THE UNIVERSITY OF MANITOBA

STUDIES ON ISOTHIAZOLIUM SALTS AND RELATED COMPOUNDS

by

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ABSTRACT:

The reactions of various isothiazolium salts with sulfur in refluxing pyridine have been studied to determine the products and mechanistic pathways involved. In the course of these investigations, three previously unreported isothiazolium salts and a new 3-isothiazoline-5-thione have been synthesized.

Various approaches to 3-thioacylmethylene isothiazoles and 3-acylmethylene isoxazoles have been investigated. However, ring decomposition has so far prevented the synthesis of such analogues to the thiothiophthene system by these synthetic routes.

A potentially useful approach to 3-unsubstituted-3-isothiazoline-5-thiones has been investigated and should prove conducive to the synthesis of these compounds.

INTRODUCTION

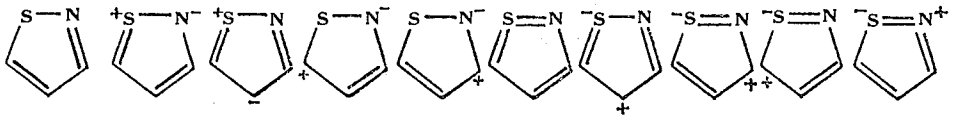
I. GENERAL INTRODUCTION:

This thesis concerns synthetic routes to a number of compounds containing the isothiazole nucleus which were required for several studies being undertaken in this laboratory. Such compounds would be useful in the investigation of 1,3-dipolar reactions, oxidation reactions, and in the synthesis of 3-thioacylmethylene isothiazoles, which are aza analogues of the thiothiophthenes. These studies will, where appropriate, be mentioned in a later section.

II. ISOTHIAZOLES:

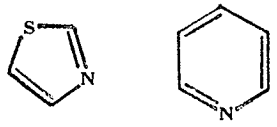
a) Description of the Molecule:

Isothiazole, Ia, is a five-membered heterocyclic molecule containing adjacent nitrogen and sulfur atoms. A number of resonance forms may be drawn for the isothiazole molecule (Ia - Ij), both requiring



Ia Ib Ic Id Ie If Ig Ih Ii Ij

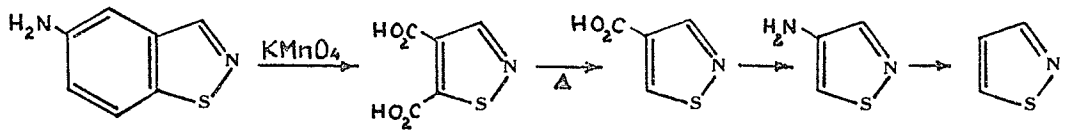
(If - Ij) and not requiring (Ia - Ie) the participation of sulfur d-orbitals. Both isothiazole and thiazole, II, are chemically and physically similar to pyridine, III, supporting the Longuet-Higgins theory of isosterism[1] which claims that in an aromatic system, the group -CH=CH- is electronically similar to the formally bivalent -S-. Taking into account the participation of sulfur d-orbitals, the replacement of =S= for =CH-CH= is also possible.



II III

b) Syntheses of Isothiazoles:

The first method of preparing isothiazole, described by Adams and Slack[2,3] involved the oxidation of 5-aminobenz[d]isothiazole:

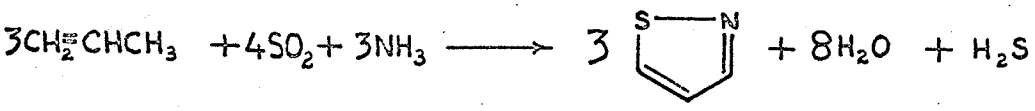


Although both benz[c]isothiazoles and benz[d]isothiazoles with benzene rings containing an amino group can thus be converted to isothiazoles, the preparations are tedious and unsuitable for general syntheses. An improved reaction[3] involves the cyclization of β-iminothiobutyramide with chlorine or hydrogen peroxide:

This reaction has been extended by Goerdeler[4,5,6] to various substituted 5-aminoisothiazoles. In a similar reaction, variously substituted thioketones afford 3-hydroxy, 3-methoxy, and 3-aminoisothiazoles[7]:

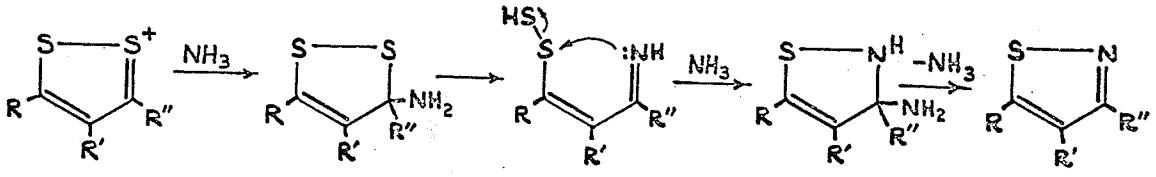
X = OH, OMe, or NH_2

An efficient synthetic method for isothiazoles has been developed by Hübenett and coworkers[8], involving the catalytic reaction of sulfur dioxide, ammonia, and an olefin. Thus, from propylene, isothiazole may be obtained in good yield. The catalyst in this case is activated

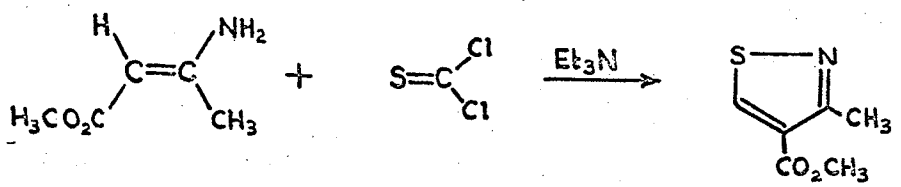


alumina. Similarly, 4-phenylisothiazole can be synthesized from α-methylstyrene, and 4-methylisothiazole from isobutylene. The stability of the isothiazole ring is evidenced by the use of reaction temperatures in the 200°C to 300°C range.[9]

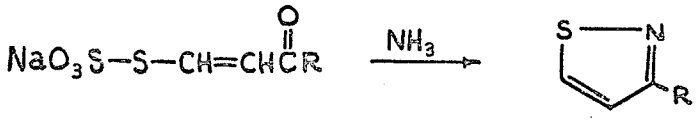
Isothiazoles have been obtained from the reaction of 1,2-dithiolium salts with ammonia in ethanol[10] or with ammonium acetate in acetic acid[11]. The postulated mechanism proceeds via nucleophilic attack at carbon atom 3 or 5:



The utilization of acidic methyne groups to produce isothiazoles is illustrated by the formation of methyl 3-methyl-4-isothiazole carboxylate from thiophosgene and methyl β-aminocrotonate in absolute ethyl ether with triethylamine as catalyst:[12]

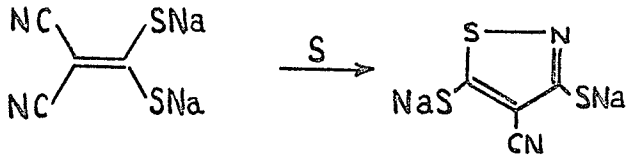


A second use of an acidic methyne group was shown by Wille and co-workers[13] who found that the addition product of acetylenic carbonyl compounds with sodium thiosulfate would cyclize in liquid ammonia to yield isothiazoles:

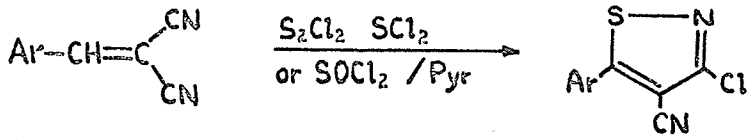


However, the instability of the intermediate cis-thiocyanate adduct results in low yields. Nevertheless, the reaction is of value since it can be adapted to the synthesis of isoselenazoles.[14]

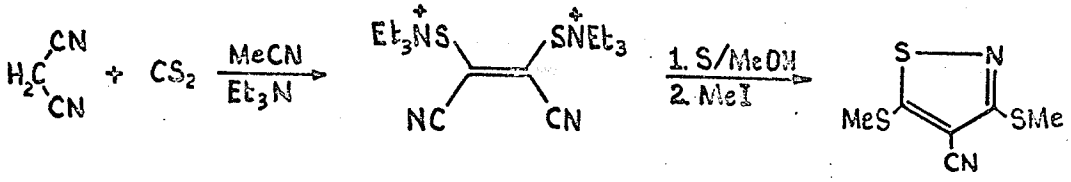
The cyclization of dicyanoethylenedithiolate to give an isothiazole was demonstrated by Soederbaeck[15] and Hatchard[16]:



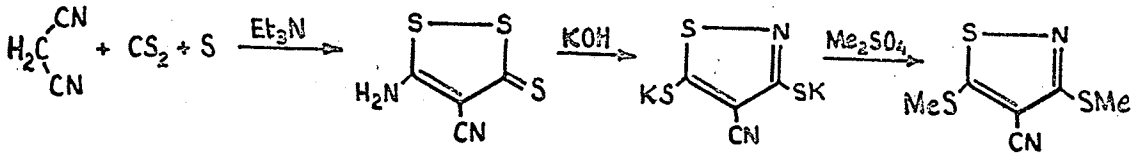
A similar reaction has recently been reported by Nakagawa et al[17] who found that benzylidenemalononitriles would react with sulfur chlorides or thionyl chloride in pyridine to give an isothiazole by an as-yet unelucidated mechanism:



A number of other isothiazole syntheses have been based on the active nucleophilic methylene groups as found in malononitrile or phenylacetonitrile. These are generally used to form intermediates in the presence of base, which on treatment with sulfur yield isothiazoles. Di(triethylammonio)methylenemalononitrile was formed in the reaction of acetonitrile with malononitrile in triethylamine/carbon disulfide. Oxidation with sulfur in methanol followed by treatment with methyl iodide afforded 3,5-di(thiomethyl)-4-cyanoisothiazole:[18]

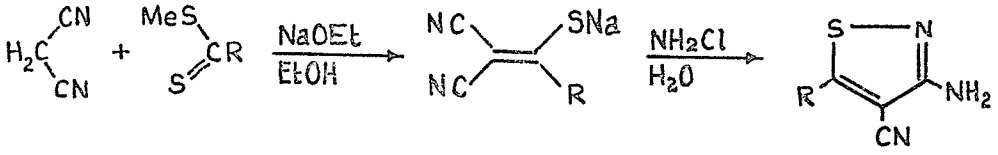


4-Cyano-5-amino-1,2-dithiole-3-thione, obtained from malononitrile, sulfur, and carbon disulfide in the presence of triethylamine, underwent ring-opening and S-S bond scission on treatment with potassium hydroxide. Isomerization and ring-closure yielded dipotassium-3,4-dithio-4-cyanoisothiazole, which on methylation gave 3,5-di(thiomethyl)-4-cyanoisothiazole[19]:

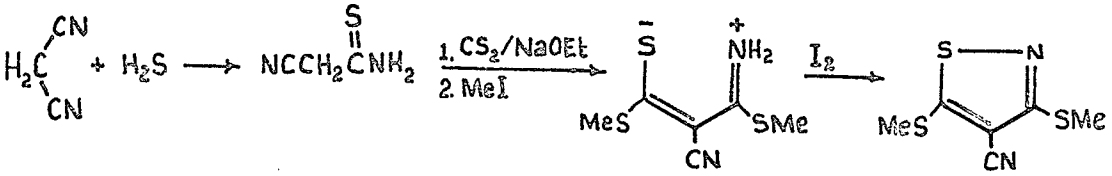


Sodium vinyl sulfides, obtained by thioacylating malononitrile with esters of dithiocarboxylic, thionocarboxylic, trithionocarboxylic, or xanthic acids in anhydrous ethanol with sodium ethoxide as catalyst,

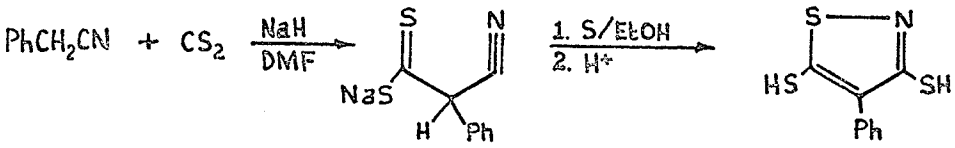
when treated with chloramine yielded 3-amino-4-cyanoisothiazoles[20]:



Cyanothioacetamide, produced from the reaction of hydrogen sulfide and malononitrile, reacts with carbon disulfide in the presence of a sodium alkoxide to give, on methylation, an intermediate which can be oxidized with iodine in ethanol to yield 3,5-di(thiomethyl)-4-cyanoisothiazole[21]:

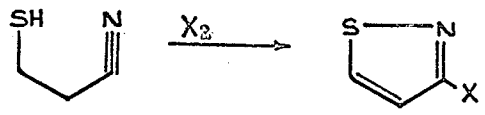


Dithioic acid salts, produced by treating phenylacetonitrile with carbon disulfide in the presence of sodium hydride and dimethylformamide, can be cyclized with sulfur in ethanol. Acidification yields 4-phenylisothiazole-3,5-dithiol[22]:



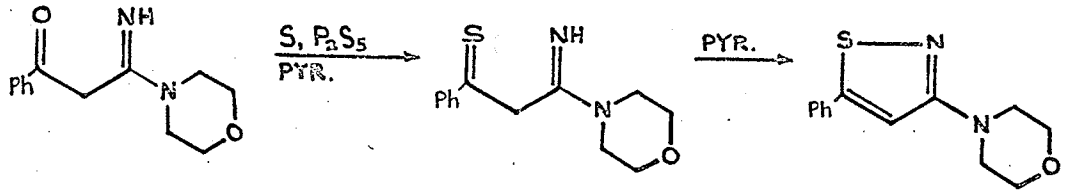
The oxidative cyclization of β-mercaptopropionitrile with halogen

to yield 3-haloisothiazoles[23] involves the loss of three protons by a mechanism which, as yet, is unclear:



X = Cl or Br

β-iminoketones, such as β-imino-β-morpholinoethyl phenyl ketone, may be sulfurized with sulfur and phosphorus pentasulfide in pyridine forming a thione which undergoes ring closure to form 3-morpholino-5-phenylisothiazole[24]:



5-phenyl-3-imino-1,2-dithiolium salts, on treatment with ammonia in alcoholic potassium hydroxide were found by Condorelli and co-workers[25] to isomerize to 3-mercapto-5-phenylisothiazole by the cleavage of the dithiol ring and formation of a nitrile intermediate. Such dithiolium salts also undergo nucleophilic attack by morpholine[25] at the 3-position with the elimination of hydrogen halide, ring cleavage, and ring closure with the displacement of sulfhydride ion by the nucleophilic imino nitrogen to yield 3-morpholino-5-phenylisothiazole.

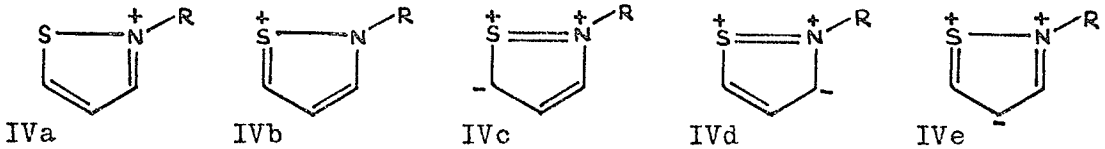
c) Reactions of Isothiazoles:

The reactions of isothiazoles pertinent to the present study are alkylation reactions to give isothiazolium salts. These reactions will be discussed in the section dealing with synthetic routes to those compounds.

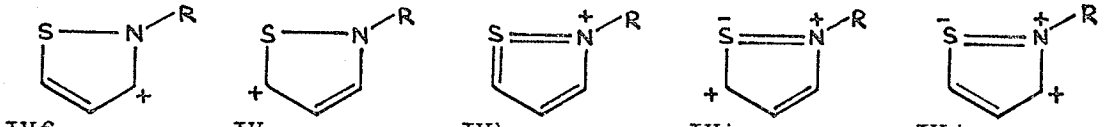
III. ISOTHIAZOLIUM SALTS:

a) Description of the Molecule:

Quaternization of the ring nitrogen of isothiazoles affords isothiazolium salts, IVa. A number of resonance structures may again be drawn, IVa to IVg not involving sulfur d-orbitals, and IVh to IVj using them:



IVa IVb IVc IVd IVe



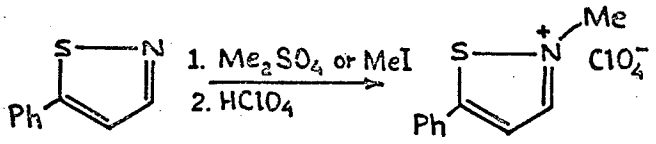
IVf IVg IVh IVi IVj

Structures involving adjacent positive centers are unlikely, due to their high energy requirement. Deprotonation has been shown[26] to occur in the 3- and 5-positions, the 5-position being favoured. Since by inductive, coulombic, or L.C.A.O. molecular orbital considerations

nitrogen should carry the bulk of the positive charge, this behaviour seems anomalous unless sufur atom d-orbital overlap stabilizes the deprotonated species. Nuclear magnetic resonance studies on isothiazolium hydrogen sulfate[27] again suggest a lower electron density at the 5-position than at the 3-position. The significant resonance structures would therefore seem to be IVf, IVg, and IVi.

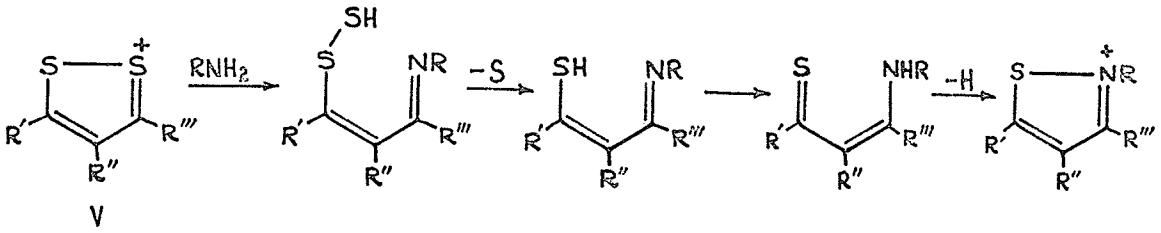
b) Preparation of Isothiazolium Salts:

Two synthetic routes to the isothiazolium salts are available, namely the alkylation of isothiazoles, or ring synthesis from a suitable precursor. The alkylation of isothiazoles is the more direct method, and isothiazolium salts have been obtained by the reaction of isothiazoles with methyl or ethyl iodide[27], by the reaction with triethyloxonium tetrafluoroborate[28], or by refluxing in benzyl bromide[27]. This approach 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:



Synthetic routes involving the ring closure of appropriate compounds were investigated by Faust[29] on the suggestion of Goerdeler[30]. Faust dehydrogenated 3-aminodithioacrylates with bromine to obtain 5-thiomethylisothiazolium bromide and tribromide.

McKinnon and Robak[31] have synthesized a number of isothiazolium salts by the iodine oxidation of 1-aminopropene-3-thiones, formed in the reaction of 1,2-dithiolium salts (V) with primary amines:



V

The availability of 1,2-dithiolium salts[32,33,34] and the generality of the reaction make it a convenient one for the synthesis of N-aryl isothiazolium salts. However, if R'= H, the instability of the intermediate thial precludes the synthesis of 5-unsubstituted isothiazolium salts by this method.

