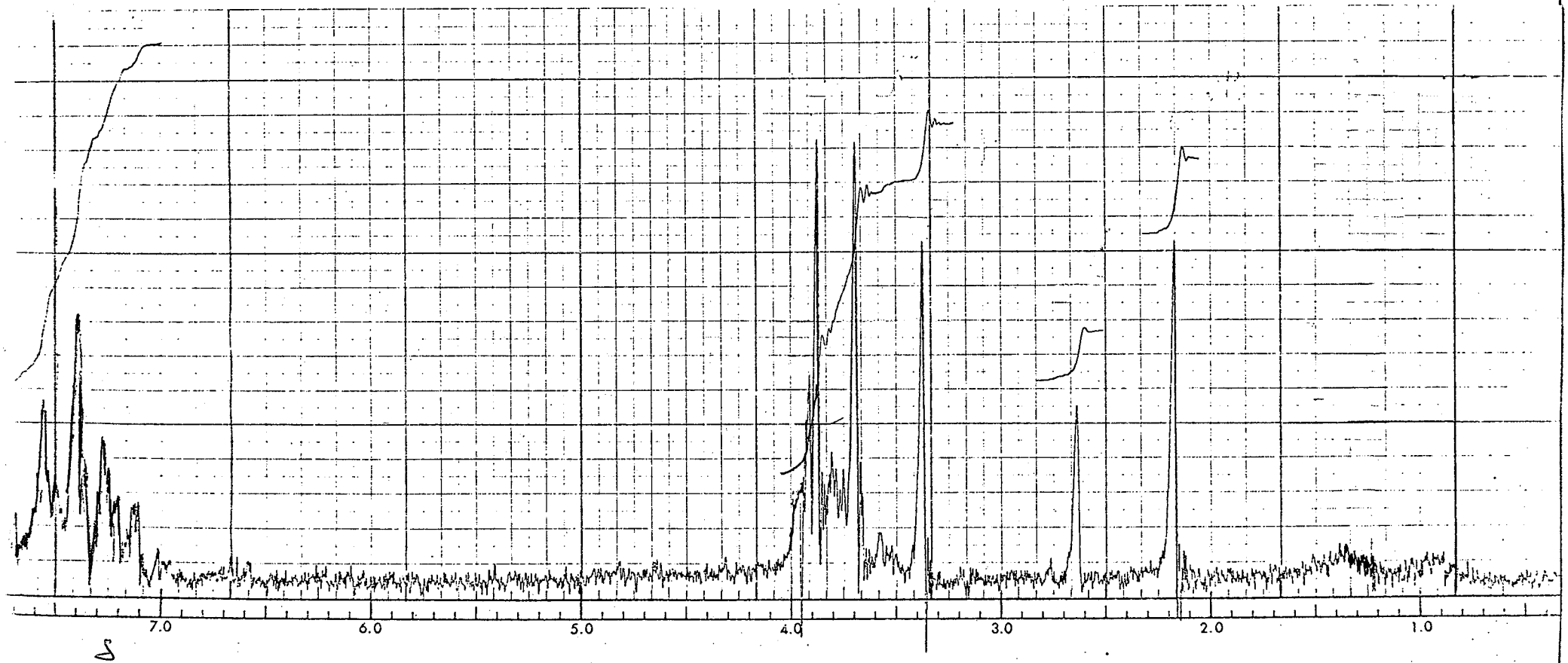
NMR SPECTRUM OF DIADDUCT



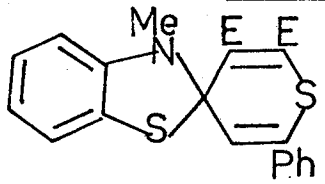