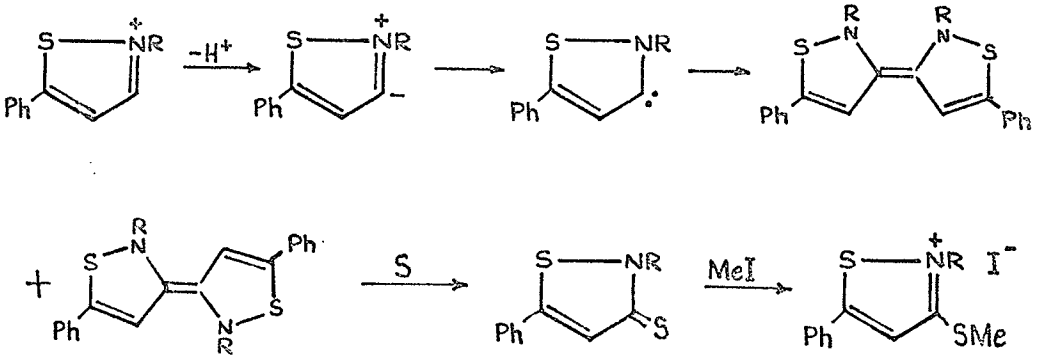
c) Reactions of Isothiazolium Salts:

Deprotonation studies[26] as mentioned earlier, suggest that nucleophilic attack should take place at either the 3- or 5-position, and preferentially in position 5. By analogy, Klingsberg[35] has shown that 1,2-dithiolium salts undergo attack by sulfur in boiling pyridine to give 1,2-dithiole-3-thiones.

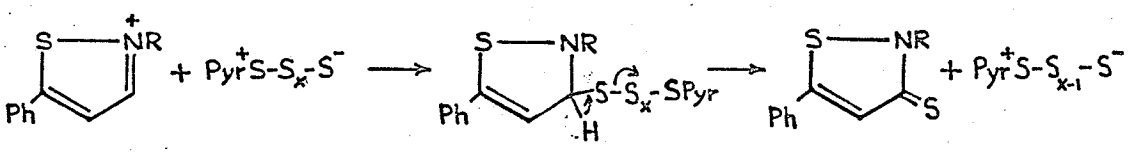
Landesberg and Olofson[28] have examined another example of nucleophilic attack on the isothiazolium system They studied the reaction of ammonia with 2-ethyl-4-phenylisothiazolium tetrafluoroborate, and found that ammonia adds at the 3-position, causing ring cleavage followed by ring closure to form 4-phenylisothiazole with the elimination of ethylamine.

Similarly, 3-phenylisothiazolium perchlorate reacted with hydrazine to give 3-phenylpyrazole, and with phenylhydrazine to give a mixture of 1,3-diphenyl and 1,5-diphenylpyrazole[11]. On treatment with base, isothiazolium salts undergo decomposition[26], as do 1,2-ditiolium salts[32] and thiazolium salts[36]. This decomposition occurs, again, by attack at the 3-position.

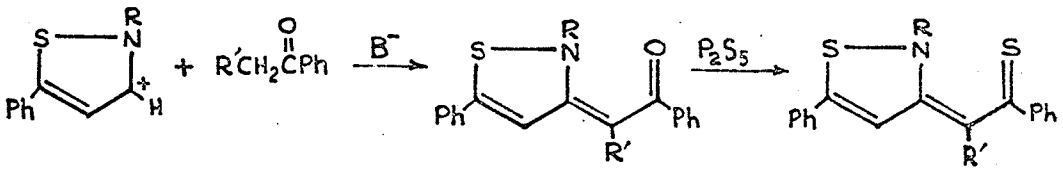
By analogy with the reaction of 1,2-dithiolium salts with sulfur in boiling pyridine to give 1,2-dithiole-3-thiones[35], McKinnon and Robak studied the same reaction involving isothiazolium salts[31]. They suggested that 2-methyl-5-phenylisothiazolium perchlorate and 2,5-diphenylisothiazolium perchlorate underwent nucleophilic addition of sulfur at the 3-position to give 4-isothiazoline-3-thiones, isolated as their methiodides. Based on work by Wanzlick[37] with thiazolium salts, the authors proposed that the first stage in the mechanism involved deprotonation:



Alternately, the reaction could involve direct nucleophilic attack by the activated polysulfide anion:



The same suthors investigated the reaction of isothiazolium salts with methyl and methylene carbonyls as a possible approach to an aza analogue of the thiothiophthenes:



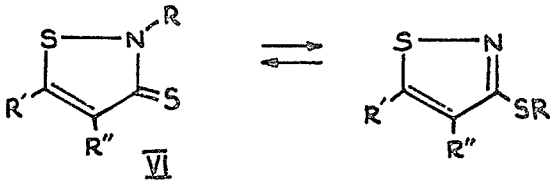
The treatment of isothiazolium salts with acetophenone in refluxing ethanol, with diazoacetophenone, and with sodium benzoylacetate afforded no identifiable products. With ethyl benzoylacetate, acetanilide was obtained from aniline displaced from the isothiazolium salt and acetic acid which was the solvent. The reaction of 2,5-diphenylisothiazolium perchlorate with dimethylformamide in the presence of base was also inconclusive.

IV. 4-ISOTHIAZOLINE-3-THIONES:

a) Description of the Molecule:

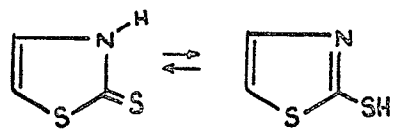
The 4-isothiazoline-3-thione system, VI, consists of an isothiazole nucleus bearing a thione function at the 3-position and a substituent

on the nitrogen atom of the isothiazole ring:

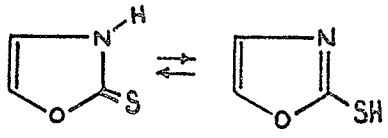


VI

Although no data are available for the possible tautomerism of VI which, when R=H, contains a potential mercapto group, thiazole-2-thiones, VII, have been shown by infrared[38] and ultraviolet[39,40] studies to exist mainly in the thione form. Similarly, oxazole-2-



VII



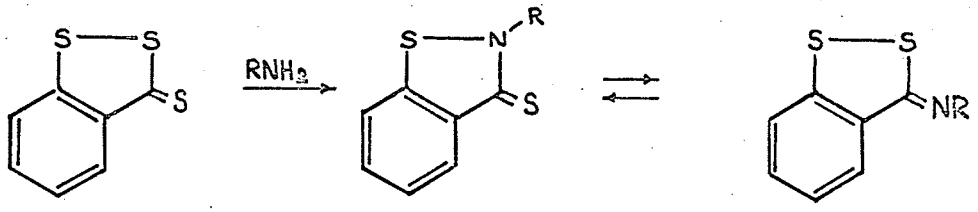
VIII

thiones, VIII, have been shown[41] to exist in the thione form. It therefore seems likely that the 4-isothiazoline-3-thione molecule could exist in the thione form rather than as 3-mercaptoisothiazole.

b) Syntheses of 4-isothiazoline-3-thiones:

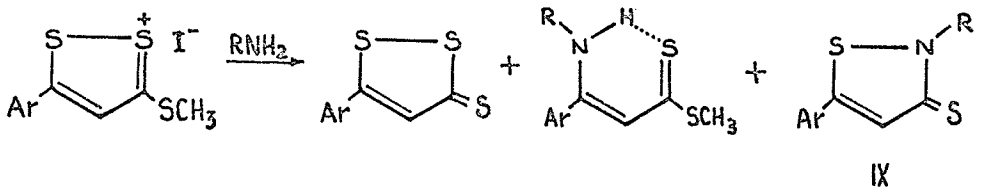
4-isothiazoline-3-thiones may have been reported as early as 1929 by McClelland and co-workers[42,43] who studied the reaction of 1,2-benzodithiole-3-thione with methylamine, ethylamine, and aniline. However, it is uncertain as to whether the product was the 4-isothiazoline-3-thione or a 3-imino-1,2-dithiole. The authors, in fact, suggested an

equilibrium which has since been disputed[44]:



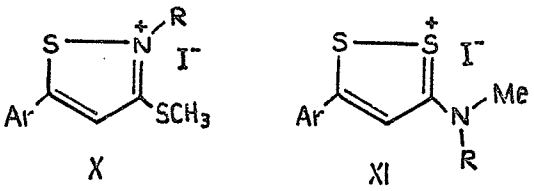
As mentioned in the previous section, McKinnon and Robak[31] previously suggested that the products of the reaction of isothiazolium salts with sulfur in refluxing pyridine were 4-isothiazoline-3-thiones, formed by one of two possible mechanisms as described previously. However, studies reported in this thesis confirm that the products of such reactions may sometimes be the isomeric 3-imino-1,2-dithioles. In addition, unpublished data[45] concerning the reaction of 2,5-diphenylisothiazolium perchlorate with sulfur in refluxing pyridine indicate that the product, in this reaction at least, is 5-phenyl-3-phenylimino-1,2-dithiole.

The formation of 4-isothiazoline-3-thiones has been reported by Le Coustumer and Mollier[41,46] in the reaction of 5-aryl-3-thiomethyl-1,2-dithiolium iodides with primary aliphatic amines. The authors expected, and initially reported[47] the formation of 5-aryl-3-arylimino-1,2-dithioles by analogy to the reaction with primary aromatic amines[44,48]. On the basis of evidence described below, it was decided that the isomeric thione, IX, had been obtained:



IX

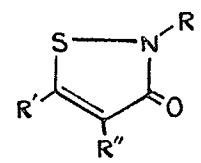
The reaction of ^{15}N-enriched IX with methyl iodide gave the salt X which showed no ^{15}N-methyl coupling which would have been evident in XI, formed from the imino compound and methyl iodide. Furthermore, the reaction of IX with benzonitrile oxide gave the corresponding 4-isothiazolin-3-one.



X XI

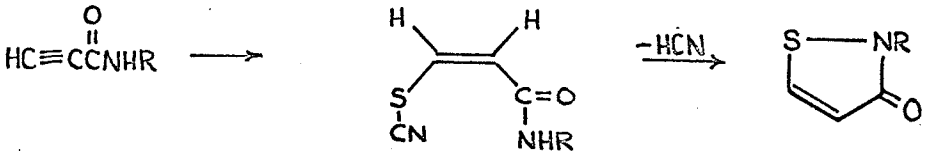
The authors also claim to have synthesized a 4-isothiazoline-3-thione from the reaction of 2-methyl-5-phenylisothiazolium perchlorate with sulfur in refluxing pyridine, a reaction, as mentioned previously, that has been found somewhat ambiguous.

The 4-isothiazoline-3-thiones should also be available by the sulfurization of the corresponding 4-isothiazolin-3-one, XII. Such ketones are accessible by the general synthesis of Crow and Leonard[49] based on the nucleophilic displacement of sulfenyl halide intermediates by amide nitrogen[50], and on a synthesis developed by Wille, Capeller, and Steiner[51]. N-sub-



XII

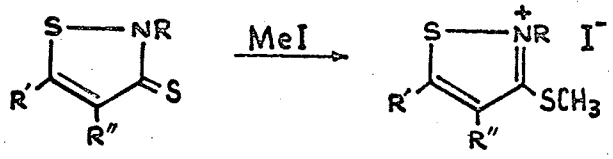
stituted propiolamides were prepared by the reaction of methyl propiolate with the appropriate amine. The amides, on treatment with thiocyanate gave cis-3-thiocyanoacrylamides, which lost hydrogen cyanide on treatment with dilute acid to form 4-isothiazolin-3-ones:



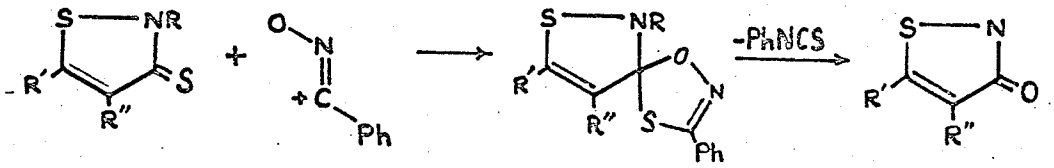
The cyclization of the intermediate cis-3-thiocyanoacrylamide can also be effected by treatment with stoichiometric quantities of Fe^{2+} or Ni^{2+} and alkali[52].

c) Reactions of 4-isothiazoline-3-thiones:

4-isothiazoline-3-thiones undergo alkylation reactions with methyl iodide[31,46]:



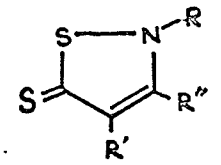
giving isothiazolium salts. As mentioned in the preceding section, 4-isothiazoline-3-thiones undergo oxidation by benzonitrile oxide to form the ketone[46]:



V. 3-ISOTHIAZOLINE-5-THIONES:

a) Description of the Molecule:

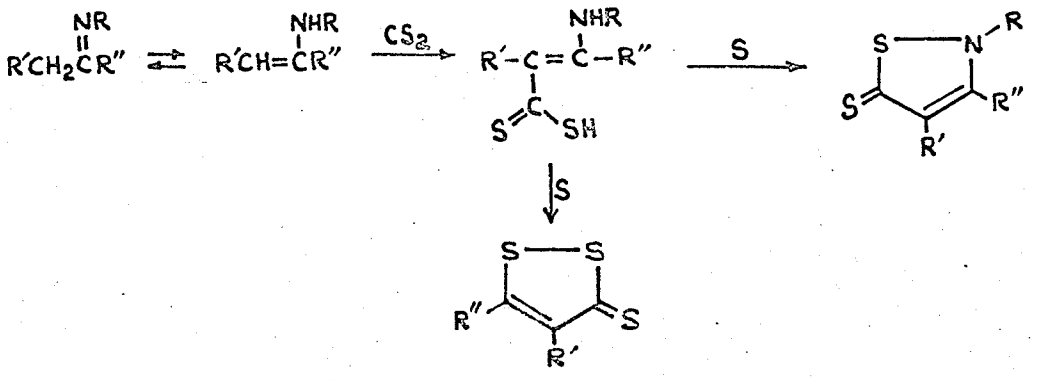
3-Isothiazoline-5-thione, XIII, is isomeric with 4-isothiazoline-3-thione, consisting of an isothiazole nucleus bearing a thione function at the 5-position, and a substituent on the nitrogen atom of the isothiazole ring. Tautomerism, when R=H, is again possible, although for reasons mentioned in IVa, it is perhaps unlikely, and the molecule probably exists almost entirely in the thione form.



XIII

b) Syntheses of 3-isothiazoline-5-thiones:

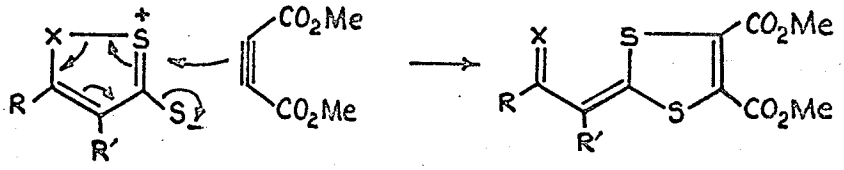
These compounds were first synthesized by Mayer and co-workers[53,54,55] from ketimines, carbon disulfide, and sulfur. They found that ketimines react with carbon disulfide to form dithioacids which in the presence of sulfur can be either S-thiolated, forming 1,2-dithiole-3-thiones with the elimination of amine, or dehydrogenated, forming 3-isothiazoline-5-thiones with the elimination of hydrogen sulfide:



The dehydrogenation can also be accomplished by iodine oxidation. The reaction product is temperature dependent, isothiazoline thiones being formed between 15°C and 20°C, and dithiole thiones at higher temperatures.

c) Reactions of 3-isothiazoline-5-thiones:

The reactions of 3-isothiazoline-5-thiones have been very little studied. Behringer, Kilger, and Wiedenmann[56] report the reaction of XIV, where R,R' = $-(CH_2)_4-$ and X = N-Ph or N-CH_2-Ph with dimethyl acetylene dicarboxylate:



XIV

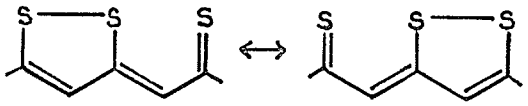
This is similar to previously reported[57] 1,3-dipolar additions of dipolarophiles to 1,2-dithiole-3-thiones.

By analogy with the 4-isothiazoline-3-thiones, the 5-thiones might be expected to undergo alkylation and oxidation reactions as well, to give the corresponding isothiazolium salts and 4-isothiazolin-3-ones.

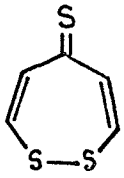
VI. THIOTHIOPHTHENES AND AN AZA ANALOGUE:

The thiothiophthene molecule, XVa or XVb was first correctly iden-

fied by Bezzi, Mammi, and Garbuglio[58] although it had been synthesized earlier by Arndt[59] who had erroneously suggested a seven-member ring disulfide of structure XVI:



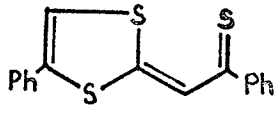
XVa XVb



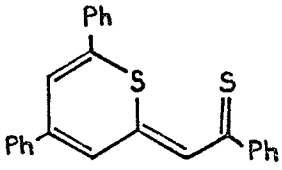
XVI

Bezzi, Mammi, and Garbuglio also suggested the existence of single bond - no bond resonance in the molecule, conferring aromatic character on the two rings. The ring carbon atoms are separated by 1.37 to 1.38 angstroms, indicating an aromatic system, and the sulfur-sulfur bond distances are 2.36 angstroms, compared to 2.04 angstroms in an aliphatic disulfide R-S-S-R, indicating a bond order of less than one.

Although the thiothiophthene structure is symmetrical according to nuclear magnetic resonance data, its ultraviolet and visible spectra are similar to those of XVII and XVIII, in which single bond-



XVII

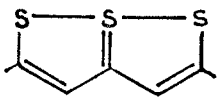


XVIII

no bond resonance is impossible[60]. This evidence was originally interpreted as indicating that the molecular symmetry may be due to rapid tautomerism rather than single bond-no bond resonance. Thus

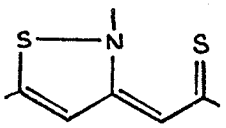
structures XVa and b should be separated by two arrows, ⇄ , rather than by the double-headed arrow of resonance.

The possibility of sulfur d-orbitals being of importance in the bonding of thiothiophthenes was investigated by Maeda[61] whose calculations, involving the use of simple L.C.A.O. techniques and approximations, suggested that the participation of $3d_{xy}$ orbitals was less likely than the participation of the $3p_z$ orbital. However, a later paper by Leaver et al[62] indicates that the properties of the system are best described by the structure XVc. The unusually long S-S bond in the thiothiophthenes has been explained by assuming delocalization of all pi-electrons, forming an eight-centered system with the S-S bonds being purely pi-bonds[63] similar to the N-N bond in N_2O_2[64].



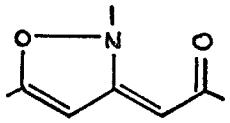
XVc

The synthesis of an S-N-S aza analogue of the thiothiophthene system, XIX, would be useful in clarifying, to some extent, the type of bonding mechanism predominant in the molecule. Since nitrogen has no available d-orbitals, valency-shell expansion is extremely unlikely. Thus, should the aza analogue be found symmetrical, its symmetry could not be due to the participation of d-orbitals, suggesting that perhaps single bond-no bond resonance or pi-electron delocalization were important in thiothioph-



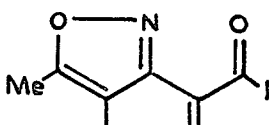
XIX

thene bonding. The compound XIX, which is a 3-thioacylmethylene isothiazole, could conceivably be synthesized either by adding the required side chain onto an isothiazole nucleus, or by sulfurizing the analogous 3-acylmethylene isoxazole, XX.

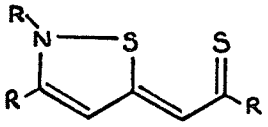


XX

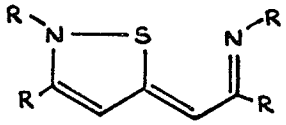
Some studies have been made on a related system, the isoxazole XXI[65]. McKinnon and Wong found that in this compound, the two methyl groups were not equivalent in the nuclear magnetic resonance spectrum, indicating that single bond-no bond resonance was not occurring, and hence was unlikely in thiothiophthene. However, spectroscopic and chemical studies did indicate that the molecule might tautomerize between two forms. It therefore seems possible that rapid tautomerism might account, at least in part, for the apparent symmetry of the thiothiophthenes. It could, however, be argued that rapid tautomerism would be less favoured in the above system than in the case of the thiothiophthenes, owing to the ring strain in XXI arising from fusion onto the benzene ring. Indeed, similar effects



XXI



XXII



XXIII

have been noted between thiothiophthene derivatives[62]. It would therefore be highly desirable to synthesize a compound such as XIX to test its properties. Although no such systems have been made, two isomeric or isoelectronic structures, XXII. and XXIII, are known[66,67,68,69].