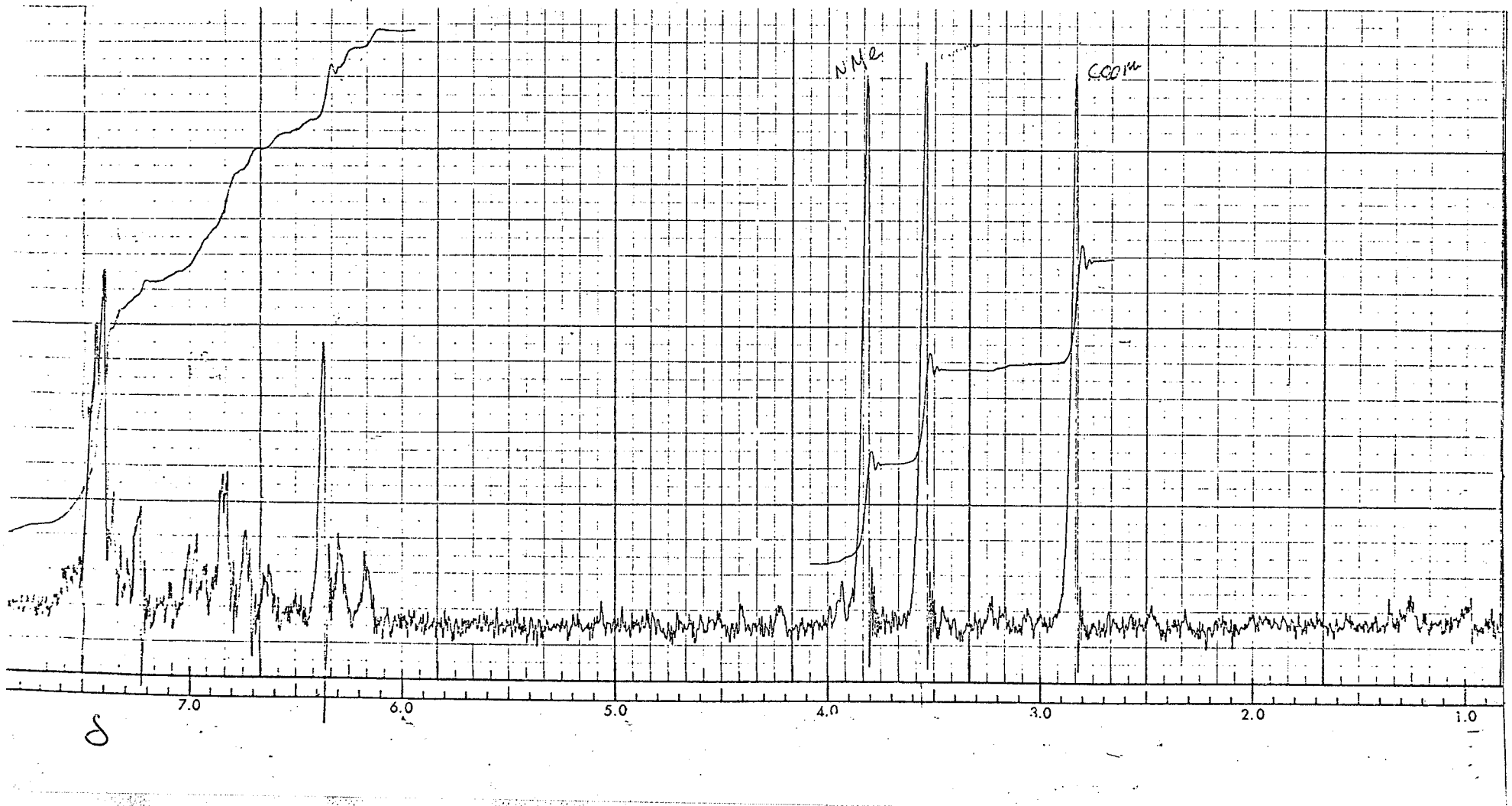
NMR SPECTRUM OF DIADDUCT



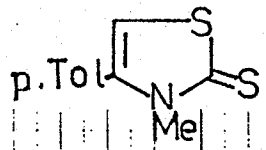