DISCUSSION

PURPOSE OF RESEARCH:

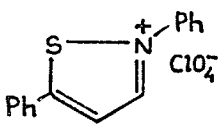
The studies reported in this thesis were undertaken with several ultimate objectives in mind. In general, isothiazoline thiones were desired for oxidation and 1,3-dipolar addition investigations as well as for use as precursors to the 3-thioacylmethylene isothiazoles. In particular, it was thought that an investigation of the nucleophilic attack of sulfur in refluxing pyridine on isothiazolium salts would be of value, since this reaction reportedly yielded 4-isothiazoline-3-thiones which would be of synthetic use in approaching 3-thioacylmethylene isothiazoles, which, as aza analogues of thiothiophthene, would be interesting compounds. In addition, the reaction was worthy of investigation since later studies seemed to indicate that, in fact, isomeric 3-imino-1,2-dithioles could be formed, rather than the thiones. However, other workers used the reaction to confirm an alternate synthesis of 4-isothiazoline-3-thiones In all, the products and mechanisms of the reaction of isothiazolium salts with sulfur in pyridine are quite unclear, and it seemed necessary to clarify the mechanistic pathways involved, as well as the products of the reactions. It also seemed necessary to develop alternate syntheses of isothiazoline thiones to confirm the reaction products of the above processes.

I. REACTION OF ISOTHIAZOLIUM SALTS WITH SULFUR:

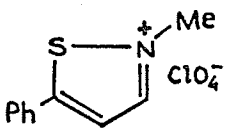
All isothiazolium salts used in these investigations were prepared by methods previously reported in the literature, using readily available 1,2-dithiole-3-thiones[32,34,70,71] as precursors. The N-phenyl salts were made by the ring-closure synthesis of McKinnon and Robak[31] while the N-methyl analogues were prepared by the methylation of isothiazoles prepared according to Olofson et al[11].

a) Isothiazolium Salts Unsubstituted in the 3-Position:

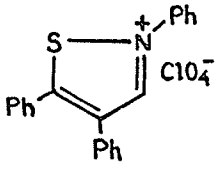
As mentioned previously, isothiazolium salts are subject to nucleophilic attack in either the 3-position or the 5-position. Therefore the first series of compounds studied had the 5-position blocked by a phenyl group, thus rendering nucleophilic attack by sulfur at the 5-position unlikely. Products would then arise almost exclusively by attack at the 3-position. The isothiazolium salts studied in this series were 2,5-diphenylisothiazolium perchlorate, XXIV, 2-methyl-5-phenylisothiazolium perchlorate, XXV, 2,4,5-triphenylisothiazolium perchlorate, XXVI, and 2-methyl-4,5-diphenylisothiazolium perchlorate, XXVII:



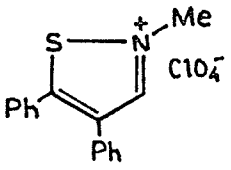
XXIV



XXV



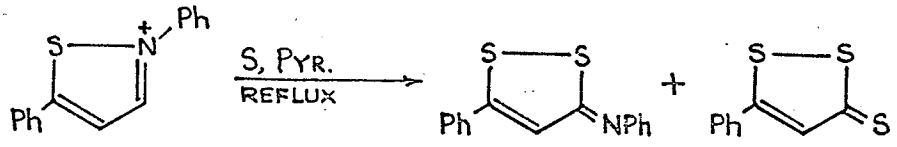
XXVI



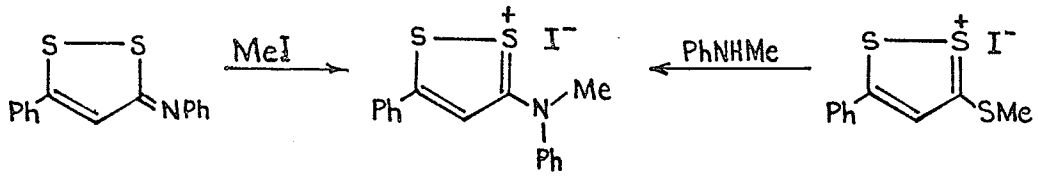
XXVII

i. 2,5-diphenylisothiazolium perchlorate:

The reaction of this isothiazolium salt with sulfur in refluxing pyridine had been studied previously and it was suggested that the product was an isothiazoline thione[31]. However, later repetition of the work[45] using identical reaction conditions indicated the only product to be 5-phenyl-3-phenylimino-1,2-dithiole. Now, separation of the reaction products by thin-layer chromatography on silica gel has revealed two major products, 5-phenyl-1,2-dithiole-3-thione, and the previously identified 5-phenyl-3-phenylimino-1,2-dithiole:

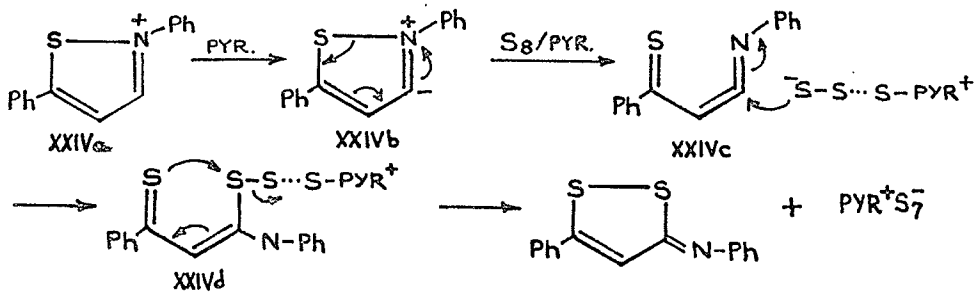


The thione was identified by its highly characteristic infrared spectrum and by its melting point. The iminodithiole was similarly characterized by comparison of its infrared spectrum and melting point with that of an authentic sample prepared by the reaction of 5-phenyl-3-methylthio-1,2-dithiolium iodide, XXVIII, with aniline[44,48]. The resulting compound was identified as the iminodithiole rather than the isomeric 2,5-diphenyl-4-isothiazoline-3-thione since identical products were obtained on methylation of 5-phenyl-3-phenylimino-1,2-dithiole and on the reaction of 5-phenyl-3-methylthio-1,2-dithiolium iodide with N-methylaniline:



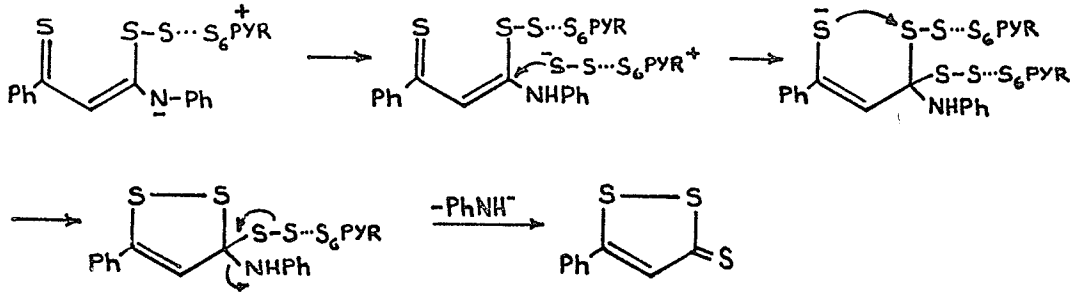
It could be argued that in the above reaction of 3-methylthio-5-phenyl-1,2-dithiolium iodide with aniline that the 2,5-diphenyl isothiazoline thione could be the product, and that this could methylate. However, it would be extremely unlikely to alkylate on nitrogen. Alkylation on sulfur would be preferred since this would lead to an aromatic product.

The formation of the iminodithiole in the reaction of 2,5-diphenyl isothiazolium perchlorate with sulfur in refluxing pyridine probably proceeds via a dipolar intermediate formed by the deprotonation of the isothiazolium salt in pyridine, followed by ring opening to a thioketoketimine. This intermediate would then undergo nucleophilic attack by a polysulfur anion[72,73] followed by ring closure to the iminodithiole:

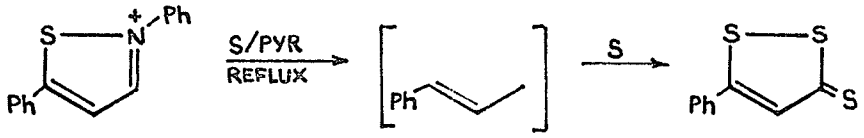


The intermediate thioketoketimine is not unreasonable since keto-ketimines were found to be intermediates[74] in similar reactions

with isoxazolium salts The mechanism leading to the formation of the 1,2-dithiole-3-thione is more speculative. The anionic intermediate XXIVd may pick up a proton and undergo attack by the polysulfide anion again, followed by ring closure and the elimination of aniline:



An alternate, and perhaps more likely mechanism under the reaction conditions involved entails the decomposition of the isothiazole ring to give a three-carbon fragment which would then undergo sulfurization to give the 1,2-dithiole-3-thione directly:

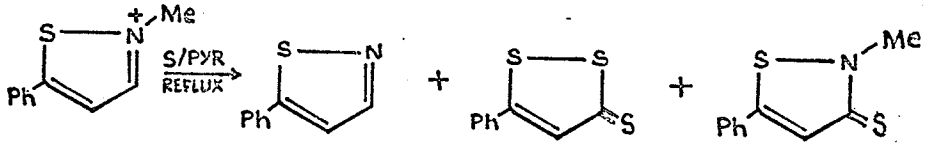


Three-carbon fragments are known to sulfurize readily to dithiole thiones at moderately high temperatures[75] suggesting that such a mechanism is at least plausible, though unproven.

One possible source of the thione might have been by nucleophilic attack of sulfur in pyridine on the imine. However, prolonged treatment of the pure imine under the reaction conditions gave no indication of thione formation.

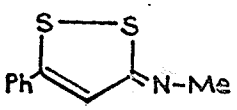
ii. 2-methyl-5-phenylisothiazolium perchlorate:

The reaction of this isothiazolium salt (XXV) with sulfur in refluxing pyridine has been claimed by McKinnon and Robak[31] to yield 2-methyl-5-phenyl-4-isothiazoline-3-thione. This was also suggested by Le Coustumer and Mollier[41,46] who used an alternate synthesis. A careful separation of the reaction products by thin-layer chromatography has now shown that three major products are formed: 5-phenylisothiazole (XXIX), 5-phenyl-1,2-dithiole-3-thione, and tentatively 2-methyl-5-phenyl-4-isothiazoline-3-thione (XXX):



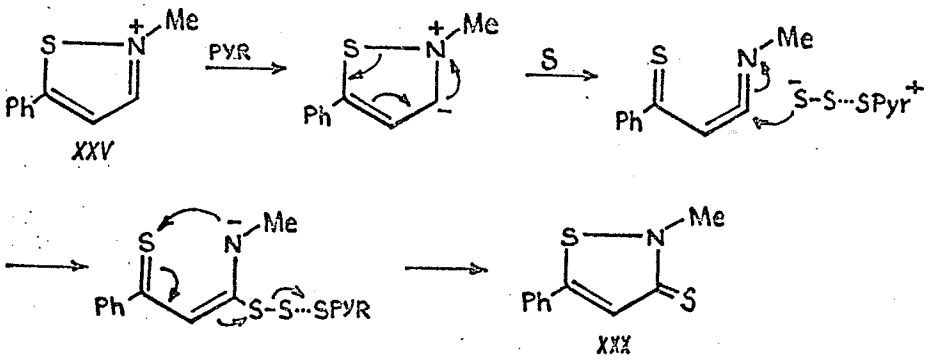
XXV XXIX XXX

The 5-phenylisothiazole was identified by comparing its infrared spectrum and melting point with that of an authentic sample; the 5-phenyl-1,2-dithiole-3-thione was again identified by its very characterisitic infrared spectrum, as well as by its melting point. It was, however, somewhat uncertain as to whether the third product had the isothiazoline thione structure, or the isomeric imino-dithiole structure, XXXI, despite the evidence of Le Coustumer and Mollier, since the N-phenyl compound had been shown to yield the iminodithiole. The molecular weight, as ascertained from the mass spectrum, was cor-

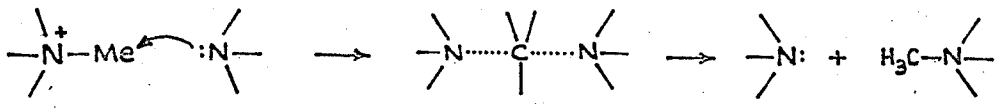


XXXI

rect for either compound, but on the basis of the studies done by Le Coustumer and Mollier[41,46] including a comparison of melting points, it seems likely that the correct structure is that of the isothiazoline thione, XXX, and that there is a basic mechanistic dissimilarity in the reaction depending on whether the nitrogen atom of the isothiazole ring is aryl- or alkyl-substituted. A possible mechanistic route might involve a similar series of steps to those involved in the formation of the iminodithiole, with an intermediate thioketoketimine attacked by a polysulfide anion, but with ring closure occuring, with the incorporation of nitrogen:



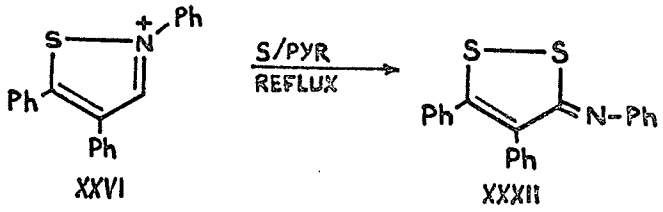
This may indeed be the case since the nitrogen atom here would be more nucleophilic, owing to the inductive effect of the the methyl group, than in the N-phenyl compound. The formation of 5-phenylisothiazole is easily accounted for by demethylation under the reaction conditions involved. An S_N2-type trans demethylation, similar to the Menschutkin Reaction, is likely:



Finally, the formation of 5-phenyl-1,2-dithiole-3-thione probably proceeds via one of the mechanisms described in the previous reaction; that is, either by the elimination of methylamine or by the sulfurization of a 3-carbon fragment formed in the decomposition of the isothiazolium salt.

iii. 2,4,5-triphenylisothiazolium perchlorate:

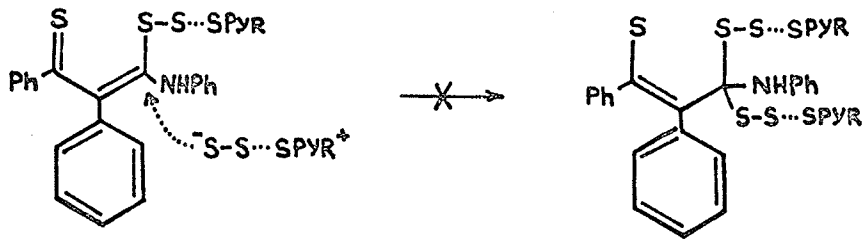
The reactions of this salt with sulfur in refluxing pyridine had not been studied, but its similarity to 2,5-diphenylisothiazolium perchlorate would lead one to expect similar behaviour. In addition, the fact that the nitrogen atom is aryl-substituted would suggest that the iminodithiole might be formed rather than the isothiazoline thione. In fact, the only product isolated from this reaction was 4,5-diphenyl-3-phenylimino-1,2-dithiole (XXXII):



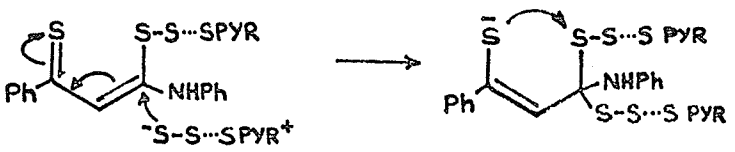
XXVI XXXII

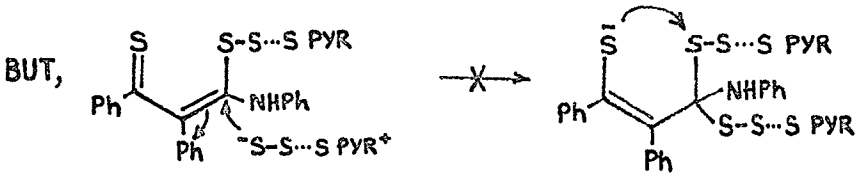
This product was identified by comparing its infrared spectrum and melting point with those of an authentic sample prepared by treating 4,5-diphenyl-3-methylthio-1,2-dithiolium iodide with aniline. Also, the melting point was identical to that reported by Paulmier, Lozac'h, and Mollier[48]. The fact that no 4,5-diphenyl-1,2-dithiole-3-thione

was formed in this reaction can perhaps be accounted for in several ways. The extra phenyl ring in the 4-position may sterically hinder the approach of the polysulfide anion in its attack at the 3-position:



Alternatively, the extra phenyl group could act as an electron sink, so that ring closure via a concerted movement of electrons is rendered unlikely:



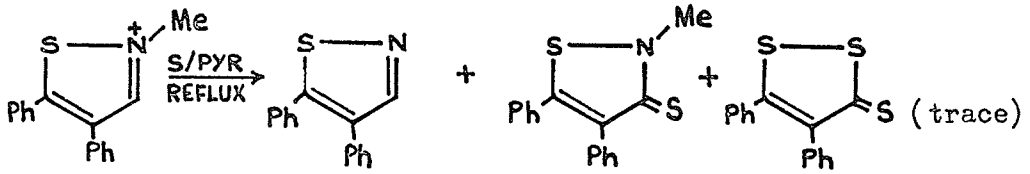


A third possibility, assuming that thione formation proceeds via a 3-carbon fragment intermediate, is that the phenyl-disubstituted 3-carbon fragment may be so stabilized by conjugative effects that reaction with sulfur does not occur to any appreciable extent.

iv. 2-methyl-4,5-diphenylisothiazolium perchlorate:

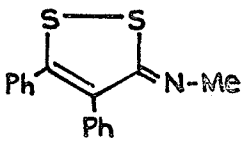
Again, the similarity of this molecule to 2-methyl-5-phenyliso-thiazolium perchlorate would suggest a similarity in their reactions

with sulfur in refluxing pyridine, and once again, since the nitrogen atom is alkyl-substituted, one might expect isothiazoline thione formation. Experimentally, two major products have been isolated: 4,5-diphenylisothiazole (XXXIII), resulting from simple demethylation, and what is probably 2-methyl-4,5-diphenyl-4-isothiazoline-3-thione (XXXIV). A trace of 4,5-diphenyl-1,2-dithiole-3-thione was also detected:



XXVII XXXIII XXXIV

The isothiazole was again identified by comparison with an authentic sample and by elemental analysis. The mass spectrum of XXXIV gave a molecular weight correct for either the isothiazoline thione, XXXIV, or the iminodithiole, XXXV. However, a sample of XXXIV was prepared by the method of Le Coustumer and Mollier[41,46] from 4,5-diphenyl-3-methylthio-1,2-dithiolium perchlorate and methylamine, and was found to be identical in melting point and infrared spectrum with the substance isolated. The extremely low yield of 4,5-diphenyl-1,2-dithiole-3-thione is again consistent with the explanations suggested in the previous section.



XXXV

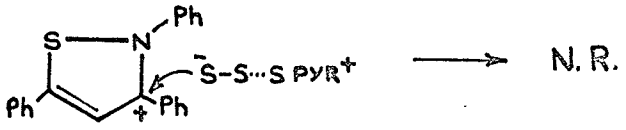
b) Isothiazolium Salts with 3- and 5-Positions Blocked:

In order to clarify several aspects of the reaction mechanism, 2,3,5-triphenyl isothiazolium perchlorate, XXXVI, was synthesized. In this salt, both positions of likely nucleophilic attack are blocked by phenyl groups, rendering attack at the 3- or 5-position unlikely.

i. 2,3,5-triphenylisothiazolium perchlorate:

On treatment with sulfur in refluxing pyridine this salt yielded only unreacted starting material, with no evidence of ether-soluble products. It would seem, therefore, that the initial step in the reaction must involve deprotonation to give a dipolar type of intermediate which undergoes subsequent attack by polysulfide anion. Since removable protons at either the 3- or 5-positions are unavailable in XXXVI, the intermediate

XXXVI

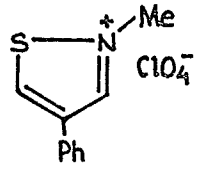


is not formed and no products result. Furthermore, this is evidence that attack by the polysulfide anion does not occur at a position occupied by a substituent. Of course, this evidence does not clarify the mechanism yielding the 1,2-dithiole-3-thione since no such product

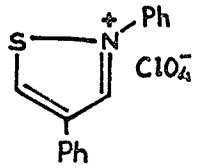
can be formed from XXXVI. Since no resonance structure of XXXVI can be drawn which localizes positive charge on the 4-position, attack by the polysulfide anion would be expected to be unlikely there.

c) Isothiazolium Salts with both 3- and 5-Positions Available:

Again, in the interest of further elucidating the mechanism of the sulfur/pyridine reaction, it was desirable to have isothiazolium salts bearing no substituents in either the 3-position or the 5-position, so that perhaps two types of thiones could be obtained. 2-methyl-4-phenylisothiazolium perchlorate, XXXVII, was synthetically available through methylation of the isothiazole. However, 2,4-

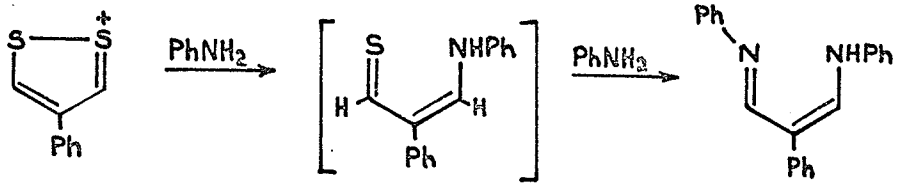


XXXVII



XXXVIII

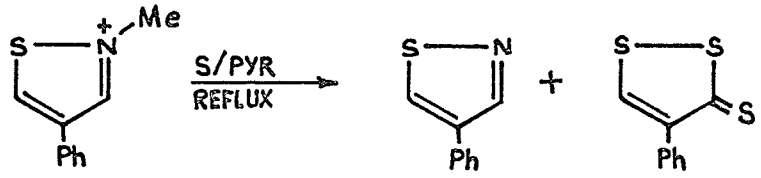
diphenylisothiazolium perchlorate, XXXVIII, presented more of a challenge, since its synthesis by the method of McKinnon and Robak[31] was impossible due to the presence of a reactive thial intermediate:



A new synthetic route was subsequently investigated, which, although it did not ultimately yield the desired salt, was found to be of synthetic interest, as later described.

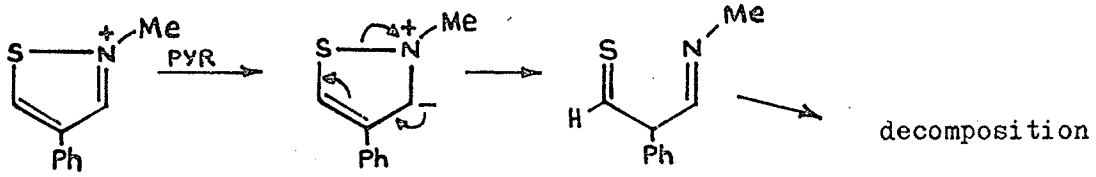
i. 2-methyl-4-phenylisothiazolium perchlorate:

The reaction of this salt with sulfur in refluxing pyridine gave two major products, the demethylated 4-phenylisothiazole, and 4-phenyl-1,2-dithiole-3-thione:

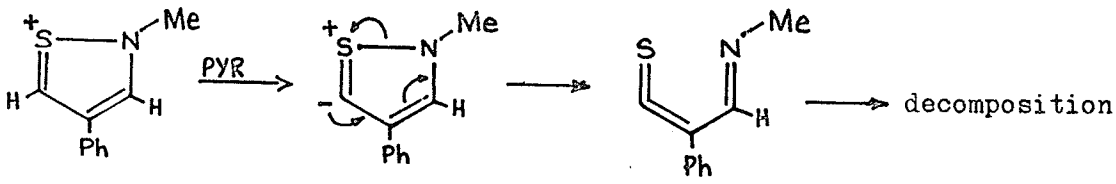


Both of the products were identified by comparing their melting points and infrared spectra with those of the authentic compounds synthesized by conventional means.

The 4-phenylisothiazole results, once again, from a conventional S_N2 trans-elimination as described previously. The 4-phenyl-1,2-dithiole-3-thione would almost certainly have to result from the sulfurization of an intermediate 3-carbon chain, since deprotonation at either the 3- or 5-position will result in an unstable intermediate. The formation of these unstable intermediates on deprotonation accounts for the over-all low yield of this reaction, and for the absence of any 4-isothiazoline-3-thione among the reaction products. If deprotonation occurs at the 3-position, an unstable thioaldehyde, or thial will result:



Alternately, if deprotonation should occur at the 5-position, an unstable iminothioketene[76,77] would be formed:

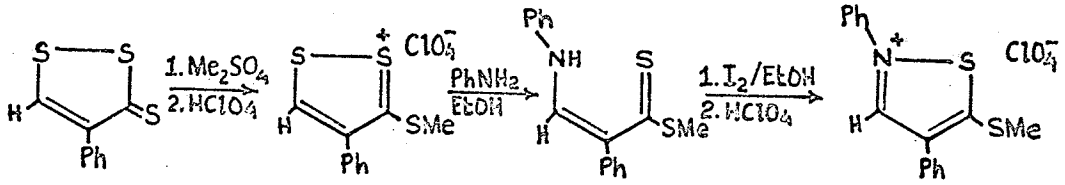


Consequently, with the unavailability of a suitable mechanistic intermediate, neither the 4-isothiazoline-3-thione nor the 3-isothiazoline-5-thione can be formed, and the results of the experiment seem to be consistent with the proposed mechanism.

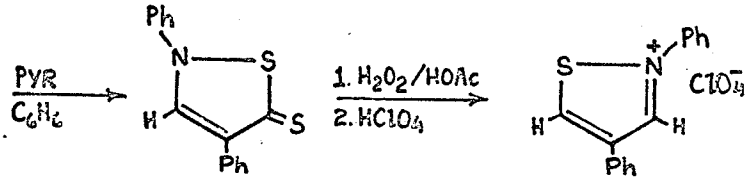
ii. 2,4-diphenylisothiazolium perchlorate:

As mentioned previously, this isothiazolium salt was unavailable by either of the conventional syntheses, so a new synthetic route was investigated, based in part on work done by McKinnon and Robak[31]. 4-phenyl-1,2-dithiole-3-thione, XXXIX, was methylated and treated with perchloric acid to give 3-methylthio-4-phenyl-1,2-dithiolium perchlorate, XL, which on treatment with aniline in ethanol underwent ring-opening to the 1-arylaminoprop-1-ene-3-thione, XLI, which on iodine oxidation gave 2,4-diphenyl-5-methylthioisothiazolium perchlorate, XLII. Demethylation of this compound yielded 2,4-diphenyl-3-isothiazoline-5-thione, XLIII, which on oxidation with hydrogen peroxide in glacial acetic acid, might have oxidized to the desired

isothiazolium salt, XXXVIII[78,79]:

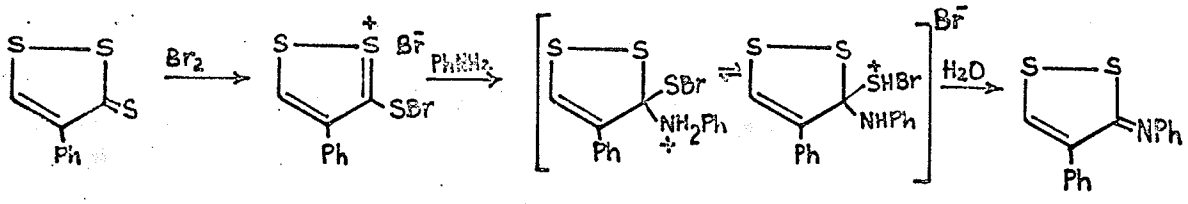


XXXIX XL XLI XLII



XLIII XXXVIII

In fact, the reaction scheme was successful up to the last step, with XLIII being isolated. This compound was found to be identical to one prepared by Adelfang[80] who treated 3-bromothio-4-phenyl-1,2-dithiolium bromide with aniline. He suggested the formation of the imine by the following mechanism:

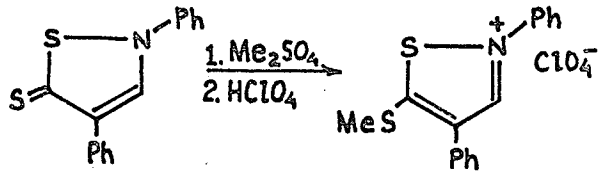


5-unsubstituted-3-imino-1,2-dithioles cannot be synthesized by the conventional method of treating the 3-methylthiodithiolium salt with an aromatic amine since nucleophilic attack occurs at the vacant 5-position with the subsequent formation of acyclic products. Subsequent investigations were accordingly undertaken to determine whether the 3-isothiazoline-5-thione or the 3-imino-1,2-dithiole had been formed;

these studies, described below, indicate that the product was indeed the 3-isothiazoline-5-thione rather than the iminodithiole claimed by Adelfang.

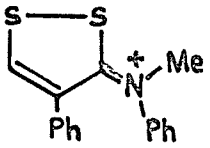
Proofs of Structure XLIII:

On treatment of XLIII with dimethylsulfate followed by perchloric acid a compound identical to XLII was obtained, indicating simple methylation of the thione sulfur atom:



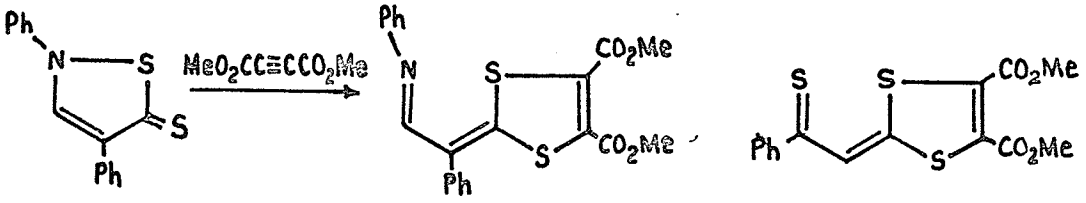
XLIII XLII

Compound XLII gave a correct elemental analysis and is essentially the only product mechanistically expected from the iodine oxidation of the precursory open-chain XLI; by the scheme shown above, it would be impossible to obtain the N-methyl-N-phenyl-N-3-[4-phenyl-1,2-dithiole] iminium salt,XLIV:



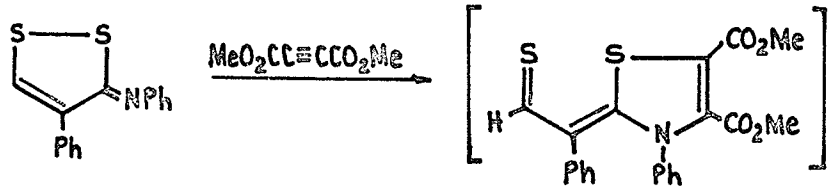
XLIV

On treatment of XLIII with dimethylacetylenedicarboxylate, a mono-adduct, XLV, was obtained from the resultant 1,3-dipolar addition reaction. XLV was identified by its characteristic nuclear magnetic

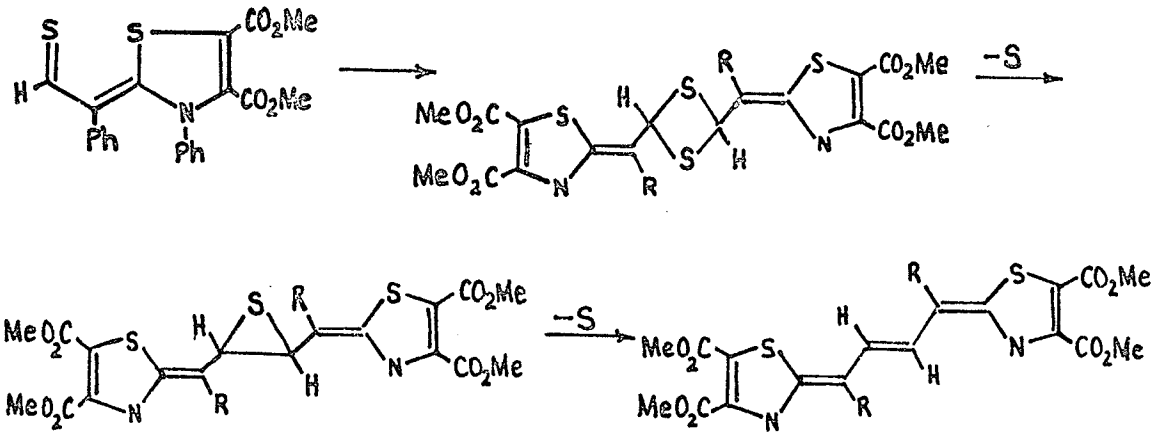


XLIII XLV XLVI

resonance spectrum which integrated correctly and was similar to spectra obtained for the adduct XLVI[57]. Furthermore, the mass spectrum of XLV indicated the correct molecular weight for the postulated structure. Had the compound in question been the 3-imino-1,2-dithiole claimed by Adelfang, the reaction with dimethylacetylenedicarboxylate would probably have yielded an unstable thial[81]:

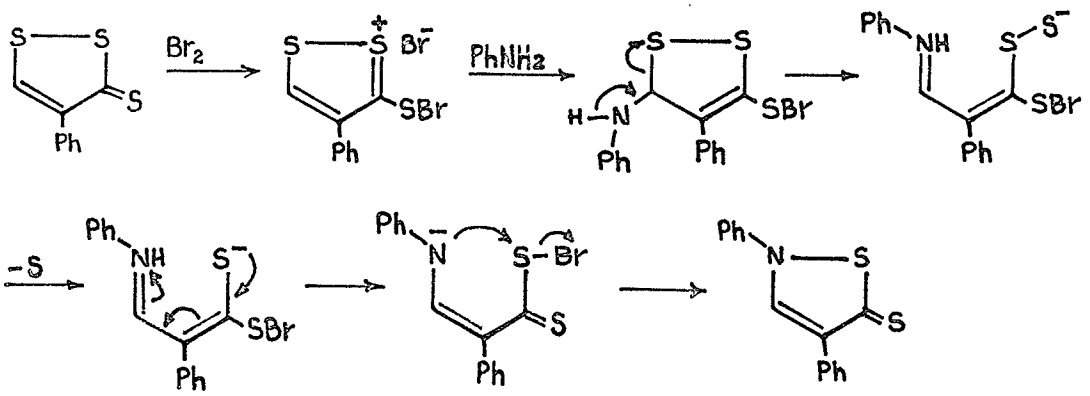


This intermediate could then dimerize and extrude sulfur[81]:



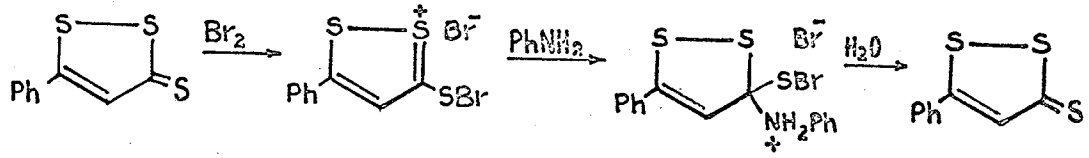
Similar results have been found for 2-thiophenylmethylene-1,3-dithioles[82].

When 5-phenyl-1,2-dithiole-3-thione was subjected to the Adelfang reaction sequence the only product obtained was the starting material, although the intermediate salts were isolated in good yield. This seems to suggest that an isolable product different from the starting material is formed only when attack by aniline can occur at the 5-position, as in the reaction with 4-phenyl-1,2-dithiole-3-thione. When the 5-position is blocked, as in 5-phenyl-1,2-dithiole-3-thione, the starting material is regenerated. Thus, in the reaction of 4-phenyl-1,2-dithiole-3-thione, a bromide salt is formed initially,

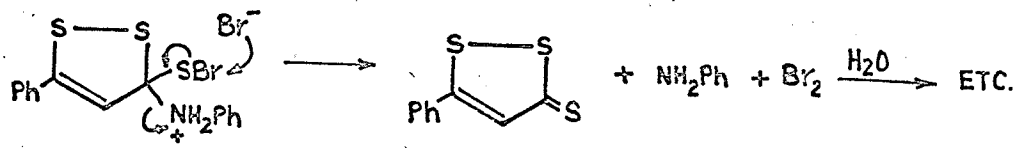


which undergoes nucleophilic attack by aniline at the open 5-position, followed by ring-opening and loss of sulfur. Nucleophilic attack by nitrogen on the bromine-bearing sulfur atom results in ring closure with the elimination of bromide ion. It is well known[48] that the reaction of 3-methylthio-4-phenyl-1,2-dithiolium salts with aniline gave acyclic products via nucleophilic attack at the free 5-position and it seems unlikely that attack on 3-methylbromo-4-phenyl-1,2-dithiolium bromide should follow a different course. In the reaction of 5-phenyl-1,2-dithiole-3-thione, although the bromide salt is

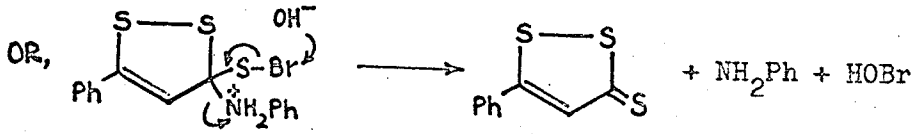
initially formed, the subsequent attack by aniline is likely to occur only at the 3-position, owing to steric hindrance to attack at the 5-position by the bulky phenyl group, and aniline is eliminated on hydrolysis to regenerate the thione:



The exact mechanism of this last part is somewhat speculative, depending on the function of the added water, which may react in a stepwise or a concerted manner:

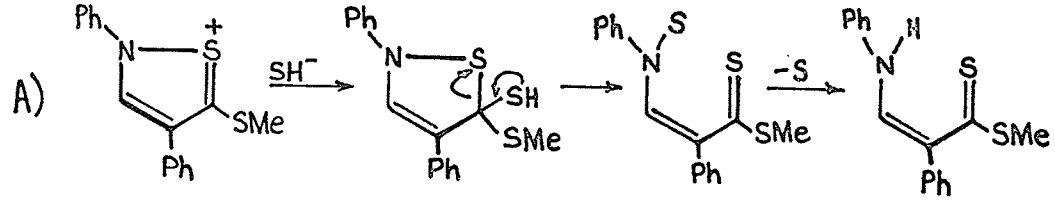


OR,

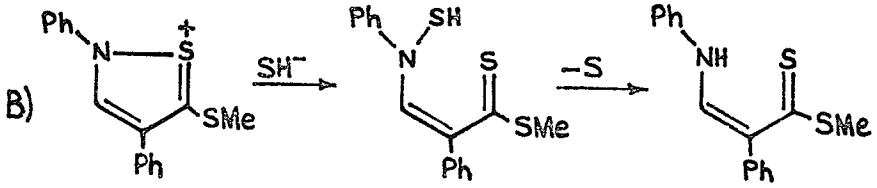


In an attempt to obtain 2,4-diphenyl-3-isothiazoline-5-thione (XLIII) in better yield from the precursor, 2,4-diphenyl-5-methylthioisothiazolium perchlorate, XLII, the latter was treated with sulfhydride ion, SH^-, to accomplish the demethylation. However, the only product obtained was the open-chain 1-anilino-3-methylthio-prop-1-ene-3-thione. This product can be accounted for mechanistically in several ways. In scheme A, attack by sulfhydride ion occurs at the 5-position, followed

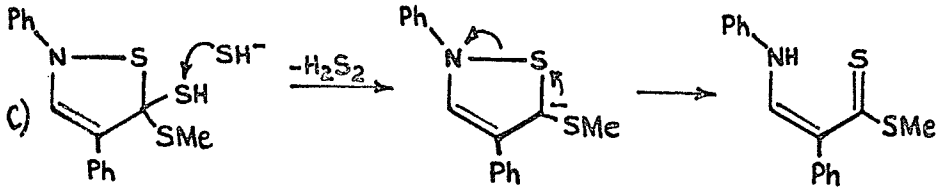
by ring-opening and the elimination of sulfur:



In scheme B, the attack by sulfhydride ion occurs at the ring nitrogen atom followed once again by ring-opening and sulfur elimination:



Finally, in scheme C, after the initial attack of sulfhydride ion at the 5-position, a second ion can attack, followed by the elimination of hydrogen disulfide:



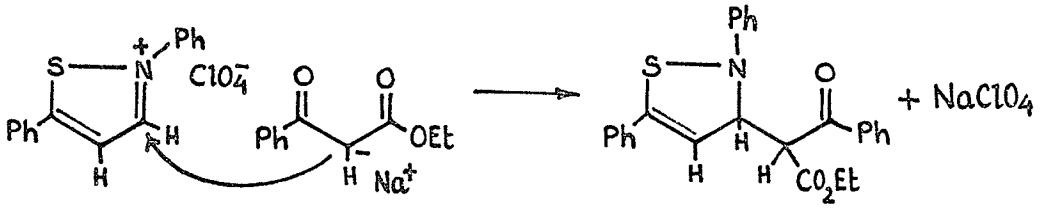
A similar mechanism has been proposed[83] in the reaction of a 1,3-dithiolium salt with hydrosulfide ion. Sulfhydride attack at the 3-position is possibly less likely due to steric interference from the phenyl groups in the 2- and 4-positions. Scheme A or scheme C are probably the most likely in accordance with normal nucleophilic attack on isothiazolium salts.