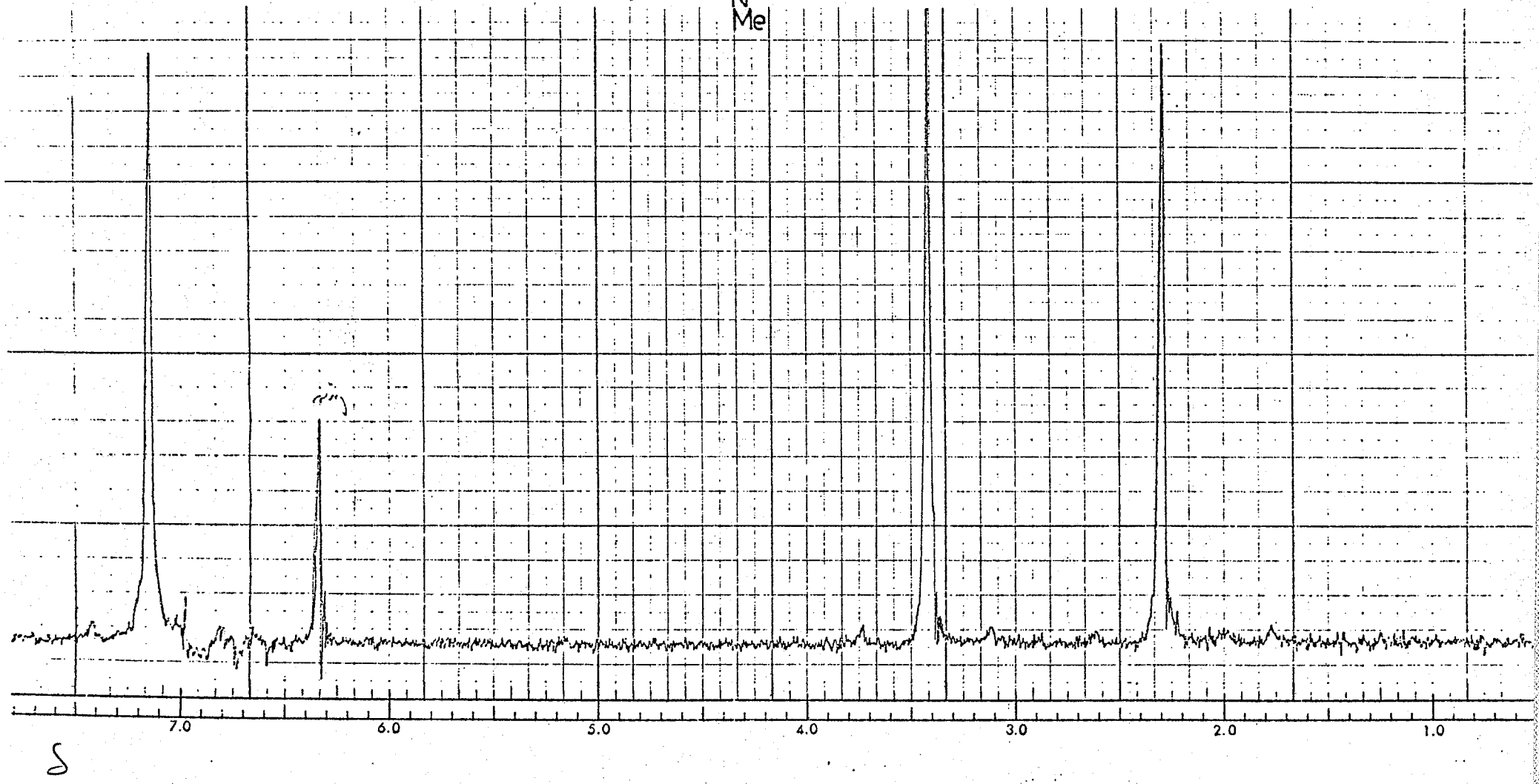
NMR SPECTRUM OF MONOADDUCT





NMR SPECTRUM OF COP. 93c





NMR SPECTRUM OF COP. 93_d