II. DIRECT APPROACHES TO 3-THIOACYLMETHYLENE ISOTHIAZOLES:

In view of the complexity of reactions of isothiazolium salts with sulfur, it appears that considerably more investigation would be required to obtain the isothiazoline thiones as synthetic precursors, and the direct synthesis of 3-thioacylmethylene isothiazoles, XIX, by the nucleophilic addition of the appropriate side chain onto an isothiazole or isoxazole nucleus was attempted by a number of routes. However, as will be seen below, it would seem that the usual result of such reactions is ring-opening with subsequent decomposition.

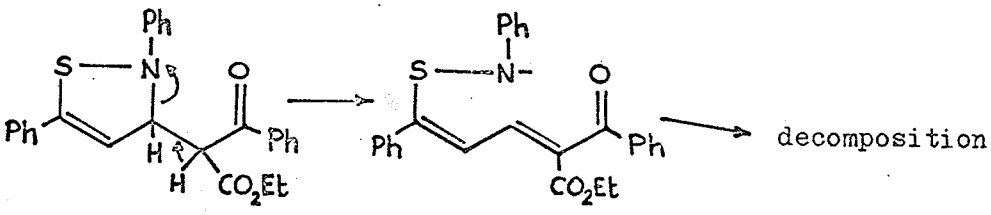
a) Nucleophilic Additions to the Isothiazole Nucleus:

It was thought that the sodium salt of ethyl benzoylacetate would undergo nucleophilic addition to 2,5-diphenylisothiazolium perchlorate:

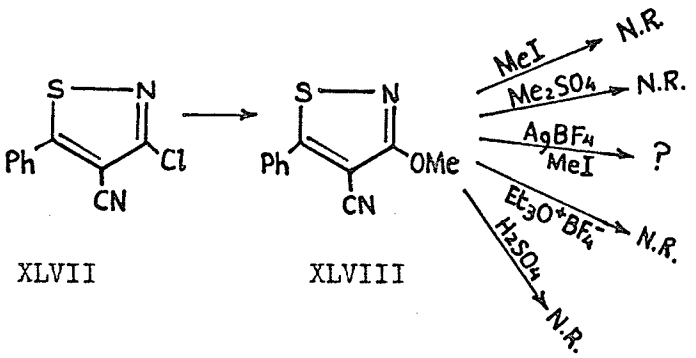


Oxidation and sulfurization would then yield the desired 3-thioacylmethylene isothiazole. However, the infrared and nuclear magnetic resonance spectra of the addition product seem to indicate that ring-opening occurred. Possibly this is due to the lability of the acidic

proton:



It was thought that the 3-chloro-4-cyano-5-phenylisothiazole synthesized by Nakagawa et al[16] would be useful as a precursor to an isothiazolium salt which could be subjected to nucleophilic addition. The halogen atom would be easily substituted by nucleophilic reagents as in the halopyridines. This reactivity should be still more enhanced by quaternization of the nitrogen atom. However, it was found that the ring nitrogen of XLVII was extremely resistant to quaternization by any of the usual methods. XLVII was converted to 3-methoxy-4-cyano-5-phenylisothiazole with sodium methoxide. Since this compound (XLVIII) was resistant to methyl iodide and dimethylsulfate, a mixture of methyl iodide and silver tetrafluoroborate was tried, according to the procedure of Acheson and Harrison[84] who had used this method to alkylate the resistant thiophene nucleus. A very small yield of ether-insoluble material was isolated, but the quantity was insufficient for characterization, and the poor yield of the reaction in any case rendered it synthetically valueless. No product was obtained with triethyloxonium tetrafluoroborate, nor would the isothiazole protonate in dilute sulfuric acid. This resistance to alkylation and protonation may be due to the nitrile group in the 3-position, which would have an electron-withdrawing deactivating influence on the ring.

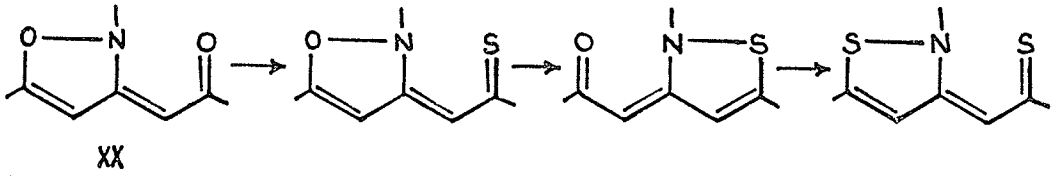


XLVII XLVIII

When XLVII was subjected to brief warming with dimethylsulfate, an ether-insoluble product could be isolated, but again the yield was extremely poor and could not be improved by varying the reaction temperature or time.

b) Nucleophilic Addition to the Isoxazole Nucleus:

A number of attempts were made to synthesize 3-acylmethylene isoxazoles, XX, which could conceivably be sulfurized with phosphorus pentasulfide to give the desired 3-thioacylmethylene isothiazole:

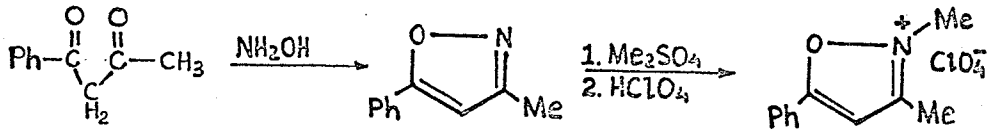


XX

The sulfurization, if successful, would provide proof of valence tautomerism.

Benzoyl acetone, XLIX, treated with hydroxylamine hydrochloride in ethanol yielded 3-methyl-5-phenylisoxazole[85], L, which was easily methylated to give 2,3-dimethyl-5-phenylisoxazolium methyl sulfate

or perchlorate. The perchlorate was treated with a number of nucleo-

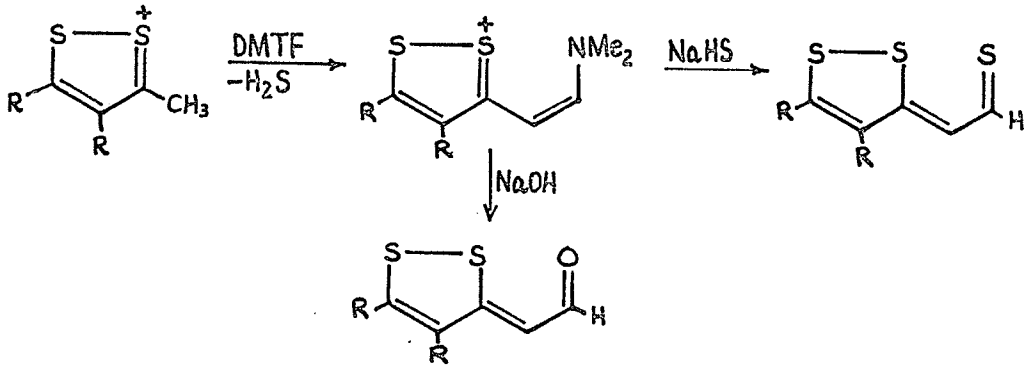


XLIX L

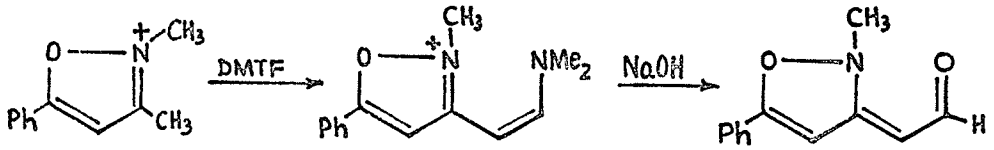
philes in the hope of adding a side-chain in the 3-position. With benzoyl chloride in the presence of triethylamine a mixture of many products was obtained, suggesting ring-opening, while with benzoyl chloride alone, no product was detected. Similarly, when treated with ethyl benzoate in the presence of sodium methoxide, many fractions were observed on separating the reaction mixture by thin-layer chromatography; ethyl benzoate in the presence of sodium methoxide/benzoyl chloride again gave a complicated mixture of products, all in low yield. Ethyl benzoate in the presence of triethylamine gave a yellow solid containing no phenyl groups, as evidenced by its nuclear magnetic spectrum. 2,3-dimethyl-5-phenylisoxazolium methyl sulfate was also treated with methyl dithiobenzoate, prepared according to Bost and Mattox[86] and purified by the method of Bost and Sheally[87]. However, these reactions also yielded at least five fractions, all in low yield. It is believed that the complicated product mixtures resulting from the above reactions is evidence for ring-opening of the isoxazole nucleus followed by decomposition of the molecule.

Dingwall, McKenzie and Reid[66] have reported the reaction of 1,2-dithiolium salts with dimethylthioformamide in acetic anhydride to give

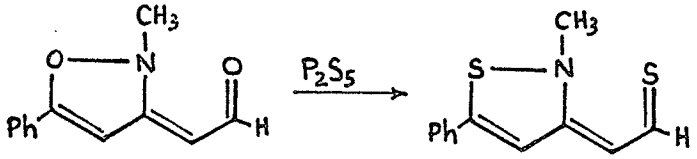
3-(2-dimethylaminovinyl)-1,2-dithiolium (Vilsmeier) salts, which react with sodium hydrogen sulfide to give thiothiophthenes and with sodium hydroxide to give 3-acylmethylene-1,2-dithioles:



It was thought that an analogous reaction might be possible starting from an isoxazolium salt to yield a 3-acylmethylene isoxazole:



which could then be sulfurized to give the 3-thioacylmethylene isothiazole:

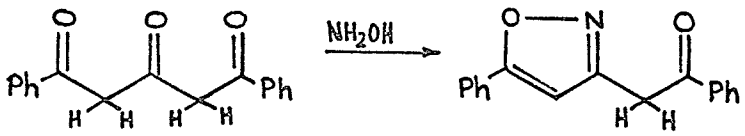


Accordingly, dimethylthioformamide was synthesized by the method of Pettit and Garson[88] and allowed to react with 2,3-dimethyl-5-phenyl-isoxazolium methyl sulfate under the conditions specified by Dingwall, Reid, and McKenzie. However, the products were always brown oils which could not be characterized by their infrared spectra. Yields were

very poor. The reaction was repeated using dimethylformamide, with similar results. The reactions were repeated a number of times and gave rather variable results. Several times only the unreacted starting material was isolated, suggesting that perhaps the brown oily 'product' was indeed an impurity in one of the reactants, and that the reaction does not proceed to any appreciable extent on substituting an isoxazolium salt for a 1,2-dithiolium salt.

c) Direct Synthesis of a 3-acylmethylene isoxazole:

Since β-diketones are known to cyclize to isoxazoles on treatment with hydroxylamine, it was thought that dibenzoylacetone might undergo partial cyclization:



However, no reaction occurred and only unreacted hydroxylamine hydrochloride was isolated from the reaction mixture. The triketone is possibly hydrolyzed under the necessary reaction conditions.

CONCLUSIONS:

The nucleophilic reaction of isothiazolium salts with sulfur in refluxing pyridine has been studied to determine the products and pathways involved, and to evaluate the usefulness of such reactions as synthetic approaches to 4-isothiazoline-3-thiones. It was found that the major products of these reactions depended on the nature of the substituent on the nitrogen atom of the isothiazole ring. Aryl substituents led mainly to 3-imino-1,2-dithioles and 1,2-dithiole-3-thiones, while alkyl substituents led to 4-isothiazoline-3-thiones, isothiazoles, and 1,2-dithiole-3-thiones. However, the yields of 4-isothiazoline-3-thiones were quite low, and without an appreciable increase in the efficiency of the reactions, their synthetic usefulness would seem to be marginal. A number of mechanistic pathways have been suggested, based on the experimental results, but further investigations would be advisable in order to decide unequivocally and verify the actual mechanisms. Useful follow-up research might involve investigation of isothiazolium salts with substituents other than phenyl or methyl on the ring nitrogen. For example, salts which were N-benzyl substituted, N-p-anilino substituted, N-p-nitrophenyl substituted, and so on, would clarify electronic effects in the mechanism. However, synthetic approaches to these more complex isothiazolium salts may be difficult and of low yield.

Several developments incidental to the above investigation have also proven to be of interest. Attempts to synthesize a previously-unavailable

isothiazolium salt led to a new route of access to 3-isothiazoline-5-thiones which should prove conductive to further studies of oxidation and 1,3-dipolar addition reactions. It was also found that a synthesis of 5-unsubstituted-3-imino-1,2-dithioles reported in the literature in fact gave isomeric 3-isothiazoline-5-thiones, thus affording another synthetic route to these otherwise rather unavailable compounds. Further investigations as to the generality of these reactions would be useful as would the ensuing oxidation and 1,3-dipolar addition studies on the resultant new compounds.

During the course of studies reported in this thesis, several new compounds were synthesized, namely three new isothiazolium salts and a previously-unreported 3-isothiazoline-5-thione.

Despite various attempts to synthesize 3-thioacylmethylene isothiazoles or 3-acylmethylene isoxazoles by the addition of a side chain to the appropriate isothiazole or isoxazole nucleus, these compounds were not obtained, due, in most cases, to apparent ring-opening reactions and subsequent molecular decomposition. The addition of an acylidene or thioacylidene side chain to an isothiazole or isoxazole seems unpromising, although the method may provide a convenient route to thiothiophthene aza-analogues, providing suitable precursors and reaction conditions can be found.

EXPERIMENTAL

All melting points were determined on a Fischer-Johns apparatus and are uncorrected. Column chromatography was done using aluminum oxide, 504-C, acidic, Brockmann #1, obtained from Mondray Limited, 4180 de Courtrai, Montreal, P. Q., Canada. Thin-layer chromatography was performed on silica gel containing 5% calcium sulfate, DSF-5, made by Camag and distributed by Mondray Limited.

Infrared spectra were recorded on a Perkin-Elmer Model 137 Infrared Spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-56/60A spectrometer, in deuterated chloroform or carbon tetrachloride, using tetramethylsilane as an internal standard. Mass spectra were performed by Mr. M. Arneson on a Finnigan 1015 mass spectrometer. Elemental analyses were done by the Alfred Bernhardt Microanalytical Laboratory, 14-16 Fritz-Pregl-Strasse, 5251 Elbach uber Engelskirchen, West Germany.

I. STARTING MATERIALS:

5-phenyl-1,2-dithiole-3-one:

The method of Klingsberg[32] was used, with recrystallization from ethanol. The yield obtained averaged 60%. M.P. 113°-115°C.

5-phenyl-1,2-dithiole-3-thione:

The method of Klingsberg[32] was used, with recrystallization from carbon tetrachloride. Yield: 85% before recrystallization. M.P. 125°C.

4-phenyl-1,2-dithiole-3-thione:

The method of Fields[89] was modified by the use of quinoline as the basic catalyst, rather than di-o-tolylguanidine. Yield: 60% M.P. 122°C.

1,2-diphenylpropan-2-ol:

The method of Koelsch and White[90] was used. Yield: 85% M.P. 49°-51°C.

1,2-diphenylpropene:

1,2-diphenylpropan-2-ol was dissolved in toluene containing a few drops of concentrated sulfuric acid and refluxed overnight in a Dean and Stark apparatus. Concentration of the solution on a rotary evaporator, followed by chilling to 0°C. yielded 85% of the product, M.P. 81°C.

4,5-diphenyl-1,2-dithiole-3-thione:

The method of Schmitt and Suquet[70] was modified by heating the reaction mixture on an oil bath at 185°C. overnight. The product, in 70% yield, was recrystallized from ethyl acetate and melted at 162°C.

5-phenyl-1,2-dithiolium perchlorate:

This salt was prepared from 5-phenyl-1,2-dithiole-3-thione by oxidation in glacial acetic acid solution with 30% hydrogen peroxide, followed by dilution with ethanol and recrystallization from glacial acetic acid containing one equivalent of perchloric acid[32]. M.P. 169°C.

4-phenyl-1,2-dithiolium perchlorate:

This was prepared from 4-phenyl-1,2-dithiole-3-thione using the same method employed for the 5-phenyl isomer. M.P. 210°C. (decomp) Yield:50%

4,5-diphenyl-1,2-dithiolium perchlorate:

This salt was prepared from 4,5-diphenyl-1,2-dithiole-3-thione by the above method to yield yellow needles, M.P. 230°C., in 60% yield.

5-phenyl-3-methylthio-1,2-dithiolium iodide:

Three grams of 5-phenyl-1,2-dithiole-3-thione and 3 grams methyl iodide were dissolved in ethyl acetate. On refluxing, red crystals separated out. The reaction mixture was cooled and the crystals filtered off to give 3.1 grams of product. The melting point was indeterminate due to apparent extrusion of sulfur on heating. Yield: 62%.

5-phenyl-3-phenylimino-1,2-dithiole:

The method of Paulmier, Mollier, and Lozac'h[48] was used to obtain the iminodithiole was bright yellow needles. Yield: 58%. M.P. 123°C.

3-methyl-5-phenylisoxazole:

Attempts to synthesize this molecule by the method of Hantzch[85] were unsuccessful; the method was therefore modified as follows. To a mixture of 16.2 grams benzoylacetone and 10 grams hydroxylamine hydrochloride in 160 ml 10% aqueous sodium hydroxide was added sufficient ethanole to obtain a clear pale-yellow solution, which was refluxed for 15 minutes. After five minutes, 5 grams of sodium hydroxide were added. After refluxing, the solution was diluted with three times its volume of water and the mixture was made neutral to litmus with HCl. The resultant solid was filtered off, washed with water, and dried. Recrystallization from ethanol gave white flakes. Yield: 72%. M.P. 68°C. Literature M.P.[97] 68°C. N.M.R. data: Singlet 7.8τ , singlet 3.8τ , multiplet centered at 2.5τ . Ratio: 3:1:5.

2,3-dimethyl-5-phenylisoxazolium methyl sulfate:

Five grams of 3-methyl-5-phenylisoxazole were just covered with dimethylsulfate in a 100ml flask fitted with a drying tube. The mixture was warmed on a steam bath for one hour. Pouring the mixture into an ether/ethanol mixture with stirring gave the methyl sulfate as a white solid.

2,3-dimethyl-5-phenylisoxazolium perchlorate:

2,3-dimethyl-5-phenylisoxazolium methyl sulfate was dissolved in the minimum amount of glacial acetic acid and one equivalent of perchloric acid was added. The perchlorate crystallized on cooling as a white deliquescent solid with an apparent M.P. of 170°C., although softening began at 160°C. Yield: 95% based on the methyl sulfate.

Methyl dithiobenzoate:

The dithioester was prepared by the method of Bost and Shealy[87] from phenylmagnesium bromide and carbon disulfide. The pure ester was not isolated, but was stored as an ether solution.

Dibenzoylacetone:

The method of Light and Hauser[91] was used to obtain dibenzoylacetone (1,5-diphenyl-1,3,5-pentanetrione), M.P. 105°C. as greenish-yellow crystals.

Dimethylthioformamide:

The method of Reister[92] was used, with the elimination of MgO. A 1:1 solution of dimethylformamide/benzene was refluxed for three hours with two equivalents of phosphorus pentasulfide. The reaction mixture was filtered and the filtrate distilled under house vacuum using a fractionating column. The fraction coming off between 140° and 160°C. was collected. Yield: 67%

Benzylidene malononitrile:

By the general method of Schonne, Braye, and Bruylants[93] an equimolar mixture of malononitrile and benzaldehyde in ethanol yielded benzylidene malononitrile as the condensation product on adding piperidine as catalyst (5ml piperidene to 0.1 mole reactant). Cream coloured needles were obtained on recrystallization from 1:1 water/methanol. Yield: 86% M.P. 86°C.

3-chloro-4-cyano-5-phenylisothiazole:

The method of Nakagawa et al[16] was used to obtain a yellow product which was recrystallized from petroleum ether to give yellow needles, M.P. 82°C. in 72% yield.

3-methoxy-4-cyano-5-phenylisothiazole:

Nakagawa et al[16] suggest the feasibility of this conversion but give no experimental details. Two grams 3-chloro-4-cyano-5-phenylisothiazole were refluxed with an excess of sodium methoxide in dry methanol for an hour. On cooling and adding water, a cream-coloured solid was obtained. No further purification was attempted. Yield: 55%, M.P. 80°C. N.M.R. data: Singlet τ 6.0, multiplet centered at τ 2.5. Ratio: 3:5.

3-methylthio-4-phenyl-1,2-dithiolium perchlorate:

4-phenyl-1,2-dithiole-3-thione was warmed with an excess of dimethyl sulfate for one hour. Dilution with ether and the addition of one equivalent of perchloric acid afforded the dithiolium salt, M.P. 216°C in 80% yield.

1-anilino-2-phenyl-3-methylthioprop-1-ene-3-thione:

One equivalent of 3-thiomethyl-4-phenyl-1,2-dithiolium perchlorate was warmed with two equivalents of aniline in ethanol until homogeneous. Water was added, followed by ether extraction. The ether solution was dried over sodium sulfate and evaporated to yield the product which was used without further purification.

2,5-diphenylisothiazolium perchlorate:

The method of McKinnon and Robak[31] was used to obtain the salt as yellow needles of M.P. 199°C. in 52% yield.

2,4,5-triphenylisothiazolium perchlorate:

The method of McKinnon and Robak[31] was used to obtain the salt as yellow needles of M.P. 213°C. in 45% yield.

2,3,5-triphenylisothiazolium perchlorate:

The method of McKinnon and Robak[31] was used to obtain the salt as yellow needles of M.P. 256°C. in 48% yield.

5-phenylisothiazole:

The method of Olofson, Landesberg, Berry, Leaver, Robertson, and McKinnon[11] was used to obtain the isothiazole as white crystals with a characteristic spicy odor. M.P. 46°C. Yield: 42%.

2-methyl-5-phenylisothiazolium perchlorate:

5-phenylisothiazole was alkylated by warming with an excess of dimethyl sulfate for one hour, followed by dilution with ether and the addition of one equivalent of perchloric acid to give the salt as yellow flakes, M.P. 140°C. in 86% yield.

2-methyl-4,5-diphenylisothiazolium perchlorate:

4,5-diphenylisothiazole was prepared by the method of reference 11, from 4,5-diphenyl-1,2-dithiole-3-thione and ammonia. The salt was

obtained as described in the previous synthesis and recrystallized from glacial acetic acid containing several drops of perchloric acid. The light yellow needles melted at 99°C. The salt was obtained in 80% yield from the isothiazole, and has not been previously reported. For $C_{16}H_{14}NSClO_4$: Required C: 54.70%, H: 3.99%, N: 3.99%, O: 18.23%, S: 9.12%, Cl: 9.97%. Found C: 54.62%, H: 3.86%, N: 3.98%, O: 18.59%, S: 9.00%, Cl: 9.95%.

4-phenylisothiazole:

The method of Leaver, McKinnon, and Robertson[94] was used with a slight modification. The ether solution obtained on pouring the reaction mixture into ether was washed five times with water. However, on evaporation, some ammonium perchlorate was still present, so the semi-solid oil was dissolved in carbon tetrachloride and filtered. Evaporation of the carbon tetrachloride afforded a brown oil which had the isothiazole odor, but would not crystallize. It was used without further purification since thin-layer chromatography indicated no substantial impurities.

2-methyl-4-phenylisothiazolium perchlorate:

The oil obtained in the previous synthesis was alkylated with dimethylsulfate in the usual way, followed by treatment with perchloric acid. The resultant light-tan solid was filtered off and recrystallized from glacial acetic acid containing a few drops of perchloric acid. The salt was obtained as off-white needles, M.P. 102°C., Yield: 85%. It has not been previously reported in the literature. Elemental

analysis gave the following: For $C_{10}H_{10}NSClO_4$, required C: 43.45%, H: 3.64%, N: 5.09%, S: 11.64%, Cl: 12.91%, O: 23.27%; found C: 42.70%, H: 3.99%, N: 5.25%, S: 11.51%, Cl: 12.70%, O: 23.85%.

3-isothiazolone (a):

The method of Leonard and Crow[95] was used, involving the cyclization of cis-(3-t-butylthio)acrylamide with chlorine to 3-isothiazolone. The product was a yellow oil which would not crystallize.

3-isothiazolone (b):

The method of Crow and Leonard[52] was used, substituting ethyl propiolate for methyl propiolate. Although the procedure was otherwise identical to that of the authors, no crystalline cis N-methyl-3-thiocyanoacrylamide could be isolated. The oil was used in the cyclization reaction, and once again a yellow, non-crystalline oil was obtained which appeared to oxidize on standing.

II. REACTIONS OF ISOTHIAZOLIUM SALTS WITH S IN PYRIDINE:

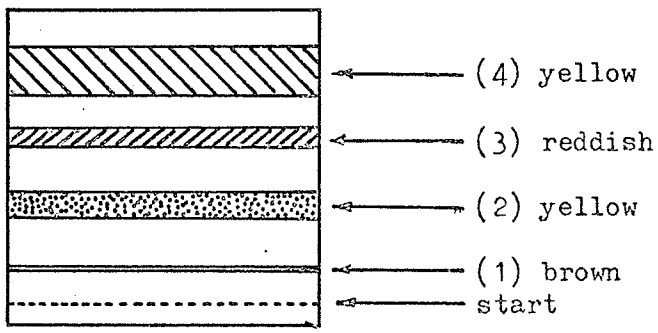
General Method:

1.0 gram of the isothiazolium salt was added in small portions to a refluxing saturated solution of sulfur in 20ml pyridine. The entire addition was done over approximately fifteen minutes. The mixture was then refluxed for thirty minutes, during which time it generally darkened to a red-brown colour. After a short cooling period, 20ml of

water were added. The resultant mixture was then transferred to a separatory funnel and extracted with ether. Any solid lumps of sulfur were pulverized under ether and the resultant ether solution added to the combined extracts. After drying over sodium sulfate, the extracts were evaporated down under reduced pressure at temperatures not exceeding 40°C. The pasty mass remaining was further evaporated down under high vacuum to remove traces of pyridine, and then dissolved in the minimum volume of benzene and spotted onto thin-layer chromatography plates. Elutants varied with the salt under study. The bands were isolated and extracted with ether; evaporation of the ether left the products.

a) 2,5-diphenylisothiazolium perchlorate:

The thin-layer chromatography plates were eluted first with 1:1 benzene/petroleum ether, followed, after drying, by chloroform. The second elution was arrested before any mixing of the bands could occurr. The appearance of the plates was then:



Bands (1) and (3) yielded only traces of products. Band (2) yielded 130mg of yellow crystals, M.P. 122°C., Yield: 17%, of the 5-phenyl-

3-phenylimino-1,2-dithiole, as identified by its melting point and infrared spectrum. Band (4) yielded 6.3mg of a red-brown solid, identified as 5-phenyl-1,2-dithiole-3-thione by its melting point of 125°C. and its characteristic infrared spectrum. Yield: 2%.

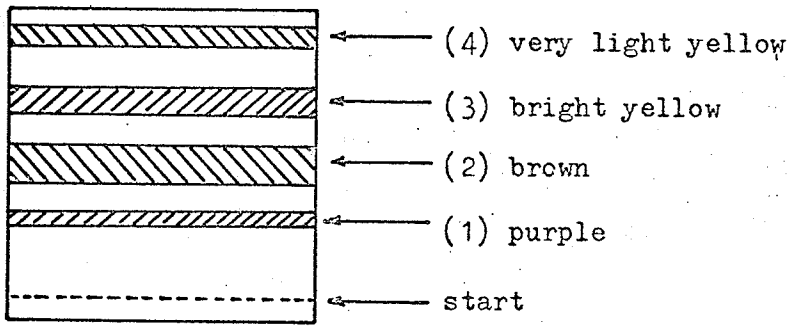
Structural Proof for 5-phenyl-3-phenylimino-1,2-dithiole:

a] 3-methylthio-5-phenyl-1,2-dithiolium iodide on treatment with aniline in ethanol yielded a yellow solid of M.P. 123°C identified as 5-phenyl-3-phenylimino-1,2-dithiole. On treatment with methyl iodide, N-methyl-N-phenyl-N-3-[5-phenyl-1,2-dithiole]iminium iodide was obtained, M.P. 162°-163°C[96] with decomposition.

b] 3-methylthio-5-phenyl-1,2-dithiolium iodide, on treatment with N-methylaniline yielded a yellow solid identical in melting point and infrared spectrum with N-methyl-N-phenyl-N-3-[5-phenyl-1,2-dithiole] iminium iodide prepared by the previous method.

b) 2-methyl-5-phenylisothiazolium perchlorate:

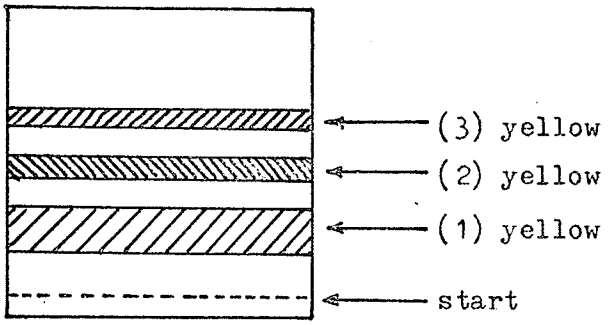
Elution of the thin-layer chromatography plates was as for the diphenyl analogue. The appearance of the resultant plates was:



Band (4) was found to be unreacted sulfur. Band (3) yielded 15mg of golden yellow flakes, identified by melting point and infrared spectrum as 5-phenyl-1,2-dithiole-3-thione, yield: 2%. Band (2) yielded 150mg of light orange crystals, identified by melting point, infrared spectrum and odor as 5-phenylisothiazole, yield: 26%. Band (1) yielded 7mg of light brown crystals, M.P. 153°C with a parent peak in the mass spectrum at 207amu, correct for 2-methyl-5-phenyl-4-isothiazoline-3-thione. Yield: 1%.

c) 2,4,5-triphenylisothiazolium perchlorate:

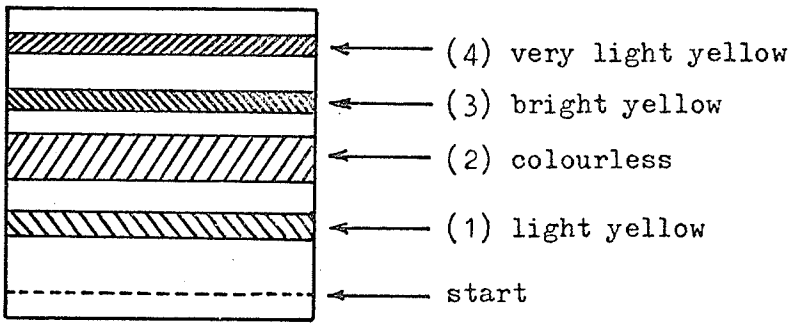
Elution was by 1:1 benzene/petroleum ether. The resultant plates appeared as:



Bands (2) and (3) faded quickly and yielded only a very small trace of any product(s). Band (1) yielded 200mg of yellow crystals, M.P. 173°C, exactly the melting point reported by Paulmier, Mollier, and Lozac'h[48] for 4,5-diphenyl-3-phenylimino-1,2-dithiole. The infrared spectrum of the compound was reminiscent of the spectra of authentic 3-imino-1,2-dithioles. Yield: 24%.

2-methyl-4,5-diphenylisothiazolium perchlorate:

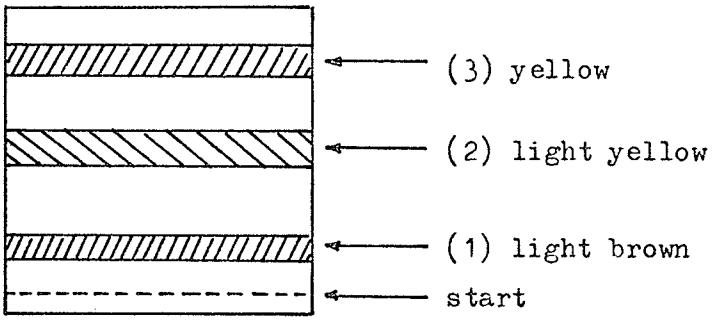
Elution of the thin-layer chromatography plates was by benzene alone. The resultant plates appeared as



Band (4) was identified as unreacted sulfur. Band (3) yielded a trace of reddish material with an infrared spectrum strongly suggesting the 4,5-diphenyl-1,2-dithiole-3-thione. Band (2) yielded 190mg of colourless crystals identified by melting point and infrared spectrum as the demethylated 4,5-diphenylisothiazole, yield: 29%. Band (1) yielded 50mg of a light yellow solid, M.P. 133°C. The parent peak of the mass spectrum indicated a molecular weight of 282, correct for 2-methyl-4,5-diphenyl-4-isothiazoline-3-thione. Furthermore, this compound was identical with the isothiazoline thione prepared by the method of LeCoustumer and Mollier[41,46]. Yield: 6%.

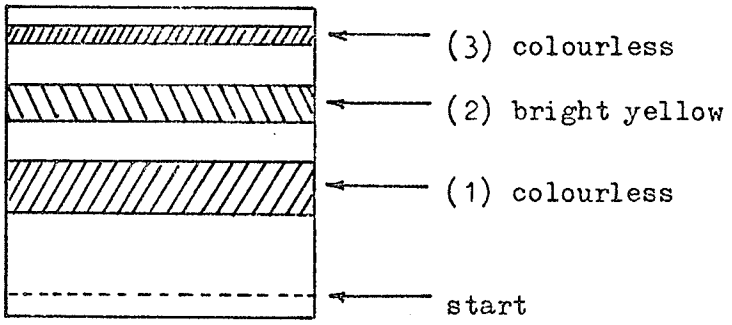
2,3,5-triphenylisothiazolium perchlorate:

Elution with benzene yielded plates appearing as illustrated. Bands (1) and (2) yielded an approximated total of 1 to 2mg of products, too minute a quantity to characterize. Band (3) was found to be unreacted sulfur.



2-methyl-4-phenylisothiazolium perchlorate:

Elution with benzene gave plates appearing as



There were also several minor bands which yielded a total of only a few milligrams of products. Band (3) was found to be unreacted sulfur. Band (2) yielded 40mg of 4-phenyl-1,2-dithiole-3-thione, identified by its melting point and infrared spectrum, yield: 5%. Band (1) yielded 210mg of colourless crystals, identified, again by melting point and infrared spectrum, as 4-phenylisothiazole, M.P. 33°C. Yield: 36%.

Reaction of 5-phenyl-3-phenylimino-1,2-dithiole with Sulfur:

The iminodithiole was treated as were the isothiazolium salts in the above reactions, but the only 'product' isolated was the starting material, even when refluxing was extended to several hours.

II. ATTEMPTED DIRECT SYNTHESES:

Attempted cyclization of Dibenzoylacetone:

2.66g dibenzoylacetone[91] and 10g hydroxylamine hydrochloride were placed in a 250ml flask with 50ml water. The mixture was warmed and ethanol was added until complete solution was achieved. Seven grams of sodium hydroxide were added while refluxing, on which the mixture turned yellowish. After refluxing for an hour the mixture was poured into 300ml water and neutralized with HCl. A precipitate formed which was identified by its infrared spectrum to be unreacted hyroxylamine hydrochloride. The experiment was repeated in pure ethanol in an attempt to suppress possible hydrolysis of the ketone, but again, no product could be isolated.

Reaction of 2,3-dimethyl-5-phenylisoxazolium perchlorate

a] with Benzoyl chloride:

To a mixture of 1.7g of the isoxazolium salt and 15ml chloroform was added 1.5g benzoyl chloride. 1ml triethylamine was added and the mixture was refluxed for two hours. On the addition of ether the unreacted isoxazolium salt precipitated out. The reaction was repeated using dry tetrahydrofuran as solvent, but the unreacted starting material was again obtained. The experiment was repeated with refluxing in chloroform for 48 hours. The resulting dark-brown mixture was extracted with water and then ether. The ether solution was dried over sodium sulfate, concentrated, and chromatographed on an acidic alumina column using benzene as elutant. A fast-moving yellow band and a slower-moving

brown band were noted. The brown band was shown by thin-layer chromatography to consist of at least three components, none of which could be obtained crystalline, and the yellow band yielded a polymeric (?) amorphous solid which could not be recrystallized from any solvent tried. The reaction was repeated using sodium methoxide as the base. 1.36g of the salt and an equivalent amount of sodium methoxide were refluxed for 10 minutes in 20ml chloroform. Then 0.70g benzoyl chloride was added. Refluxing was continued for 24 hours. The reaction mixture was then extracted with ether and separated by T.L.C. using ether as the elutant. Many bands were observed, all yielding minute amounts of non-crystallizing oils.

b] with Ethyl benzoate:

1.7g of the salt, 20ml ethyl benzoate, and 25ml ethanol were refluxed for two hours. The resultant dark-brown solution was extracted with ether and yielded a dark-brown oil with a pronounced odor of ethyl benzoate. An attempt to remove the ester by distillation at reduced pressure (5mm Hg) resulted in polymerization to a black tarry material. The reaction was repeated with chromatography of the ether extract on an acidic alumina column using chloroform as the elutant. Three fractions were obtained. The first yielded unreacted ethyl benzoate, while the other two, identical by their nuclear magnetic resonance spectra, were found to contain no phenyl groups, indicating molecular decomposition. The reaction was repeated using sodium methoxide as the base. 1.17g of the salt, 0.32g sodium methoxide, and 0.64g ethyl benzoate were refluxed in 20ml methanol for 12 hours. The reaction mixture was poured into 100ml ether and the precipitate filtered off. The resulting

clear brown solution was evaporated down and chromatographed by T.L.C. using 1:1 ether/chloroform as elutant. Three bands were isolated but they yielded only very small amounts (approximately 10mg) of yellow oils which did not crystallize.

c] with Methyl dithiobenzoate:

To 0.57g of the salt in 20ml ether was added 0.21g triethylamine and an estimated equimolar amount of the thioester in ether solution. The mixture was refluxed for three hours, followed by ether extraction, washing with water, drying, concentration, and chromatography by T.L.C. using benzene as elutant. Four bands were observed and isolated. The top band proved to be unreacted methyl dithiobenzoate, while the other three yielded small amounts of yellow oils which would not crystallize. Repitition of the experiment with the exclusion of solvents (the ether solution of methyl dithiobenzoate was concentrated to give essentially pure ester) gave essentially similar results, except that one band yielded a substance tentatively identified by its infrared spectrum as methyl thiolbenzoate, PhCOSMe.

d] with Dimethylformamide:

2.71g (0.01 mole) of the salt, 3.9ml dimethylformamide (0.05 mole) and 30ml acetic anhydride were refluxed together for five minutes. The reaction mixture was then cooled and poured into 200ml ether, whereupon a brown oil separated out. On the addition of 30ml ethanol containing 1ml perchloric acid, a brown solid formed which was filtered off and dissolved in the minimum amount of acetonitrile at room temperature. On pouring this solution into ether and cooling, a yellow

solid formed, which was redissolved in 12ml dimethylformamide. 10 milliliters of 2N sodium hydroxide solution were added. The solution was extracted with ether after dilution with water, yielding a brown oil which would not crystallize. On treatment with perchloric acid in ethanol the oil yielded a brown solid with an infrared spectrum strongly resembling that of the original isoxazolium salt.

e] with Dimethylthioformamide:

2.71g of the salt, 4.2ml dimethylthioformamide and 30ml acetic anhydride were refluxed for 5 minutes and then poured into 200ml ether. On the addition of 30ml ethanol containing 1ml perchloric acid a solid separated out, which was washed with ether and recrystallized from acetonitrile. The 'product' was found to be unreacted starting material.

2,5-diphenylisothiazolium perchlorate with sodium ethylbenzoylacetate:

1.17mmoles of the salt were treated with a solution of 0.32g ethyl benzoylacetate and 0.04g sodium metal in 25ml ethanol under reflux for one hour. Evaporation of the solvent left an orange solid which gave cream-coloured crystals from ethanol/water. The infrared spectrum suggests a ring-opened product. Yield: 27%.

Attempted Methylation of 3-chloro-4-cyano-5-phenylisothiazole:

The isothiazole was added to enough dimethylsulfate to form a thin paste and heated briefly to boiling followed by immediate cooling in ice water. Ether and several drops of perchloric acid were added, followed by cooling in a dry ice/acetone bath. The resultant precipitate, light-yellow in colour, melted at 165°C but was formed in only 5% yield. Subsequent repetitions of the reaction under apparently iden-

tical conditions yielded no methylated product.

Attempted Methylation of 3-methoxy-4-cyano-5-phenylisothiazole:

a] 0.1g of the isothiazole was dissolved in 2ml methyl iodide and heated at 100°C for a half hour. The mixture was left at room temperature overnight. On the addition of 20ml ether, no precipitate formed. A drop of perchloric acid was added, but no product appeared.

b] To 0.14g of the isothiazole was added 1ml dimethylsulfate. The mixture was heated at 100°C for an hour. On cooling and adding ether, no precipitate or cloudiness was observed.

c] The above reaction was repeated at the refluxing temperature of dimethylsulfate for several minutes. A black tarry material resulted.

d] To 0.1g of the isothiazole dissolved in 5ml dichloroethane was added 0.2g silver tetrafluoroborate and 0.5g methyl iodide. The mixture was allowed to stand for 24 hours. The precipitated silver iodide was filtered off and washed with methylene chloride, then acetone. The filtrate was poured into cold ether, whereupon cloudiness and a very small yield of crystals (2%) resulted.

e] 0.5g of the isothiazole was dissolved in dry ether and 1g triethyloxonium tetrafluoroborate was added. The mixture was stirred at room temperature for two hours. Dilution with ether did not give any evidence for an alkylated product.

3-methoxy-4-cyano-5-phenylisothiazole and dilute sulfuric acid:

a] 2g of the isothiazole, 15ml water, and 10ml ethanol were mixed. 10 drops of concentrated sulfuric acid were added with stirring and

the mixture was refluxed for two hours. The unreacted starting material was obtained on cooling.

b] 2g of the isothiazole, 15ml ethanol, and 10 drops water were mixed. 10 drops of concentrated sulfuric acid were added, followed by refluxing for two hours. The unreacted starting material was deposited on cooling.

III. APPROACH TO 2,4-DIPHENYLISOTHIAZOLIUM PERCHLORATE:

2,4-diphenyl-3-methylthioisothiazolium perchlorate:

1-anilino-2-phenyl-3-methylthioprop-1-ene-3-thione was dissolved in the minimum amount of ethanol. Saturated iodine/ethanol was added dropwise until the solution just stayed cloudy. The addition of ether then afforded a yellow cloudy mixture which on the addition of perchloric acid deposited the product as a yellow solid in 34% yield. Recrystallization from glacial acetic acid containing several drops of perchloric acid gave yellow needles melting at 158°C. The product has not been mentioned previously in the literature. The analysis calculated for $C_{16}H_{15}NS_2ClO_4$ requires C: 50.00%, H: 3.81%, N: 3.65%, S: 16.62%; found: C: 50.10%, H: 3.76%, N: 3.72%, S: 16.57%.

Demethylation of 2,4-diphenyl-3-methylthioisothiazolium perchlorate:

0.5g of the salt, 1ml pyridine, and 20ml benzene were refluxed overnight. Water was then added, and the mixture was extracted with ether. The extract was dried and concentrated, traces of pyridine being removed under high vacuum. On the addition of ether to the remaining

oil, a yellow solid formed, which was dissolved in benzene and chromatographed by T.L.C. using benzene as the elutant. Three main bands were observed, but only the bottom band yielded any appreciable product. From it, approximately 25mg of a yellow solid were isolated, M.P. 165°C. The mass spectrum of this substance indicated a molecular weight of 269amu, correct for 2,4-diphenyl-3-isothiazoline-5-thione. The analysis calculated for $C_{15}H_{11}NS_2$ requires C: 66.91%, H: 4.09%, N: 5.20%, S: 23.80%; found C: 67.41%, H: 4.02%, N: 5.21%, S: 23.80%.

Attempted Oxidation of 2,4-diphenyl-3-isothiazoline-5-thione:

10mg of the thione and 5ml glacial acetic acid were warmed while adding 1ml 30% hydrogen peroxide dropwise. The mixture was then diluted with ether. On the addition of a drop of perchloric acid, an amorphous yellow solid was precipitated which could not be recrystallized.

2,4-diphenyl-3-isothiazoline-5-thione and SH^-:

To 0.50g of the thione in 3ml ethanol was added 20ml of ethanol saturated with sodium hydrosulfide. The mixture became reddish-brown and was warmed until homogeneous. The reaction mixture was then poured into water and extracted with ether, yielding a red, semi-crystalline oil, identified by its infrared spectrum as 1-anilino-2-phenyl-3-methylthioprop-1-ene-3-thione[48].

Alternate Synthesis of 2,4-diphenyl-3-isothiazoline-5-thione:

4-phenyl-1,2-dithiole-3-thione was treated by the method of Adelfang[80] with the object of obtaining 4-phenyl-3-phenylimino-1,2-dithiole. The

product was obtained as a yellow oil which crystallized on standing to give yellow crystals, M.P. 164°C. The infrared spectrum of the product indicated that it was identical to the previously-synthesized 2,4-diphenyl-3-isothiazoline-5-thione. In addition, the melting points and mass spectra were the same. The thione was obtained in about 50% yield.

Further Proof of 3-isothiazoline-5-thione Structure:

a] 0.2g of 2,4-diphenyl-3-isothiazoline-5-thione and an equivalent (0.1g) of dimethylacetylene dicarboxylate were warmed at 35°C overnight in 25ml benzene. Evaporation of the benzene left a reddish oil which was redissolved in benzene and chromatographed on a 1"x10" alumina column using benzene as elutant. One main band was obtained and isolated as a red oil. Residual benzene was removed under high vacuum leaving a non-crystalline glass, which was dissolved in carbon tetrachloride to obtain a nuclear magnetic resonance spectrum. The spectrum showed a 'doublet' centered at 6.2τ, and singlets at 2.9τ, 2.7τ, and 2.0τ. Integrations were correct for the monoadduct, XLV. Furthermore, the mass spectrum gave the correct molecular weight of 411amu.

b]Treatment of the thione with dimethylsulfate followed by dilution with ether and the addition of perchloric acid gave 2,4-diphenyl-3-methylthioisothiazolium perchlorate, identified by its melting point and infrared spectrum.

Adelfang Reaction on 5-phenyl-1,2-dithiole-3-thione:

Treatment of 0.1mole of thione with one equivalent of bromine in carbon tetrachloride according to the method of Adelfang[80] afforded a

yellow, ether-insoluble, amorphous solid, which was treated, after washing with ether and drying, with one equivalent of aniline. This reaction was vigorous and required external cooling. On dilution with ether, 17.5g of a yellow product were obtained. This aniline salt was hydrolyzed in 50ml warm water for two hours. Ether extraction and chromatography on an alumina column using carbon tetrachloride as elutant yielded only one fraction, identified by its infrared spectrum as the starting material, 5-phenyl-1,2-dithiole-3-thione.

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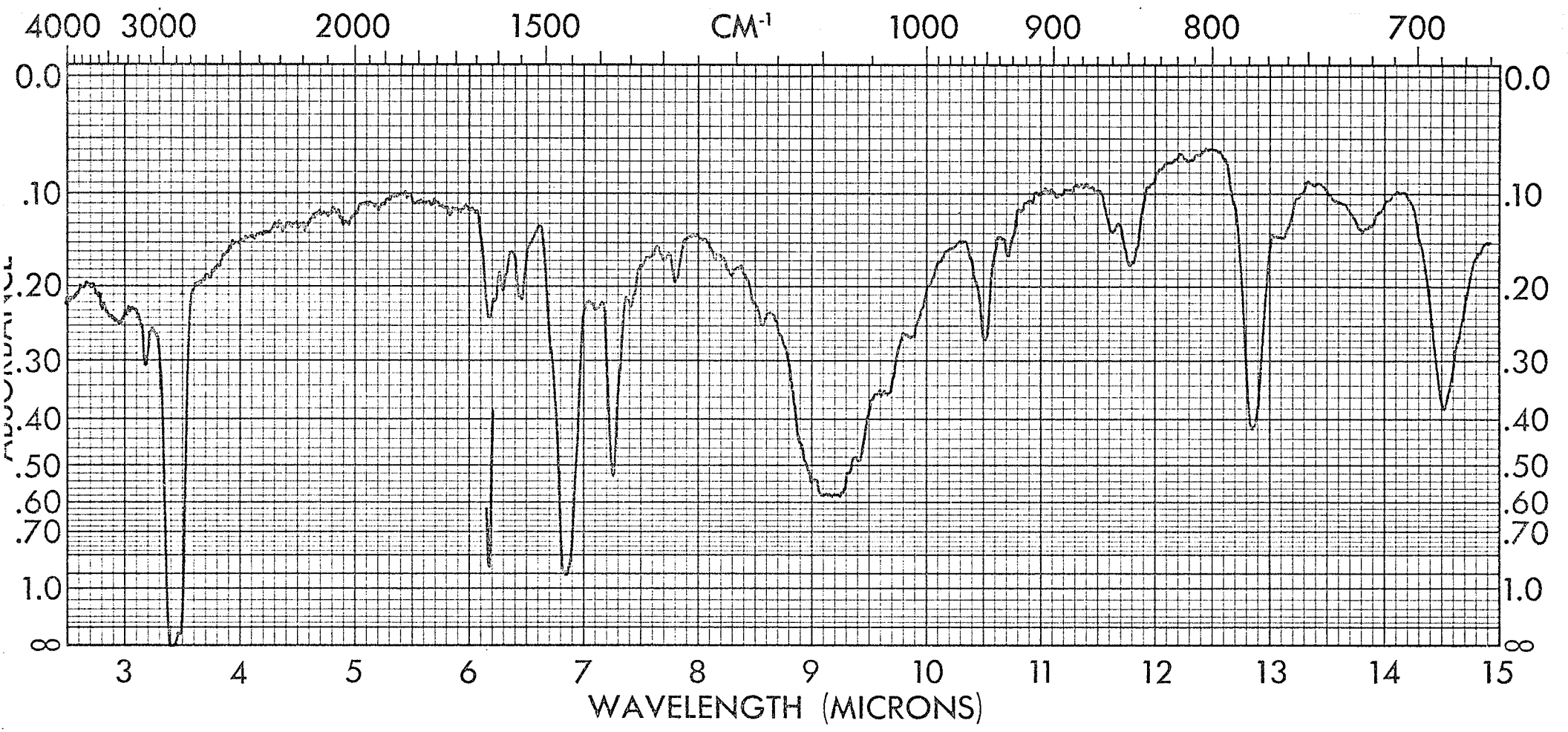
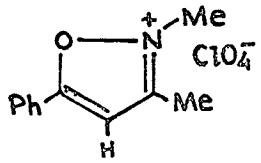
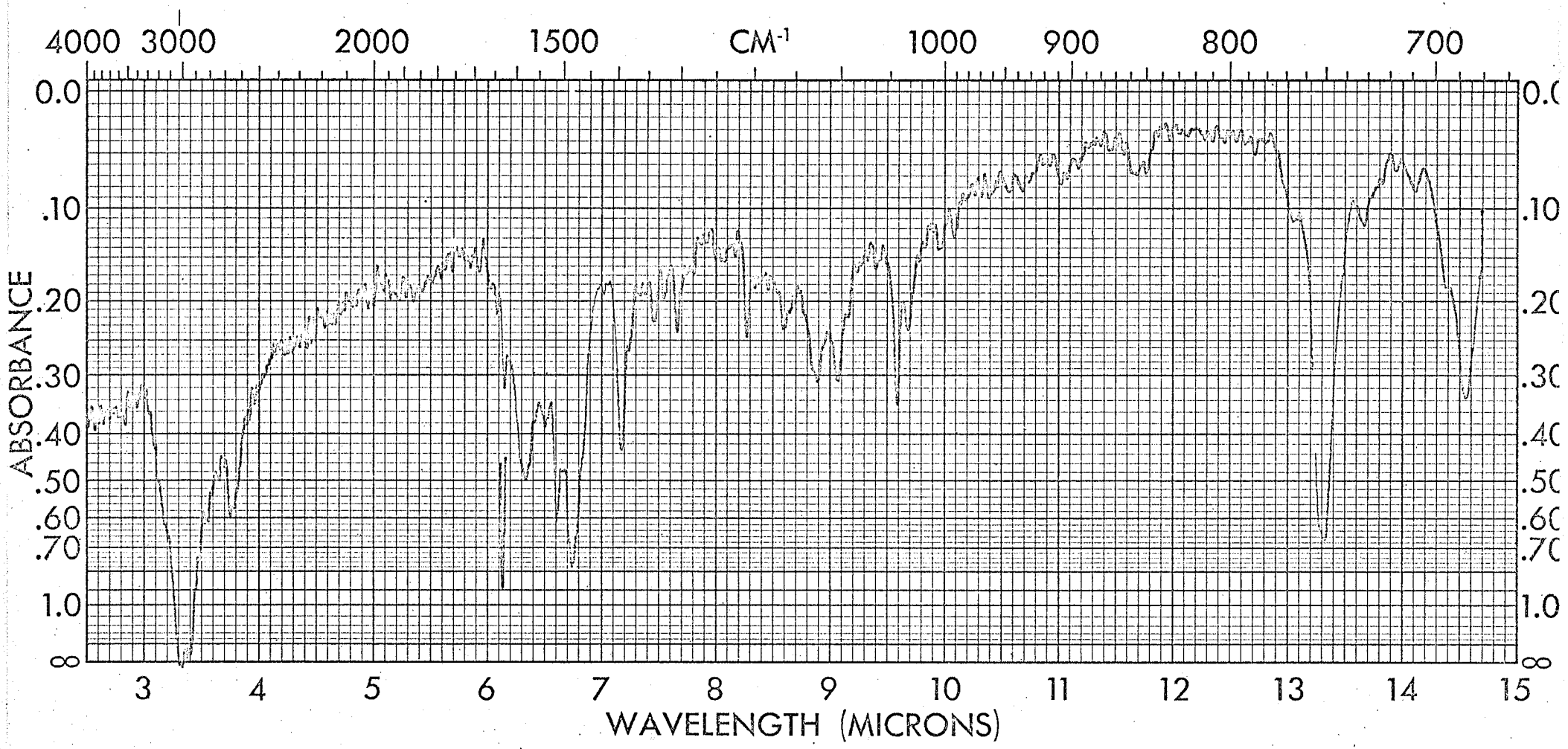
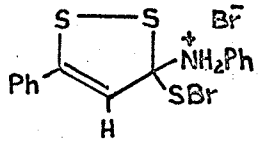
SPECTRA





2,3-DIMETHYL-5-PHENYLISOXAZOLIUM PERCHLORATE
(Nujol mull)





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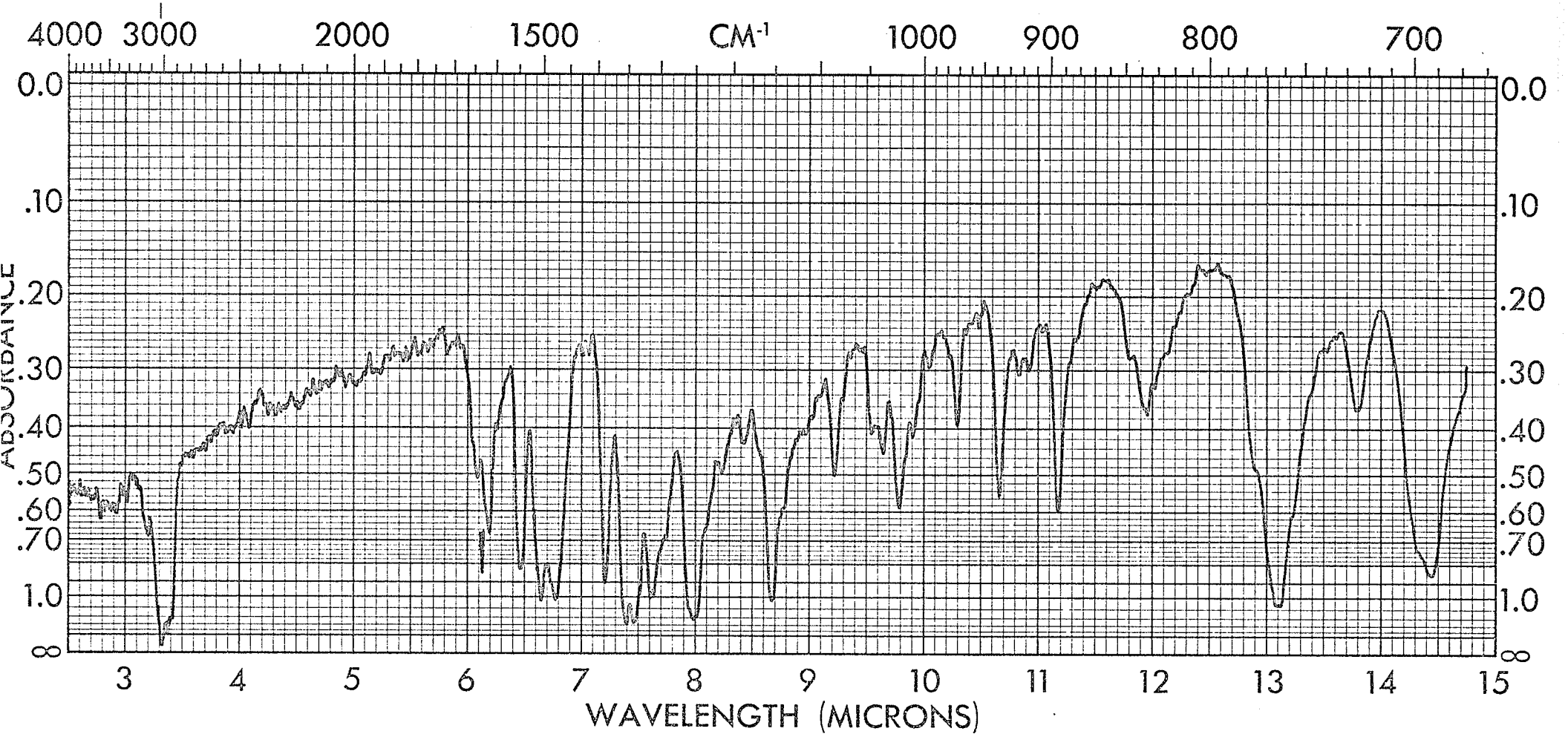
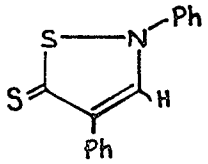
(nujol mull)

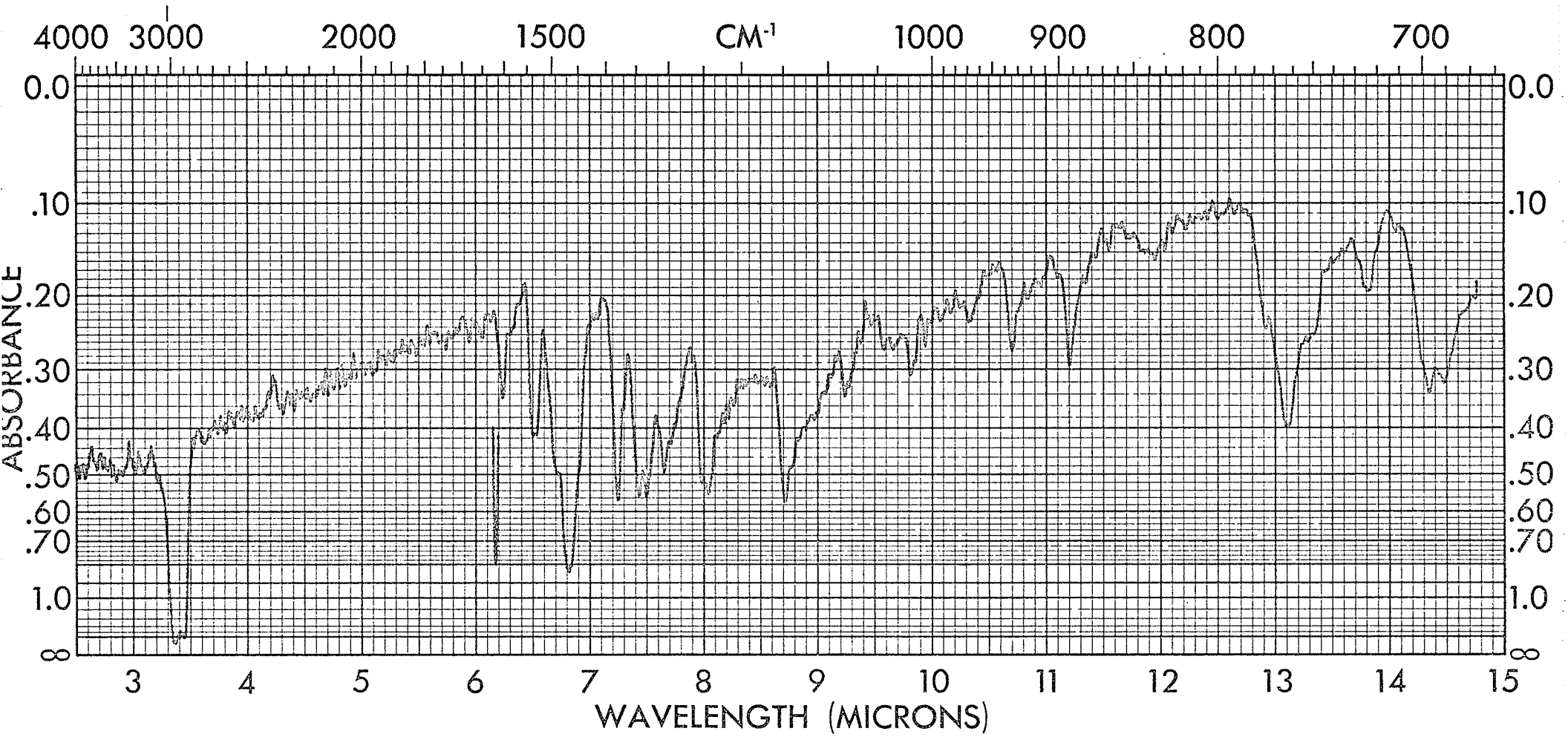


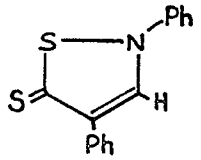


2,4-DIPHENYL-3-ISOTHIAZOLINE-5-THIONE

Synthesized by Adelfang method and reported to be 4-phenyl-3-phenylimino-1,2-dithiole

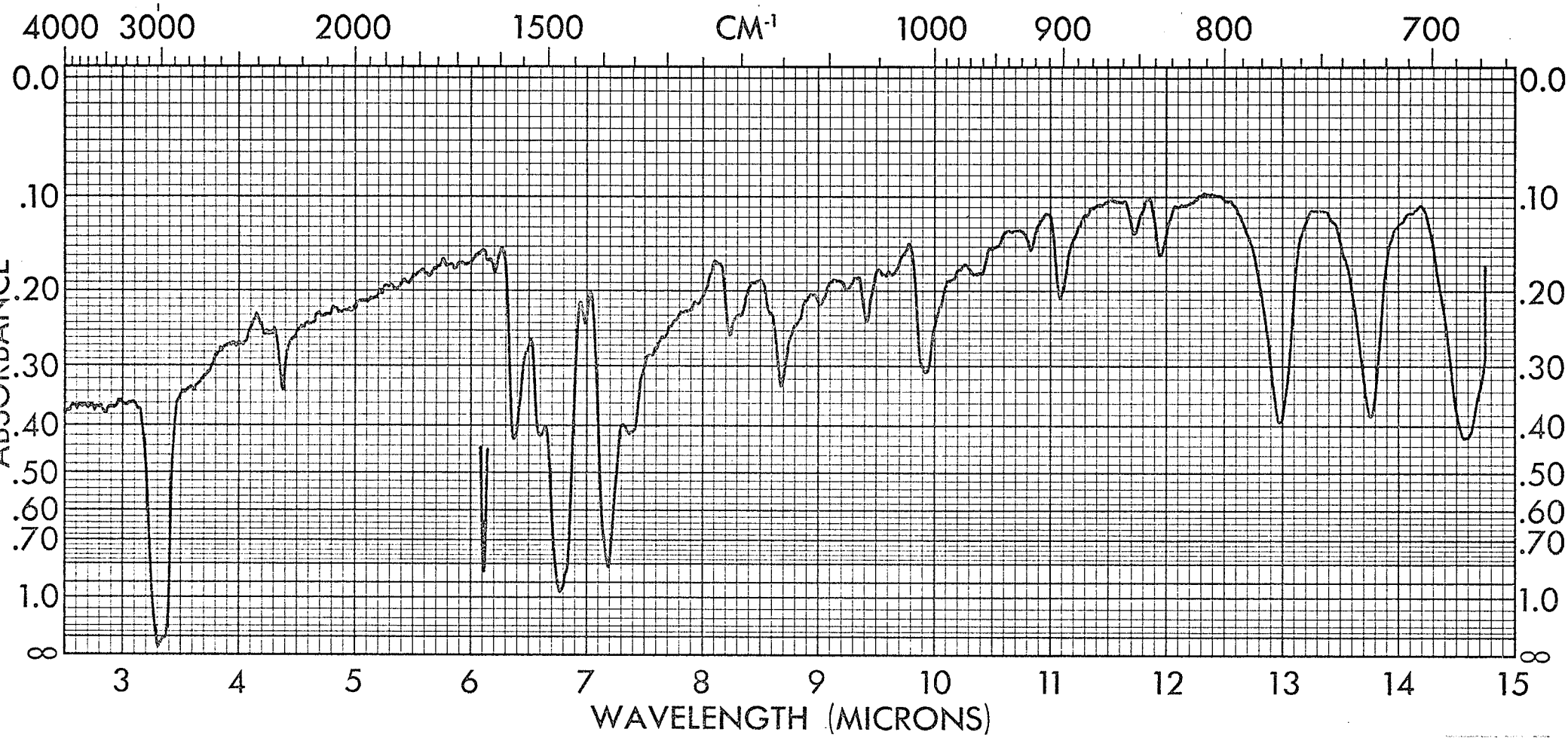
(Nujol mull)

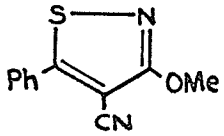




2,4-DIPHENYL-3-ISOTHIAZOLINE-5-THIONE

(Nujol mull)





3-METHOXY-4-CYANO-5-PHENYLISOTHIAZOLE
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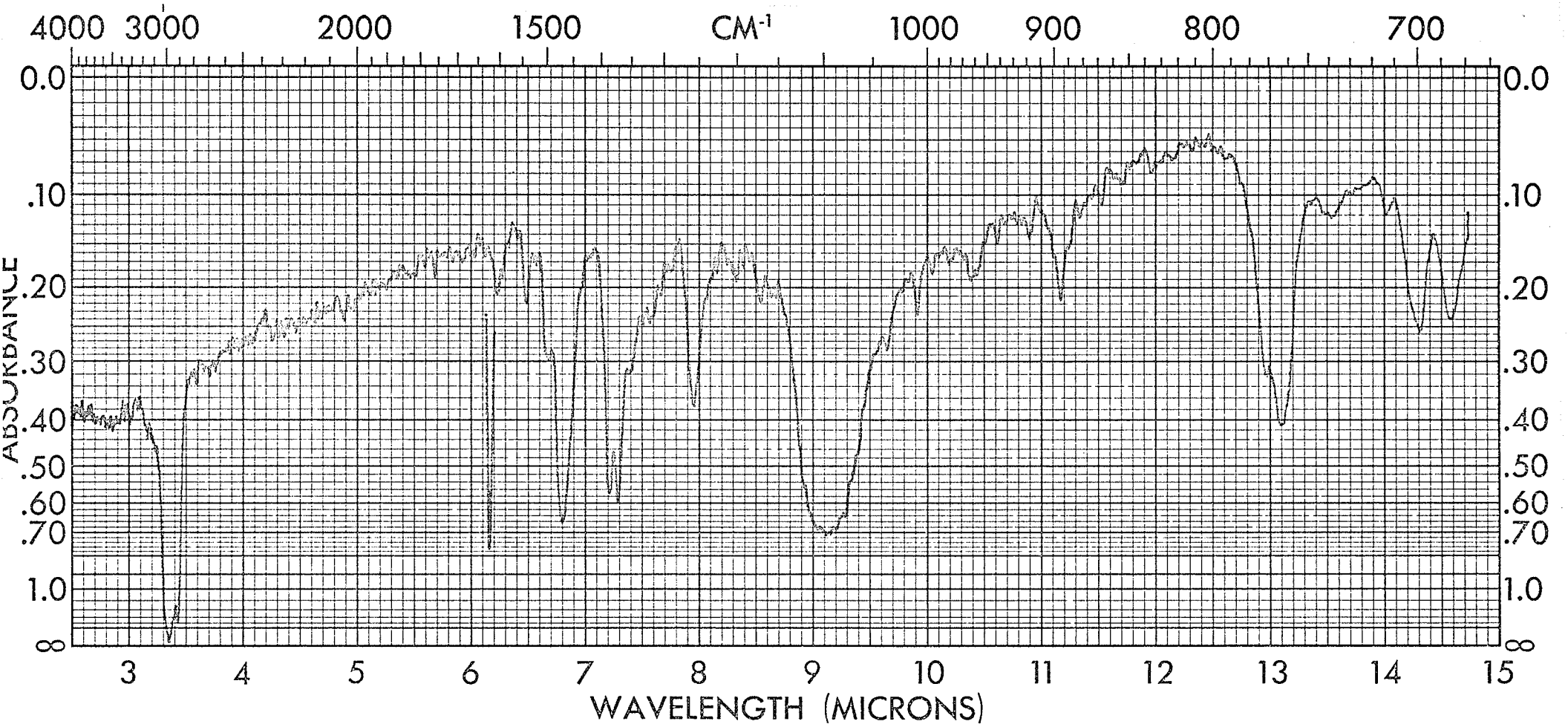
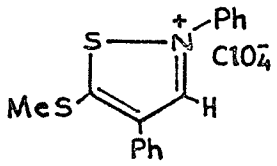
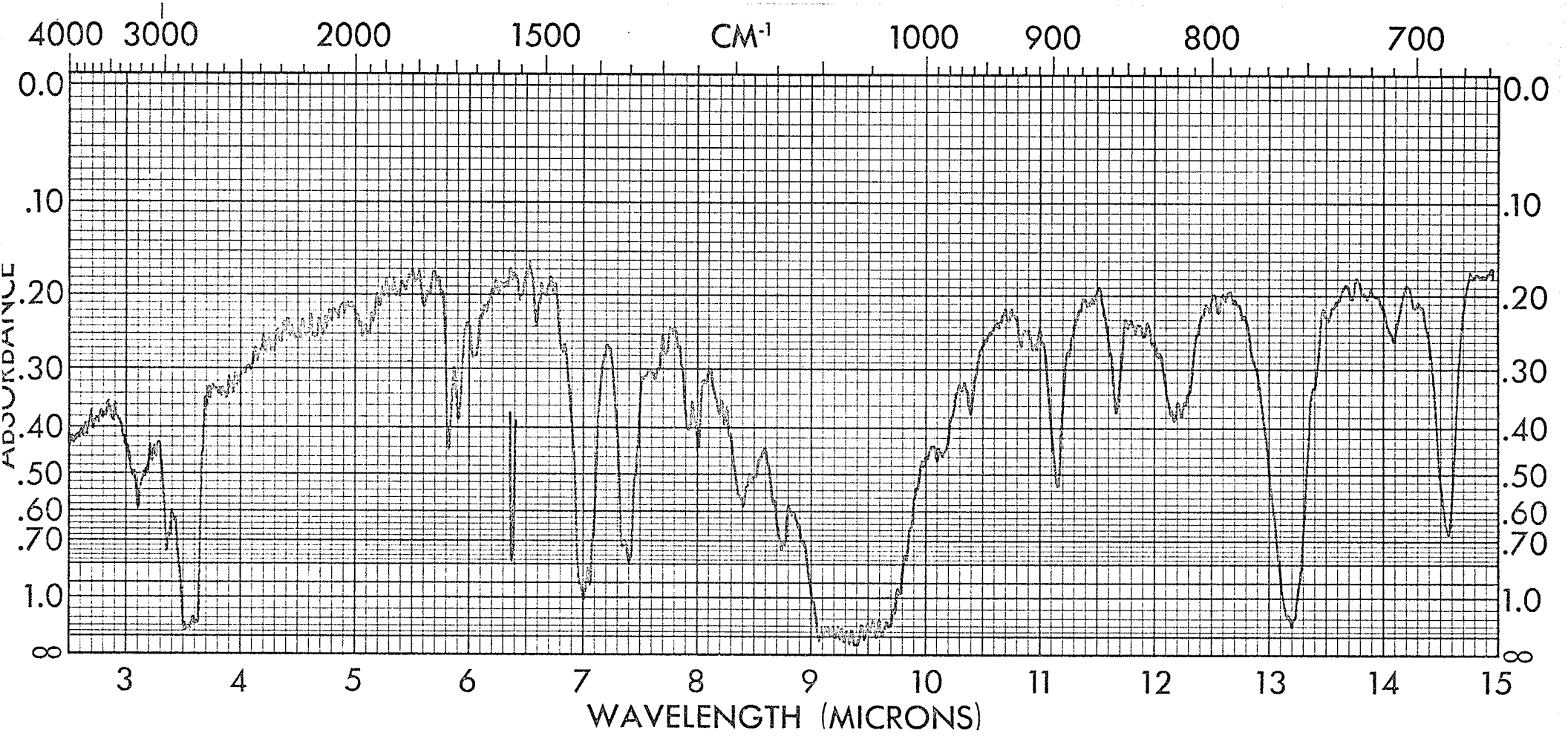
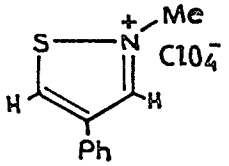




2,4-DIPHENYL-5-METHYLTHIOISOTHIAZOLIUM PERCHLORATE

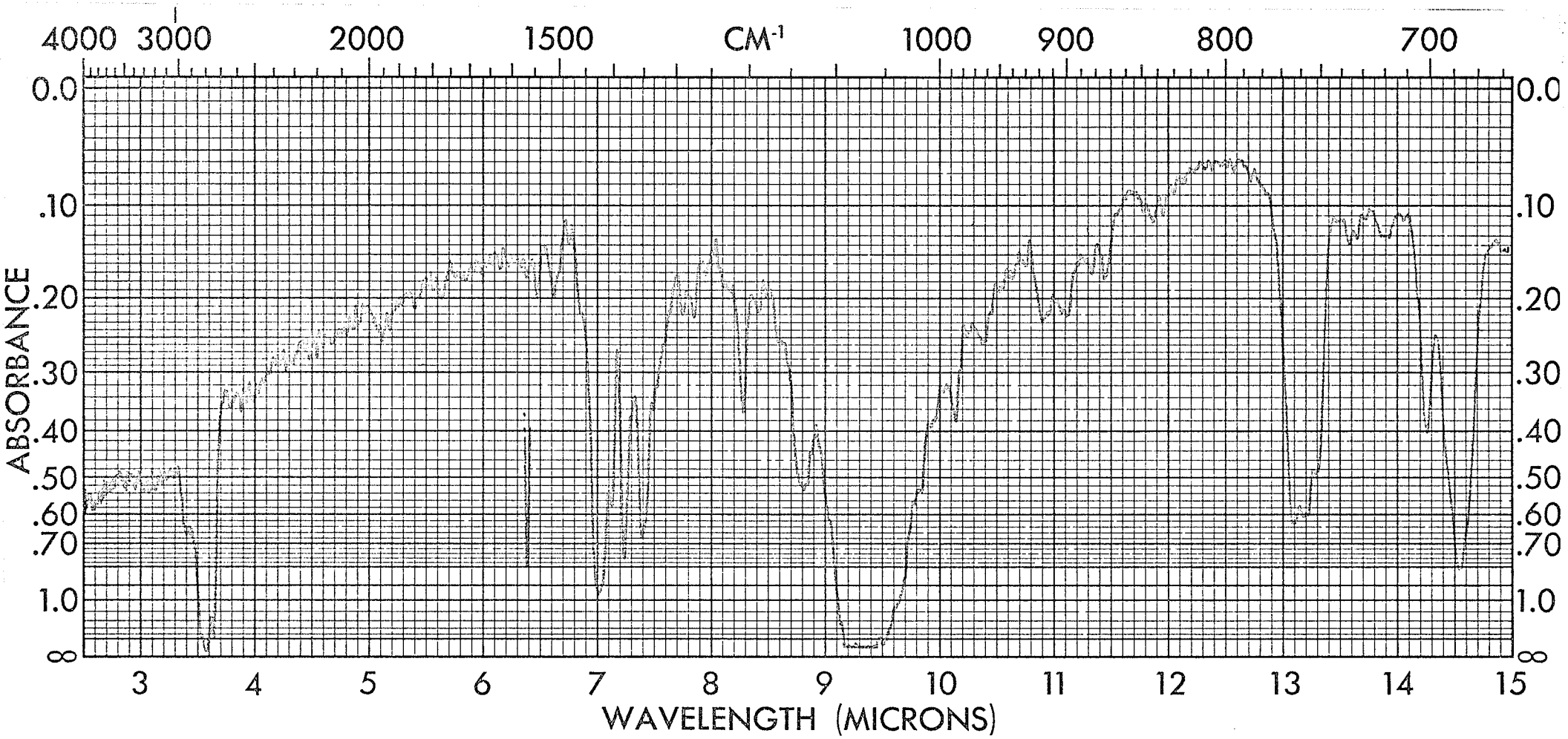
(Nujol mull)

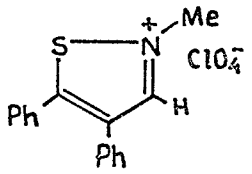




2-METHYL-4-PHENYLISOTHIAZOLIUM PERCHLORATE

(Nujol mull)





2-METHYL-4,5-DIPHENYLISOTHIAZOLIUM PERCHLORATE

(Nujol mull)